

MINIMISING RISK FACTORS FOR CERVICAL SPINE MANIPULATION

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Thesis submitted for the degree of

Doctor of Philosophy

The University of Newcastle, Australia

January 2013

This is to certify that the thesis entitled “**Minimising risk factors for cervical spine manipulation**” submitted by **Lucy Thomas** in fulfilment of the requirements for the degree of Doctor of Philosophy is in a form ready for examination.

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DECLARATION

I, **Lucy Thomas**, hereby declare that the work contained within this thesis is my own and has not been submitted to any other university or institution as a part or a whole requirement for any higher degree. I certify that the work embodied in this thesis contains published papers of which I am the lead author. I have included a written statement, endorsed by my supervisor, attesting to my contribution to these joint publications.

In addition, ethical approval from the University of Newcastle Human Research Ethics Committee and Hunter New England Research Ethics Committee was granted for the four studies presented in this thesis. Participants were required to read a participant information statement and informed consent was gained prior to data collection. Ethical approvals for all studies are included in Appendix A.

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SUPERVISOR STATEMENT

I, Professor Darren Rivett, attest that Research Higher Degree candidate Lucy

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Thomas, L, Rivett, D, Levi, C (2012). Study protocol: Risk factors and clinical features of craniocervical arterial dissection. A prospective study. BMC Musculoskeletal Disorders 13:164-169.

Thomas, L, Rivett, D, Levi, C (2012). Risk factors, radiological features and infarct topography of craniocervical arterial dissection. International Journal of Stroke. DOI:10.1111/j.1747-4949.2012.00912.x.

Thomas, L, Rivett, D, Attia, J, Parsons, M, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. Manual Therapy 16: 351-356.

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ACKNOWLEDGMENTS

I would like to extend my sincere thanks and appreciation to my supervisors, Professor Darren Rivett and Professor Christopher Levi for their enthusiasm, encouragement and guidance for the research and in the completion of this thesis, and to Associate Professor Louise Ada for her advice on the overall structure of the thesis. I would also like to thank Professor John Attia, Associate Professor Mark Parsons, Dr Grant Bateman, Associate Professor Peter Stanwell, Mr Peter Osmotherly and Mr Todd Alchin for their assistance with the studies contained in the thesis.

I would like to acknowledge and thank my son James Thomas for his assistance with the radiological figures in the Chapters 4 and 6 and thank my husband Peter and children Caroline and Patrick for their support and encouragement throughout the long process of study to complete this thesis.

Finally, I would like to dedicate the thesis to my father John Orton who always encouraged me to 'try harder' and never to give up.

PUBLICATIONS

Parts of the work presented in this thesis have been published or presented in the following forums:

PUBLISHED PAPERS

Thomas, L, Rivett, D, Bateman, G, Stanwell, P, Levi, C. The effect of selected manual therapy interventions for mechanical neck pain on vertebral and internal carotid arterial blood flow and cerebral inflow. *Physical Therapy*. Published ahead of print June 27, 2013, doi:10.2522/ptj.20120477

Thomas, L, Rivett, D, Levi, C (2012). Study Protocol: Risk factors and clinical features of craniocervical arterial dissection. A prospective study. *BMC Musculoskeletal Disorders*. 13:164-169.

Thomas, L, Rivett, D, Levi, C (2012). Risk factors, radiological features and infarct topography of craniocervical arterial dissection. *International Journal of Stroke*. DOI:10.1111/j.1747-4949.2012.00912.x.

Thomas, L, Rivett, D, Attia, J, Parsons, M, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. *Manual Therapy* 16: p 351-356.

Thomas, L (2011). Risk factors and clinical features of craniocervical arterial dissection. Invited article. In *Motion*, July issue

PUBLISHED ABSTRACTS

Thomas, L, Rivett, D, Levi, C (2012). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. *Proceedings of the 8th International Federation of Orthopaedic Manipulative Physiotherapists (IFOMPT)*. Quebec City, Canada, October 2012. *Journal of Orthopedic and Sports Physical Therapy* (2012); 42(10):A1-A83.

Thomas, L, Rivett, D, Levi, C. (2012). Radiological features of craniocervical arterial dissection and topography of the resultant infarct: Relation with risk factors. *Stroke* 2012. Sydney, August 2012. *International Journal of Stroke*. September 2012 Volume 7, Issue Supplement S1, p 14.

Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. In *Proceedings of Musculoskeletal Physiotherapy Australia 17th Biennial Conference*. Brisbane, October 2011

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Thomas, L, Rivett, D, Levi, C (2009). Risk factors and clinical features of craniocervical arterial dissection. In *Proceedings of the 16th Biennial Conference of Musculoskeletal Physiotherapy Australia*. Sydney October 2009.

Thomas, L, Rivett, D, Levi, C (2009). Risk factors and clinical features of craniocervical arterial dissection. In *Proceedings of the 3rd International Conference on Movement Dysfunction*. Edinburgh October 2009.

CONFERENCE AND OTHER INVITED PRESENTATIONS

Thomas, L, Rivett, D, Levi, C (2012). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. Oral presentation . International Federation of Orthopaedic Manipulative Physiotherapists (IFOMPT). 'Rendez-vous of Hands and Minds.' Quebec City, Canada, October 2012.

Thomas, L, Rivett, D, Levi, C (2012). Radiological features of craniocervical arterial dissection and topography of the resultant infarct: Relation with risk factors. Oral presentation. Stroke 2012. Sydney, August 2012.

Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. Oral presentation . Musculoskeletal Physiotherapy Australia 17th Biennial Conference. Brisbane, October 2011.

Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. Oral presentation . World Confederation of Physical Therapy Congress: World Physical Therapy 2011. Amsterdam, Netherlands June 2011.

Thomas, L (2011). Risk factors for Craniocervical arterial dissection. Invited speaker NSW Australian Physiotherapy Association Webinar series. May 2011.

Thomas, L, Rivett, D, Levi, C (2010). Risk factors and clinical features of craniocervical arterial dissection. Invited speaker at Australian Physiotherapy Association NSW Branch Symposium. Sydney May 2010.

Thomas, L, Rivett, D, Levi, C (2009). Risk factors and clinical features of craniocervical arterial dissection. Oral presentation at 16th Biennial Conference of Musculoskeletal Physiotherapy Australia. Sydney October 2009.

Thomas, L, Rivett, D, Levi, C (2009). Risk factors and clinical features of craniocervical arterial dissection. Oral presentation at 3rd International Conference on Movement Dysfunction. Edinburgh October/November 2009.

Thomas L, Levi C, Rivett D (2008). Risk factors and natural history of craniocervical arterial dissection. Poster Presentation with two minute talk. International Federation of Orthopaedic Manipulative Therapists: IFOMT 2008 'Conference Connecting Science to Quality of Life' June 2008.

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ABSTRACT

The overall aim of the work presented in this thesis was to examine the risk factors for cervical manipulation and make recommendations for clinical practice. Cervical spine manipulation is a manual technique used for the treatment of neck pain and associated headache. The most commonly described serious neurovascular adverse event following cervical manipulation is dissection of one or more of the craniocervical arteries, which comprise the main blood supply to the brain. Current pre-manipulative screening guidelines are limited in their ability to identify patients at risk of adverse events or screen patients for signs of brain ischaemia. The aim of the thesis is to guide practitioners in minimising the risk of neurovascular events associated with cervical manipulation, and this was approached in two ways. Firstly, by identifying risk factors and early presenting clinical features associated with craniocervical arterial dissection and secondly, by identifying neck positions inherent in common manipulative techniques which might have a greater impact on craniocervical arterial blood flow.

The thesis comprises four studies investigating the risk factors for adverse neurovascular events following neck manipulation and the presenting features of arterial dissection. Study one examined the risk factors and clinical features of craniocervical arterial dissection in a retrospective medical records review and found that mechanical trauma, vascular anomaly and less so recent infection were associated with dissection, and that typical cardiovascular risk factors were generally less important. Study two examined the radiological features of craniocervical arterial dissection and their association with risk factors, and found that mechanical

trauma and vascular anomaly were associated with a higher incidence of cerebral infarction. Study three examined the risk factors and clinical features of dissection in a prospective group of patients. Preliminary findings are reported that mechanical trauma was associated with dissection, and that 70% of patients reported 'early warning signs' of brain ischaemia. The final study investigated the effects of various head and neck positions commonly utilised in manual therapy on blood flow in the craniocervical arteries and consequent blood supply to the brain. The study found that selected neck positions did not have any significant effect on blood flow compared with the neutral position, and that combined end-range rotation and distraction positions of the head and neck did not have any greater effect on blood flow than localised segmental rotation positions.

There are specific recommendations which can be made as a result of these findings. Clinicians should screen patients presenting with headache or neck pain for a recent history of trauma or recent infection, and closely examine for transient features of brain ischaemia. If potential ischaemic features are identified, prompt referral for medical assessment should be made. Generally cardiovascular risk factors do not appear to be useful indicators of risk of adverse events following manual therapy of the neck, and probably do not need to be considered contraindications to manual therapy applied to the neck. Neck positions commonly used in manual therapy practice such as end-range head and neck rotation and/or distraction do not appear to be any more hazardous in terms of their effects on craniocervical arterial blood flow than techniques performed in positions in neutral or with more localised segmental rotation. The positions for manipulative techniques commonly used in clinical practice therefore do not appear to be inherently dangerous, although the thrust

component was not evaluated. The findings also do not support the utility of measurement of blood flow in a single vessel such as the vertebral artery during pre-manipulative screening to identify deficits in brain perfusion imposed by some neck positions. Isolated measurement of vertebral artery blood flow is therefore not supported for inclusion into clinical screening guidelines.

CHAPTER 1
INTRODUCTION

RATIONALE OF THE THESIS

Aims

Hypotheses

OUTLINE OF THE THESIS

Studies

Scope/De-limitations

Significance

RATIONALE OF THE THESIS

Manual therapy including cervical spine manipulation is a commonly used treatment for neck pain and associated headache by a number of health professionals despite the well-documented, though likely low risk of iatrogenic stroke. The term cervical manual therapy describes manual procedures applied to the cervical spine for the treatment of neck pain and headache. This may include cervical manipulation, that is high velocity thrust techniques over which the patient has no control once underway, or more gentle oscillatory or sustained mobilisation techniques which the patient can stop should they become too uncomfortable. In general, manual therapy of the cervical spine has been shown to be an effective and safe form of management of musculo-skeletal pain in or referred from the cervical region (Jull, Trott et al. 2002; Gross, Kay et al. 2002a).

As will be discussed in Chapter 2, adverse events related to cervical manual therapy have been described in the literature for over 100 years but these are usually relatively innocuous, such as a temporary increase in local pain or tenderness, or less frequently include transient dizziness or nausea (Cagnie, Vinck et al. 2004). However, in rare cases, more serious complications have been reported, notably, compromise of neurovascular structures which may have led to stroke or even death. The most commonly described serious adverse neurovascular event, in cases where it has been possible to establish a diagnosis with radiological evidence, is dissection of the craniocervical arteries (the vertebral or internal carotid arteries) and subsequent stroke (Haldeman, Kohlbeck et al. 1999; Caso, Paciaroni et al. 2005; Paciaroni and Bogousslavsky 2009). Where reported, vertebral artery dissections occur more commonly than internal carotid in relation to manual therapy (Haldeman, Carey et al.

2001).

The craniocervical arteries pass through the cervical region in close association with the cervical spine and together comprise the main blood supply to the brain. The anatomy and biomechanics of the craniocervical arteries, in particular in the upper cervical spine may predispose them to manipulative injury (Schievinck 2001). This is thought to be particularly the case in the presence of anatomical anomalies or vascular pathologies.

Concern has been raised both widely in the media and in parts of the medical profession about the safety of neck manipulation (Lee, Carlini et al. 1995; Norris, Beletsky et al. 2000). Presently some controversy exists in the literature as to whether the nature of the manipulative techniques themselves are to blame, or instead that the practitioner fails to recognise a patient with a dissection already in progress and proceeds with manual treatment (Cassidy, Boyle et al. 2008). In this latter instance there is also potential for the manual treatment to extend an existing dissection or cause propagation of an embolus from the dissection site.

Difficulties arise for health professionals in the identification of patients both at risk of dissection or who may be in the early stages of arterial dissection. Current pre-manipulative screening guidelines (Rivett, Shirley et al. 2006; Rushton, Rivett et al. 2012) may not identify all patients at risk of adverse events, and neck pain and headache may themselves be symptoms of craniocervical arterial dissection. That is, patients may present to a health professional seeking manual treatment for headache or neck pain due to a dissection already in progress. It is therefore of critical importance for health professionals to be able to accurately identify putative risk

factors as well as early clinical signs and symptoms of arterial dissection, which may in some cases be subtle, in order to avoid inappropriate manual treatment and to expedite urgent medical review. Early commencement of medical treatment is important to lessen the likelihood or impact of a potential stroke.

On the other hand, some authors suggest neurovascular complications associated with cervical manipulation are a result of mechanical insult to the artery during the manipulative procedure itself. It has been shown that cervical rotation, common to many manual therapy procedures, can temporarily alter blood flow in the cervical arteries thus potentially increasing biomechanical stress to the vessel wall, although as will be discussed in Chapter 2 (page 62), conflicting findings exist in the literature. Many of the recommended manipulative procedures involve cervical rotation and distraction which may therefore theoretically place increased stress on the craniocervical arteries. It is possible that certain manipulative procedures may impose greater stress on the craniocervical arteries than others and consequently cause greater alterations in blood flow. This consideration will be discussed in Chapter 6.

Aims

The overall aim of this thesis is to identify the risk factors for adverse neurovascular events subsequent to cervical spine manipulation in order to inform the professions using manual therapy. The primary aim was to explore the risk factors for craniocervical arterial dissection in order to enhance the recognition of individuals with an underlying susceptibility. In addition, the thesis aims to characterise the initial presenting clinical features of a dissection in progress so that clinicians might more readily identify the early presentation of this serious pathology. The secondary

aim was to identify potentially hazardous activities, such as specific manipulative techniques which might be more likely to trigger an adverse event in a susceptible individual.

Hypotheses

1. Risk factors for craniocervical arterial dissection will be identifiable in the patient history and/or physical examination
2. Characteristic clinical features of craniocervical arterial dissection will be identifiable in the patient history and/or physical examination
3. Positions of the head and neck used in selected manual interventions will influence blood flow in the craniocervical arteries and resultant blood supply to the brain in comparison to the neutral head position.

OUTLINE OF THE THESIS

The thesis comprises a literature review followed by a series of papers which describe the four studies undertaken, the findings of which are consolidated and further discussed in a final concluding chapter. Chapter 2 is a review of selected aspects of the literature presented to enable the reader to understand the context and methodologies of the four studies. Chapter 3 reports the first study which is a retrospective medical records review of participants with craniocervical arterial dissection, while Chapter 4 is a review of radiological features of these participants. Chapter 5 is a prospective study examining participants presenting with craniocervical arterial dissection. Chapter 6 is a functional magnetic resonance imaging (MRI) study examining the effects of neck positions used in selected manual therapy techniques on blood flow in the vertebral and internal carotid arteries. The

final chapter provides a summary of the key findings of the four studies and the conclusions which can be drawn, with recommendations for future research and clinical practice.

Studies

Study one (Chapter 3) is a retrospective review of the medical records of participants from the local area health authority who had suffered a craniocervical arterial dissection between 1997 and 2007. The purpose of undertaking this study was to gain an overview of the scope of the condition including reported risk factors and clinical features, and to review the relative frequency of craniocervical arterial dissection in the local population compared with reported incidence rates in the literature. The demographic characteristics of the participants, their pre-existing health status, and the chronological history of the presenting clinical features of the dissection and preceding events were recorded and analysed.

Study two (Chapter 4) is a review of the radiological features of the retrospective study sample from the first study. Radiological features in the vertebral and internal carotid arteries and areas of brain infarction were identified and topographical distribution of the infarct mapped. These features were then compared with the identified risk factors in the first study to determine any link between risk factors and the nature of the pathological features identified.

Study three (Chapter 5) is a prospective study of craniocervical arterial dissection participants at the time of their dissection. This study was informed by the earlier retrospective studies and the limitations identified by this methodology. The study

included a patient interview in order that more detailed information about presenting features and preceding events could be ascertained directly from the participant. This study aimed to identify more specific details about risk factors and presenting clinical features which might be helpful for primary care practitioners when screening patients presenting with head and neck pain or assessing them prior to manual treatment of the neck. The preliminary results for twenty dissection participants and twenty control participants are presented in this thesis. However, this study is on-going, as craniocervical arterial dissection is a reasonably rare condition with only around six to seven patients presenting per year to the recruiting centre.

Study four (Chapter 6) is a comparative magnetic resonance imaging study investigating the effects of selected manual therapeutic procedures on blood flow in the craniocervical arteries and overall blood supply to the brain. The purpose was to investigate the relative safety of particular therapeutic procedures by comparing the effects on blood flow between techniques utilising combined end-range rotation and distraction positions with those employing more localised segmental rotation.

Scope/De-limitations

The thesis is focussed on craniocervical arterial dissection because this is the most commonly reported serious adverse neurovascular event which may occur following cervical manipulation. It does not investigate in detail other vascular pathologies because these have not been reported as being associated with adverse events following manual therapy to the cervical spine, such as atherosclerosis, or may be transient, such as vasospasm.

Significance

Information gained from the first three studies should assist practitioners in risk assessment prior to manual treatment of the cervical spine. The final imaging study should inform manual therapy practitioners of the effects of particular neck positions on craniocervical blood flow. This should provide guidance on the safety of manual procedures and the utility of some positional tests or blood flow measurement in pre-manipulative screening.

CHAPTER 2

LITERATURE REVIEW

CERVICAL MANIPULATION

- Definitions**
- Indications**
- Contraindications**
- Adverse events**

CRANIOCERVICAL ARTERIES

- Vertebral artery**
- Internal carotid artery**

CRANIOCERVICAL ARTERIAL DISSECTION

- Definition**
- Incidence**

AETIOLOGY OF CERVICAL ARTERIAL DISSECTION

RISK FACTORS FOR CRANIOCERVICAL ARTERIAL DISSECTION

- Intrinsic factors**
- Cardiovascular risk factors**
- Extrinsic factors**

PATHOPHYSIOLOGY OF CRANIOCERVICAL ARTERIAL DISSECTION

CLINICAL FEATURES OF CERVICAL ARTERIAL DISSECTION

- Internal carotid arterial dissection**
- Vertebral arterial dissection**

DIAGNOSIS OF CRANIOCERVICAL ARTERIAL DISSECTION

RADIOLOGICAL DIAGNOSIS OF CERVICAL ARTERIAL DISSECTION

- Angiography**
- Computed Tomography**
- Magnetic Resonance Imaging**
- Ultrasound**
- Diagnostic radiological features of craniocervical dissection**

IDENTIFICATION OF PATIENTS AT RISK BY MANUAL THERAPISTS

- Description of pre-manipulation screening guidelines**
- Limitations of pre-manipulative screening guidelines**

CLINICAL CONSIDERATIONS PRIOR TO NECK MANIPULATION

- Blood flow compromise**
- Cardiovascular factors**
- Connective tissue screening**

Manual therapy procedures

BIOMECHANICAL EFFECTS OF CERVICAL MANIPULATION

Positions for manual therapy procedures

Forces applied

Effect of neck movement on craniocervical arterial blood flow

Limitations of previous blood flow studies

SUMMARY

In this chapter, an overall review of the literature is presented. Additional papers pertaining to the area for each study are also included in the relevant chapters describing the studies, as the state of knowledge in the area evolved. In this chapter, a discussion of cervical spine manipulation and its associated complications is presented, with particular emphasis on craniocervical arterial dissection. A detailed description of the anatomy, biomechanics and pathophysiology of the vertebral and internal carotid arteries is provided, along with their typical clinical presentation following arterial dissection. The pathophysiology and aetiology of arterial dissection is described in detail. The issues surrounding the validity of current pre-manipulative screening are also discussed. Finally, biomechanical considerations concerning cervical manipulation are reviewed; in particular the effect of different head and neck positions used in common manual therapy procedures on craniocervical arterial blood flow dynamics.

CERVICAL MANIPULATION

Cervical manipulation is one of a number of manual techniques used by physiotherapists for the treatment of neck pain and headache, which may frequently be attributed to biomechanical dysfunction of the cervical spine joints. Neck pain is one of the most common disorders of the musculoskeletal system, surpassed in frequency only by low back pain and osteoarthritis (National Health and Medical Research Council 2004). Approximately 10-15% of the population will be suffering from neck pain at any one time and 40% will suffer neck pain during a twelve-month period (Ariens, Borghouts et al. 1999).

Definitions

The term 'manipulation' has been specifically defined as a high velocity, low amplitude thrusting technique applied to a joint, over which the patient has no voluntary control (Maitland 1986; Grieve 1991; Corrigan and Maitland 1998). The thrust is usually performed with minimal force at the limit of the available physiological range of motion for a specific joint, with the aim of moving the joint beyond its available range, but still within normal physiological range. The procedure is often, but not always accompanied by a 'click', a noise thought to be caused by cavitation of the joint, as the two joint surfaces are pulled apart (Corrigan and Maitland 1998). This form of specific treatment is commonly used by musculoskeletal practitioners such as physiotherapists, chiropractors, osteopaths and medical practitioners (Hurwitz, Aker et al. 1996).

The term 'manipulation' is also sometimes applied generically to any manual technique involving movement of joints or soft tissues. Non-thrusting techniques which move joints are more usually known as 'mobilisation' and are typically slower and more gentle than manipulation, and importantly, lie within the patient's control. Such discrepancies in nomenclature may lead to problems of interpretation of studies which describe the efficacy of cervical manipulation (Hurwitz, Aker et al. 1996; Gross, Kay et al. 2002b), and also particularly those which report adverse events associated with manipulation.

For the purposes of this thesis the term 'cervical manipulation' refers to the more narrow definition of a high velocity thrust technique applied to the cervical zygapophyseal joints. The term 'mobilisation' refers to more gentle oscillatory or

sustained techniques applied to the cervical zygapophyseal joints. The more generic term ‘manual therapy’ refers to any manual technique including manipulation, mobilisation and massage.

Indications

Cervical spine manipulation is primarily used for the treatment of neck pain and cervicogenic headache and is generally indicated when progress has slowed with more gentle passive joint mobilising techniques (Maitland 1986; Hurwitz, Aker et al. 1996). Occasionally it is used in the early stages of a course of treatment, where an ‘irritable’ joint, i.e. one in which pain is easily aggravated, may be aggravated by a repetitive oscillatory mobilisation technique, and in which a single quick thrust is deemed preferable.

Contraindications

There are a number of specific contraindications to cervical manipulation but in general manipulative procedures are avoided in cases where patients are suffering from severe pain or muscle spasm (Maitland 1986; Grieve 1991), and where instability or hypermobility of the cervical intervertebral segment is suspected. Manipulation is also avoided when the patient is unable to relax for the procedure (Grieve 1991). Absolute contraindications to manipulation are listed in Table 2.1.

Table 2.1 Absolute contraindications to cervical manipulation (Refshaug, Parry et al. 2002)

Bony disorders	Neurological compromise	Systemic disorders
Inflammatory joint disease e.g. rheumatoid arthritis or ankylosing spondylitis	Vertebral artery insufficiency or pathology	Tumours of bony or soft tissues of the cervical spine
Fractures or dislocations in the cervical spine	Severe or acute nerve root compromise	Infective disease of the spine e.g. osteomyelitis, tuberculosis
Metabolic bone disease e.g. osteoporosis	Neurological diseases e.g. multiple sclerosis	Advanced diabetes with associated poor tissue viability
Advanced degenerative disease involving the cervical spine	Spinal cord compression	Psychogenic disorders
Developmental abnormalities, particularly in upper cervical joints		Anticoagulant medication or blood clotting disorders
Spondylolysis/ spondylolisthesis		Undiagnosed pain
Cervical disc prolapse		
Intervertebral joint instability		

Adverse events

Cervical manipulation may be associated with adverse neurovascular events in rare cases, and these most commonly involve the posterior cerebral circulation. In cases where it has been possible to establish a cause with radiological evidence, vertebral artery dissection, and less frequently internal carotid artery dissection has been demonstrated (Frisoni and Anzola 1991; Assendelft, Bouter et al. 1996; Hurwitz, Aker et al. 1996; Caso, Paciaroni et al. 2005; Paciaroni and Bogousslavsky 2009). Vertebral and internal carotid artery dissections together are commonly described as cervical or craniocervical arterial dissections. The incidence of adverse neurovascular events attributed to cervical manipulation is probably under-estimated as many estimates are based on medico-legal reports which may report only the more serious cases. In addition, craniocervical arterial dissections may in some cases go

unrecognised and heal spontaneously (Ernst 2002; Debette and Leys 2009).

Neurovascular adverse events have been reported to occur in varying proportions ranging from one 1 in 163,000 manipulations ((Rivett and Reid 1998) to as few as one in 1,000,000 (Carnes, Mars et al. 2010). However, the potential for such adverse outcomes must be taken into serious consideration by manual practitioners because of the potential for permanent disability or even death (Hurwitz, Aker et al. 1996). Because of the serious nature of craniocervical arterial dissection it is recommended that practitioners understand the anatomy and function of the craniocervical arterial system in order to enhance the safety of manual therapeutic practice, as well as to better recognise of the signs and symptoms of vascular compromise in this region.

CRANIOCERVICAL ARTERIES

The craniocervical arteries are arteries which carry blood through the cervical region to the brain. They comprise the vertebral and internal carotid arteries and feed into the Circle of Willis to ensure a constant supply of blood to the brain (Figure 2.1). The vertebral arteries supply the posterior cerebral circulation and the internal carotid arteries the anterior circulation. A description of the course and distribution of the vertebral and internal carotid arteries follows.

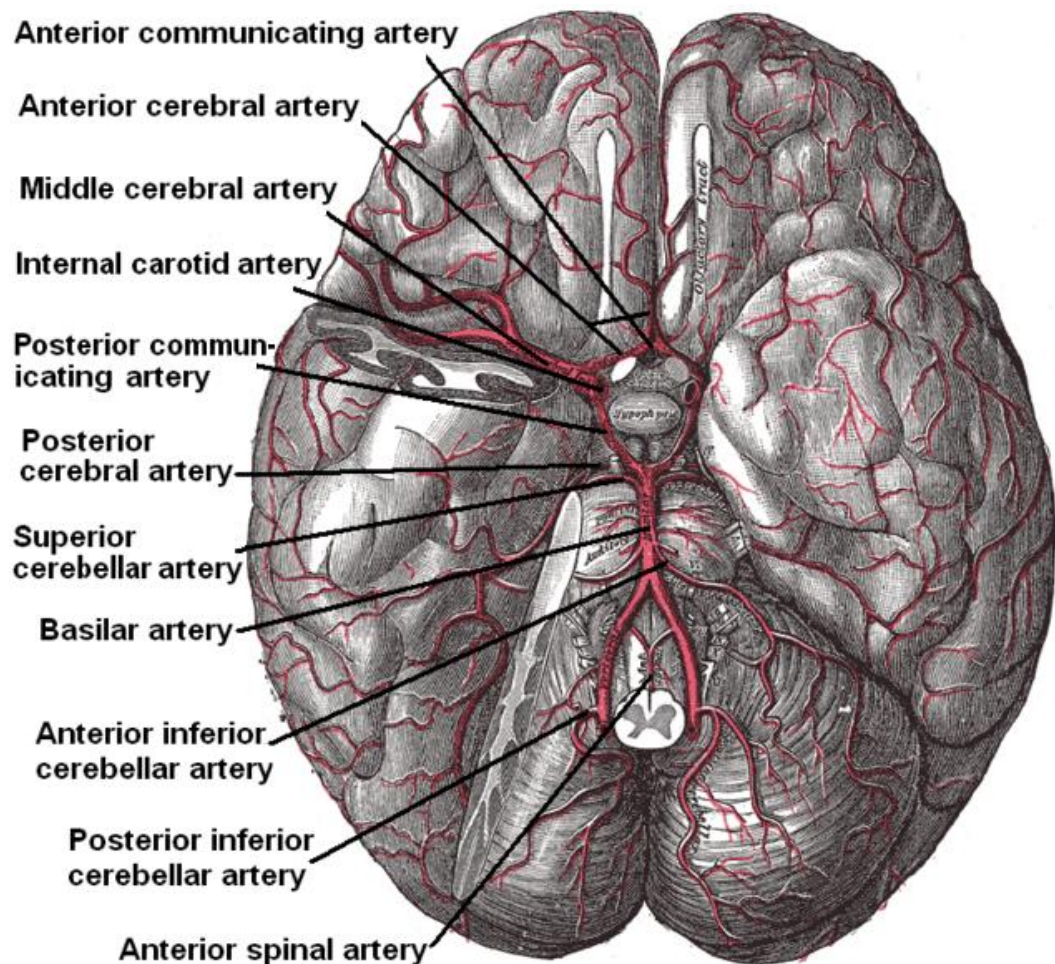


Figure 2.1 *Blood supply to the brain and Circle of Willis*
http://en.wikipedia.org/wiki/Circle_of_Willis

Vertebral artery

The vertebral arteries supply 20% of blood flow to the brain including many vital structures, namely the brainstem, cerebellum, spinal cord, cranial nerves III-XII and their nuclei, and some of the posterior cerebral cortex. The vertebral artery is generally described in four segments, corresponding to the anatomical location (Argenson, Franke et al. 1980) as shown in Figure 2.2:

- V1 pre-transverse segment
- V2 transverse segment

- V3 atlanto-axial segment
- V4 intracranial segment

The first part of the artery is given off the superoposterior aspect of the subclavian artery near its origin on the aortic arch. Infrequently the left vertebral artery may arise from the aortic arch itself and the right from the brachiocephalic trunk. Other variations are also described (Argenson, Franke et al. 1980). The artery then ascends in a superoposterior and slightly medial direction towards the ipsilateral transverse process of the sixth cervical vertebra, passing between the longus colli and sternocleidomastoid muscles. It passes posterior to the internal carotid artery and the vertebral vein. The thoracic lymphatic duct lies to the left of the artery and the inferior thyroid artery lies anterior. The sympathetic cervicothoracic ganglion (stellate ganglion) lies in close association to it (Warwick and Williams 1975).

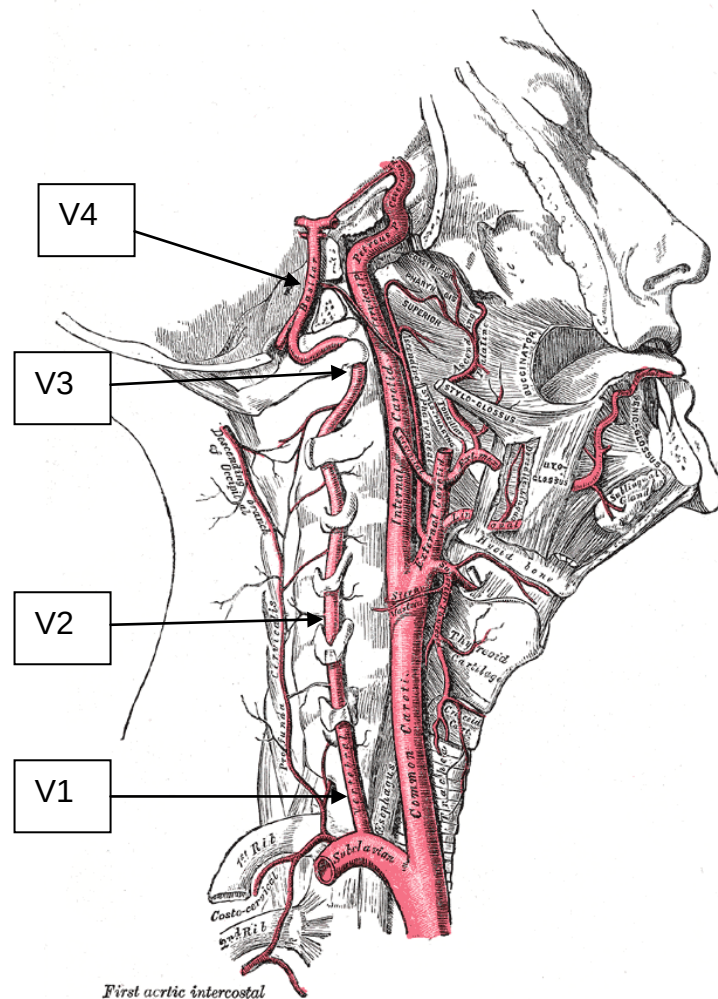


Figure 2.2 *The course of the vertebral artery showing the relations of the four segments. V1 = pre-transverse segment, V2 = transverse segment, V3 = atlanto-axial segment, V4 = intracranial segment (Bartelby 2005)*

The second part or transverse segment commences as the vertebral artery enters the foramen transversarium of the sixth cervical vertebra (C6). In 90% of cases the artery enters at the C6 level but it may enter at a vertebral level above or below. In rare instances it may enter as high as the C3 or C4 level (Argenson, Franke et al. 1980). The artery then ascends in a fibro-periosteal sheath in the foraminae transversarii of the cervical vertebrae to the C2 level. The artery lies lateral to the uncovertebral joints and anterolateral to the zygapophyseal joints, and is surrounded by a plexus of

veins and sympathetic nerves. The ventral rami of the spinal nerves lie posterior to the artery (Bogduk 1994).

The third part of the artery or atlanto-axial segment is described from the point at which the artery enters the foramen transversarium of the C2 vertebra (axis) (Franke, Di Marino et al. 1981). The artery emerges from the foramen of the axis and curves outwards forming a convex posterolateral loop. It then travels superiorly to reach the foramen transversarium of the first cervical vertebra (atlas). The artery passes through the foramen and then courses along the posterior arch of the atlas deep to the cervical muscles: semispinalis capitis, obliquus capitis inferior and rectus capitis posterior major. The rectus capitis lateralis attaches to the superior surface of the C1 transverse process immediately lateral to the artery. The vessel then turns abruptly posterior and medially to pass behind the lateral mass and run in a groove around the posterior aspect (Warwick and Williams 1975). The artery is held in place by a fibrous casing reinforced laterally by the transverse ligament and posteriorly by the retroglenoid ligament (Franke, Di Marino et al. 1981). These fibrous elements may be ossified and are then known as the posterior ponticles and form the arcuate foramen (Haynes 2002b). This phenomenon has been described in 33% of cases by (Lamberty and Zivanovic 1973). The artery lies posterior to the atlanto-occipital joint in this groove or foramen and anterior to the posterior atlanto-occipital membrane. As the artery emerges from the groove it passes under the membrane and enters the vertebral canal accompanied by the occipital nerve. The vertebral artery is most at risk from manipulative injury in this atlanto-axial region.

The fourth or intercranial part of the artery begins as the artery pierces the dura and arachnoid mater and enters the foramen magnum. Once inside the cranial vault the artery ascends anteriorly to the medulla oblongata where it unites with the contralateral vertebral artery to form the basilar artery.

In the atlanto-axial region the vertebral artery follows four distinct contours or curves (Franke, Di Marino et al. 1981) (Figure 2.3):

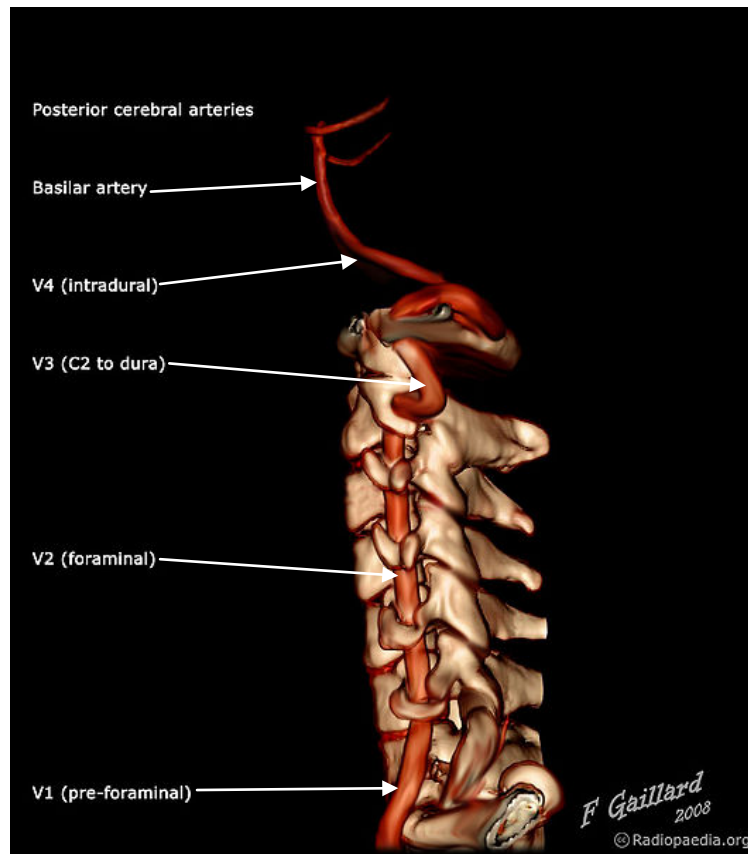


Figure 2.3 3-D computed tomography surface rendered image of the lateral segments of the vertebral artery (Gaillard 2008 <http://radiopaedia.org>)

- The artery travels within the foramen transversarium of the axis (C2) deviating laterally and sometimes slightly posteriorly, forming a groove on the underside of the superior articular process of the axis. The contour may become more pronounced with age to form a hairpin bend.
- The second curve is formed as the artery leaves the foramen of the axis and arches postero-laterally forming a loop convex infero-laterally.
- The third contour occurs as the artery turns and runs in an antero-superior direction to enter the foramen transversarium of the C1 vertebra (atlas).
- The final curve brings the artery out of the foramen of the atlas, along the posterior arch and around the lateral mass.

The branches of the vertebral artery may be divided into two groups, those in the neck and those within the skull (Warwick and Williams 1975). Spinal branches enter the vertebral canal via the intervertebral foramina and divide into two branches; one supplying the spinal cord and its membranes and the other forming an anastomotic chain around the vertebral bodies with branches from vertebral levels above and below which supply zygapophyseal joints, vertebral bodies and communicate with branches from the opposite side. Muscular branches are also given off the vertebral artery as it passes around the lateral mass of the atlas and these supply the deep cervical muscles and anastomose with the occipital, ascending and deep cervical arteries (Warwick and Williams 1975).

Meningeal branches are given off the vertebral artery at the level of the foramen magnum and supply bone and the falx cerebri - a septa of dura mater which sits vertically between the two cerebral hemispheres. The posterior spinal artery may

arise from the vertebral artery at the side of the medulla oblongata, but more frequently comes from the posterior inferior cerebellar artery and descends in the spinal canal supplying the cord and spinal nerves. The anterior spinal artery is given off near the origin of the basilar artery and joins its counterpart from the opposite side and descends in the spinal canal supplying the spinal cord, along with branches from the vertebral, ascending cervical, posterior intercostal and first lumbar arteries (Warwick and Williams 1975; Franke, Di Marino et al. 1981).

The posterior inferior cerebellar artery is the largest branch of the vertebral artery but may be absent. It arises near the olive of the medulla oblongata and ascends behind the roots of cranial nerves IX and X to the pons. It then runs along the inferior border of the fourth ventricle to the cerebellum where it gives off medial and lateral branches supplying the cerebellar hemisphere and anastomosing with branches from the anterior inferior cerebellar and basilar arteries. It also supplies the medulla oblongata and nucleus of the hypoglossal nerve (cranial nerve XII) (Franke, Di Marino et al. 1981)

It can be seen that the branches of the vertebral artery are extensive but that there is considerable overlap with other vessels in the area. This gives substantial opportunity for collateral supply in the case of interruption of blood supply to any area.

Variations in normal anatomy are relatively common in the vertebral artery with asymmetry of the two arteries occurring as well as hypoplasia of one vessel (Cagnie, Petrovic et al. 2006). Most commonly the left vertebral artery is dominant (Touboul, Bousser et al. 1986).

The basilar artery is formed by the junction of the two vertebral arteries. It travels superiorly in the brainstem and joins the Circle of Willis, which is the major blood supply of the brain. The basilar artery gives off numerous branches before it reaches the Circle of Willis and these supply regions of the brain and brainstem through which they pass (Warwick and Williams 1975). Pontine branches are given off as the basilar artery passes through the pons and supplies the pons and adjacent parts of the brain. The labyrinthine artery supplies the inner ear. The anterior inferior cerebellar and superior cerebellar arteries supply the cerebellum and adjacent structures, and the posterior cerebral artery supplies the temporal and occipital lobes of the brain, then divides into central and cortical branches which supply the brain cortex.

The anterior and posterior circulations communicate with each other via an anastomosis, the Circle of Willis, which effectively joins the vertebral and the internal carotid arteries (Figure 2.4). The Circle of Willis is formed anteriorly by the two anterior cerebral arteries which are joined to each other by the anterior communicating artery, and posteriorly by the basilar artery which divides into two posterior cerebral arteries each of which is joined to the internal carotid artery of the ipsilateral side by the posterior communicating artery (Warwick and Williams 1975)

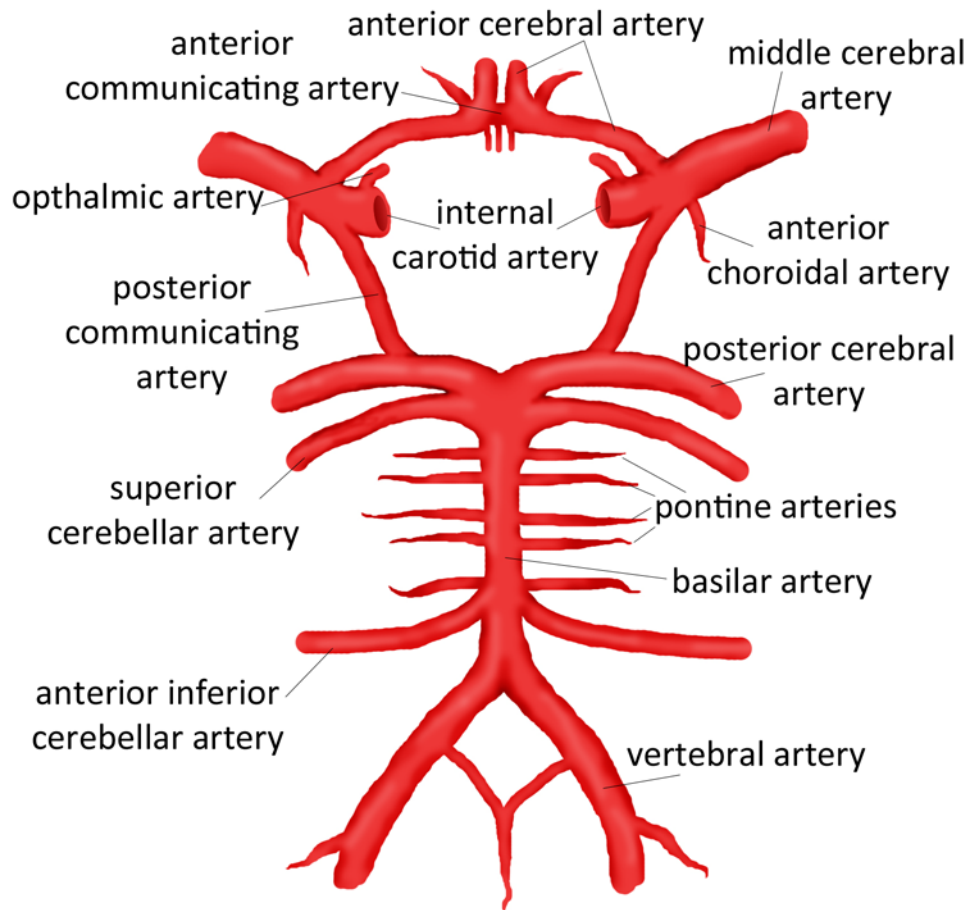


Figure 2.4 *Circle of Willis showing the branches of the craniocervical arteries*
(<http://www.chw.org>)

Internal carotid artery

The internal carotid arteries arise from the common carotid artery, which is a branch of the subclavian artery. The two internal carotid arteries constitute the main blood supply to the brain and contribute around 80% of the total blood supply (Figure 2.5).

The internal carotid arteries supply the anterior part of the brain, and the eye and surrounding structures. The right and left internal carotid artery are generally considered to be of similar size in a healthy individual (Kane, Dillon et al. 1996; Krejza, Arkuszewski et al. 2006).

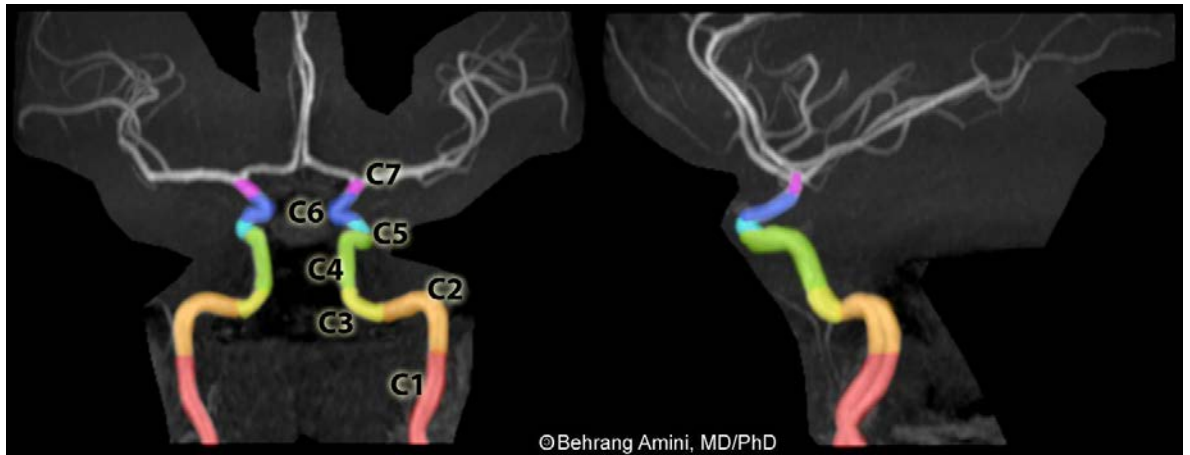


Figure 2.6 *Segments (C1-C7) of the internal carotid artery, delineated on a magnetic resonance image of the head (Amini 2009
<http://en.wikipedia.org/wiki/File:ICAs.jpg>)*

The cervical or C1 segment is the only segment which is extracranial and extends from the origin through the neck to where the artery enters the skull. The internal carotid artery arises from the common carotid artery at the carotid bifurcation at the level of the third cervical vertebra where the common carotid divides into the internal and external carotid arteries. The internal carotid artery dilates slightly to form the carotid sinus then continues cranially passing anterior to the transverse processes of the upper three cervical vertebrae to enter the skull at the carotid canal. It is overlain by the sternocleidomastoid and platysma muscles. It then passes deep to the parotid gland and is crossed by the digastric and stylohyoid muscles. More cranially it lies behind longus capitis. Once inside the skull it is known as the petrous segment (C2) and passes inside the petrous portion of the temporal bone (the carotid canal), above the foramen lacerum (C3) and then through the cavernous sinus (cavernous segment C4) which contains cranial nerves III, IV, V and VI, and the sympathetic plexus. It pierces the dura in the C5 or clinoid segment and enters the subarachnoid

space. The final or cerebral segment (C6 and C7) runs parallel to the optic nerve to the origin of the posterior communicating artery and then passes between the optic and oculomotor nerves to the lateral cerebral fissure and divides into the anterior cerebral and middle cerebral arteries, part of the Circle of Willis.

The internal carotid artery has several branches; the ophthalmic, anterior cerebral, and middle cerebral arteries (Figure 2.7). The largest branch is the middle cerebral artery which supplies a large proportion of the cerebral cortex. The ophthalmic artery is given off just before the internal carotid artery joins the Circle of Willis and supplies the eye and oculomotor muscles. The anterior cerebral artery supplies the anterior portions of the cerebral cortex.

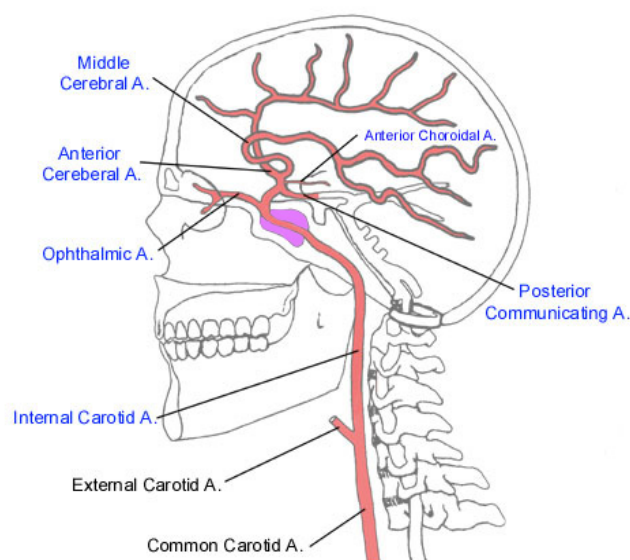


Figure 2.7 *Distribution of the internal carotid artery*
(<http://www.meddean.luc.edu>)

CRANIOCERVICAL ARTERIAL DISSECTION

Definition

Cranio cervical arterial dissection is defined as a tear in the wall of either the vertebral or internal carotid arteries in the cervical region which may lead to ischaemic stroke in the region supplied by the relevant artery. It is often described as occurring spontaneously as it typically occurs in otherwise healthy individuals without known risk factors for stroke (Brandt, Hausser et al. 1998; Baumgartner and Bogousslavsky 2005). Spontaneous cervical arterial dissection is increasingly being recognised as a cause of ischaemic stroke in young to middle aged individuals (Rubinstein, Haldeman et al. 2006). Arterial dissection accounts for 2% of all ischaemic strokes across all ages but 10-25% of ischaemic strokes in the young to middle aged group (Schievinck 2001; Arnold and Boussier 2005). Notably, craniocervical arterial dissection has been reported as a rare complication of cervical spine manipulation.

Incidence

The annual incidence of internal carotid dissection has been reported as being in the order of 2.5:100,000, and for vertebral artery dissection between 1-1.5:100,000 (Schievinck 2001). Dissections are reported in all age groups but are more common between 35-50 years, with a peak in the fifth decade and occur more frequently in women than men at a ratio of 2:1 (Thanvi et al 2004). Some dissections however, may well be asymptomatic or cause only minor symptoms and therefore may not be reported as they heal spontaneously (Debette and Leys 2009). The true incidence of such events is therefore hard to determine with accuracy (Thanvi et al 2004).

Adverse neurovascular events such as craniocervical arterial dissection following cervical manipulation have been reported to occur in varying rates of incidence ranging from one in 163,000 manipulations (Rivett and Reid 1998), to as few as one in 1,000,000 (Carnes, Mars et al. 2010). Vertebral artery dissections are more commonly reported than dissections of the internal carotid artery. Despite the relatively low incidence, the potential for arterial dissection subsequent to manipulation needs to be taken into consideration by manual practitioners because of the potential for permanent disability or even death to occur (Hurwitz, Aker et al. 1996).

AETIOLOGY OF CRANIOCERVICAL ARTERIAL DISSECTION

The pathogenesis of craniocervical arterial dissection is not fully understood but is generally considered to have a contribution from both intrinsic and extrinsic causes. Recent evidence suggests that the mechanism involves a pre-existing intrinsic susceptibility, such as an underlying arteriopathy which predisposes the arteries to damage in the presence of a precipitating extrinsic event, which may be fairly innocuous (Rubinstein, Peerdeman et al. 2005; Volker, Besselman et al. 2005; Debette and Leys 2009; Schievink and Debette 2011).

The underlying intrinsic predisposition is thought to be in the form of an arteriopathy involving the cervical arteries, an anatomical variant or a genetic pre-disposition (Brandt, Hausser et al. 1998; Debette and Markus 2009). Arteriopathy may be due to factors such as connective tissue disorders, amyloid deposition (Ringelstein & Nabavi 2005), hyperhomocysteinaemia (Rubenstein et al 1995), inflammatory states and thyroid autoimmunity (Pezzini et al 20006). The arteriopathy is thought at least

in part to be genetically determined and permanent, but the increased susceptibility may be transient, possibly triggered by an infectious agent (Schievink and Debette 2011).

The extrinsic factor or precipitating event may be an external trigger such as mechanical trauma to the vessel. A transient situation caused by an infection or pro-inflammatory state which might cause a temporary friability or weakness of the arterial vessel wall pre-disposing it to damage is also postulated (Grau, Brandt et al. 1999; Debette and Leys 2009)

The following section provides a more detailed discussion of potential risk factors. The role of both intrinsic factors and extrinsic triggers are presented.

RISK FACTORS FOR CRANIOCERVICAL ARTERIAL DISSECTION

Intrinsic factors

The following factors have been described in the literature as possible intrinsic risk factors for craniocervical arterial dissection.

Anatomical variants

Anatomical variants such as tortuosity of the vertebral artery, aplasia or dysplasia of the carotid or vertebral arteries, or enlargement of the aortic root, have been demonstrated in some patients (Debette and Leys 2009; Schievink and Debette 2011). Other anomalies such as hyper-distensibility and increased stiffness of the arterial wall have been described (Guillon, Tzourio et al. 2000)

Arteriopathy

Indirect evidence of arteriopathy has also been demonstrated in some patients with findings such as intracranial aneurysms, widened aortic root, arterial loop redundancies and increased arterial distensibility. Common carotid artery diameter change ($>11.8\%$) during the cardiac cycle on ultrasound was shown to be greater in internal carotid dissection patients (Guillon, Berthet et al. 2003), also suggesting abnormality of the extracellular matrix (Rubinstein, Peerdeman et al. 2005).

Connective tissue disorders

Connective tissue disorders have been proposed as a predisposing factor for vertebral and internal carotid artery dissections (Brandt, Hausser et al. 1998; Guillon, Tzourio et al. 2000; Schievinck 2001). Some studies have shown up to 50% of patients may have connective tissue aberrations in their skin, including composite fibrils of collagen and fragmented elastic fibres (Debette and Leys 2009). Connective tissue provides the arterial wall with structural integrity and elasticity. Deficits of collagen and elastic fibres could have major implications for mechanical stability and predispose the arterial walls to rupture (Rubinstein, Peerdeman et al. 2005).

Connective tissue disorders which have been associated with spontaneous vertebral or internal carotid arterial dissection are Ehlers-Danlos syndrome type IV, Marfan's syndrome, autosomal dominant polycystic kidney disease and osteogenesis imperfecta type I. In patients with spontaneous vertebral or internal carotid artery dissections, 1-5% actually show evidence of some known heritable connective tissue disorder. In addition, 20% of patients have a clinically apparent connective tissue disorder but one which is not classically recognised at present (Schievinck 2001). The presence of these disorders in some cases of dissection has led to suggestions

that there may well be a predisposing genetic link. However, recent studies have failed to find convincing evidence of connective tissue disorders in patients presenting with dissection (Dittrich, Heidbreder et al. 2007; Heidbreder, Ringelstein et al. 2008).

Family history

Family history is a recognised factor in patients with spontaneous vertebral or carotid artery dissections. Five percent of patients have at least one family member with a history of dissection of the aorta or its main branches, usually carotid or vertebral. There may also be an association with congenital abnormalities of the aortic valve in the heart and cutaneous lentigines (worm like features on the skin). The tunica media of the aorta, melanocytes and aortic valve cusps all derive from the same embryological origin, in neural crest cells, suggesting an underlying abnormality of these cells (Schievinck 2001).

Fibromuscular dysplasia

Fibromuscular dysplasia has been identified on angiogram in 15% of patients with spontaneous dissection, and cystic medial necrosis has been found on post-mortem in some patients. Both of these conditions are non-specific and have been associated with a number of generalised systemic disorders (De Bray, Marc et al. 2007).

Ultrastructural connective tissue abnormalities

Ultrastructural abnormalities of dermal connective tissue have been identified in two-thirds of patients with spontaneous dissection (Brandt, Hausser et al. 1998). Abnormalities included enlarged or irregular collagen fibrils and pronounced elastic

fibre fragmentation. It has been proposed that these dermal findings and the association of connective disease with dissection support the hypothesis of a general connective tissue susceptibility state being involved in the pathogenesis (Volker, Besselman et al. 2005).

Proteinase inhibitors

Proteinase inhibitors act to inhibit enzymes which may degrade connective tissue of arterial walls by proteolytic activity. Deficiency of proteinase inhibitors could contribute to arterial wall degradation due to inadequate protection. The major proteinase inhibitors are alpha1anti-trypsin (α_1 -AT) and alpha 2 macroglobulin (α_2 -MG). The genetic variants causing α_1 -AT deficiency are S and Z alleles. These can be assessed in serum levels and this is performed after the acute phase of dissection with immunological testing. Decreased levels of α_1 anti-trypsin were found to be associated with cervical artery dissection in some studies (Vila, Millan et al. 2003; Konrad, Langer et al. 2005; Pezzini, Caso et al. 2006), but were not statistically significant in others (Grond-Ginsbach, Engelter et al. 2004; Konrad, Langer et al. 2005).

In contrast, another factor which may be involved in dissection is high plasma concentrations of proteases which break down connective tissue. One study investigated the hypothesis that extracellular matrix defect is involved in craniocervical arterial dissection by measuring levels of metalloproteinase and elastase (Guillon, Peynet et al. 2007). These enzymes are involved in regulating the remodelling of the vascular wall. Patients with dissection were found to have higher

levels of these proteinase enzymes than controls with ischaemic stroke from some other cause.

Cardiovascular risk factors

The presence of general cardiovascular risk factors in patients with craniocervical arterial dissection is somewhat controversial. Some studies of younger patients with dissection have suggested that general vascular risk factors are not a major feature in dissection compared to other ischaemic stroke patients but others have shown no difference between these patients and those with dissection. There have been few studies comparing dissection patients with normal healthy controls, with one recent study showing no association (Pezzini, Caso et al. 2006) but another reporting reduced body mass index in dissection patients (Arnold, Pannier et al. 2009).

Hyperhomocysteinemia

An increased level of homocysteine in blood plasma (hyperhomocysteinemia) has been implicated in causing endothelial damage, notably, reduced elastin concentration in arterial walls, increased elastolytic activity and reduced cross-linking between collagen and elastin (Pezzini, Caso et al. 2006). This may contribute to arterial wall fragility, rendering patients more susceptible to damage by minor mechanical trauma. Hyperhomocysteinemia has been demonstrated in cervical artery dissection (Pezzini, Caso et al. 2006).

Migraine

Migraine has been shown to be associated with vertebral or internal carotid artery dissection by some authors (D'Anglejan-Chatillon, Ribeiro et al. 1989; Tzourio,

Benslamia et al. 2002; Guillon, Berthet et al. 2003), and has been demonstrated in up to 49% of patients with craniocervical dissection. The mechanism remains unexplained but is proposed to be due to underlying arterial wall disease (Tzourio, Benslamia et al. 2002).

Hypertension

Hypertension has been significantly associated with spontaneous craniocervical dissection (Mokri, Sundt et al. 1986; Pezzini, Caso et al. 2006), compared with healthy control participants. In addition, there have been case reports of patients with vertebral arterial dissection following a morning surge in blood pressure (Eguchi, Tachikawa et al. 2005). Other authors have questioned whether patients with dissection have higher incidence of hypertension than control patients (D'Anglejan-Chatillon, Ribeiro et al. 1989; Debette, Grond-Ginsbach et al. 2011).

Extrinsic factors

Individuals with such an underlying intrinsic susceptibility may be at greater risk of dissection if exposed to an external triggering event. The underlying intrinsic susceptible state may be permanent as outlined previously or a transient situation such as a temporary pro-inflammatory or pro-thrombotic state, and the triggering event may be fairly innocuous (Debette and Leys 2009).

Minor mechanical trauma

Minor trauma to the head and neck has frequently been identified in the history of patients with spontaneous dissection. Activities are often associated with sustained rotation or extension of the neck, such as painting a ceiling, looking overhead at a

plane, yoga, martial arts, hair washing in a salon basin, coughing, sneezing, vomiting, and having resuscitation performed (Haldeman, Kohlbeck et al. 1999; Rubinstein, Peerdeman et al. 2005). More serious events such as motor vehicle or sporting accidents or other serious head and neck trauma have also been associated with vertebral and internal carotid artery dissection. Chiropractic manipulation is also considered as a type of minor trauma in reports. This has been more frequently associated with vertebral artery than internal carotid artery dissection (Haldeman, Carey et al. 2001).

Cervical manipulation

Iatrogenic causes of injury to the vertebral artery have been described (Klougart, Leboeuf-Yde et al. 1996). Most vertebro-basilar injuries, where the manipulative technique is known, have generally involved procedures with a rotatory component (Hurwitz, Aker et al. 1996; Di Fabio 1999). There is also evidence that multiple manipulations performed during one treatment session increases the likelihood of complications (Carey 1994; Grant 1994; Klougart, Leboeuf-Yde et al. 1996; Symons, Leonard et al. 2002). Similarly, repeating the manipulative procedure over a number of treatment sessions may also increase risk of vertebral artery injury. Repeated manipulations may cause injury to the vertebral artery possibly due to the cumulative effect of micro-injuries to the arterial wall (Grant 1994; Di Fabio 1999; Symons, Leonard et al. 2002). However, a recent , small, in vitro animal study by Austin et al (Austin, DiFrancesco et al. 2010) investigating repeated tensile strain on the vertebral artery suggested the vertebral artery could withstand repeated strains similar to those measured in cervical manipulation without incurring damage. So, repeated

manipulation in a healthy artery may not pose a risk. However, this may not be the case if the artery is compromised by some intrinsic factor.

The use of excessive force has also been cited as a cause of manipulative trauma to the vertebral artery (Kleynhans and Terrett 1985; Bogduk 1994). The forces generated during cervical manipulation have been investigated by measuring the force applied at the skin and were found to be approximately 118 N (Herzog, Conway et al. 1993). However, this does not necessarily reflect the force imparted to the vertebral artery (Mann and Refshauge 2001). Indeed, a cadaveric study (Symons and Westaway 2001) found that manipulation causes an average strain of 6.2% to the vertebral artery but that a strain of greater than 139% was required to reach failure. Nevertheless, there is large variability in the forces needed to produce mechanical failure in different vertebral arteries (Johnson, How et al. 2000b; Symons and Westaway 2001). Moreover, the effects of repeated forceful manipulations have not been assessed and may produce different results (Mann and Refshauge 2001). Other iatrogenic causes may include direct injury to the arterial wall by surgical means via endoscopic procedures, such as aneurysm coiling or stenting of vessels.

Recent infection

Seasonal variation with peaks of vertebral or internal carotid artery dissections in autumn and spring suggests that acute infections may act as a trigger. Recent infection (particularly respiratory) has been suggested by some authors to predispose to cervical artery dissection (Grau, Brandt et al. 1999; Guillon, Berthet et al. 2003). In a case-controlled study, the presence of acute infection was more frequent in patients with apparent spontaneous craniocervical dissection than in control

participants (Guillon, Berthet et al. 2003). There is a general susceptibility state involved in spontaneous cervical artery dissection and it has been suggested that inflammation may have a role in this. Some studies have shown dissection patients have elevated blood levels of C-reactive protein (CRP), which is an inflammatory marker, greater than those with cryptogenic stroke, suggesting inflammatory mechanisms may play a role in its pathogenesis (Genius, Dong-Si et al. 2005). There has also been pathological evidence found of inflammatory exudates in the walls of dissected arteries (Volker, Besselman et al. 2005; Volker, Dittrich et al. 2011). Recent infection has been described more frequently in internal carotid artery dissection as opposed to vertebral artery dissection by some authors and this is thought to be due to the close proximity of the artery to the upper respiratory tract (Guillon, Berthet et al. 2003; Caso, Paciaroni et al. 2005).

Thyroid auto-immunity

It has been further suggested that dissection patients may have an underlying auto-immune condition. Thyroid auto-immunity has been investigated, as it is the most common auto-immune condition (Pezzini, Del Zotto et al. 2006). However a study of 29 patients with dissection and 29 control patients with non-dissection ischaemic stroke did not show a statistically significant presence of thyroid auto-immunity (Pezzini 2006), and this has since been confirmed by other authors (Lichy, Pezzini et al. 2009).

PATHOPHYSIOLOGY OF CRANIOCERVICAL ARTERIAL DISSECTION

Dissections of the vertebral and carotid arteries usually arise from a tear of the inner wall (tunica intima) of the artery where they are described as being sub-intimal, or of

the outer adventitial layer (sub-adventitial), commonly caused by damage to the vaso vasorum, the blood vessel which supplies blood to the artery wall. An intimal tear allows blood under arterial pressure to enter the deeper layers of the arterial wall forming an intramural haematoma within the vessel wall (Haneline 2005, Shievinck 2001) (Figure 2.8). This haematoma or 'false lumen' dissects the artery causing alteration of blood flow and may be detected on magnetic resonance imaging (Figure 2.9). More recent studies have suggested that the majority of spontaneous craniocervical arterial dissections may not in fact be caused by an intimal tear but appear to be a sub-adventitial tear caused by a haemorrhage in the arterial wall in the tunica media or tunica adventitia (Volker, Dittrich et al. 2011). This leads to the formation of a pseudaneurysm or degeneration of the media-adventitial border with the formation of microhaematomas, thus weakening the vessel wall (Volker, Dittrich et al. 2011). Medial adventitial degeneration may also occur as a result of inflammatory changes in the vessel wall (Pfefferkorn, Saam et al. 2011).

Alternatively, there may be formation of a haematoma within the walls of the artery (intramural haematoma) subsequent to damage of the vaso vasorum (Volker, Besselman et al. 2005). This would cause a primary intramural haematoma without intimal tear, unless it ruptured into the arterial lumen. It would be difficult in this instance however, to distinguish it from a primary intimal tear (Shievinck 2001). An intramural haematoma often causes stenosis of the vessel, with a subsequent higher risk of embolic brain infarction (Konrad 2005) (Figure 2.9).

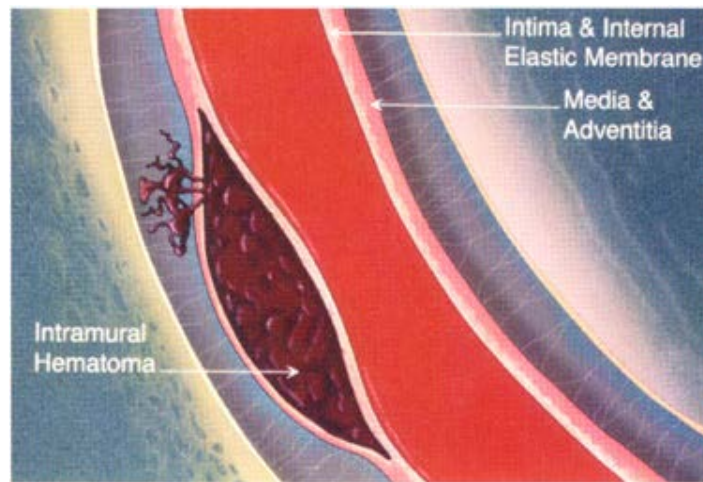


Figure 2.8. *A primary intramural hematoma of the basilar artery (Schievinck, Eelco et al. 2000)*

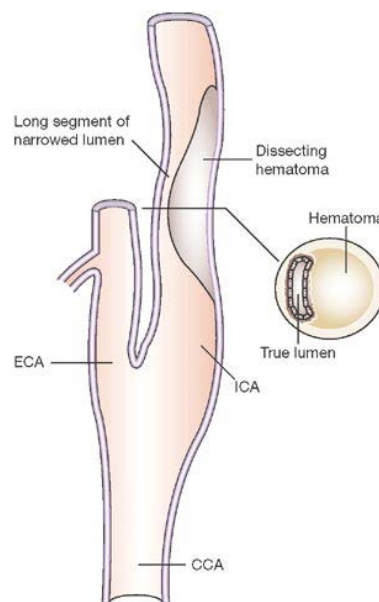


Figure 2.9 *Dissection of the internal carotid artery with evidence of intramural haematoma showing lumen narrowing (Schievinck 2001)*

Spontaneous dissections may occur throughout the body, but are much more likely in extra-cranial segments of the vertebral and internal carotid arteries because of these arteries' greater mobility and potential for bony contact (Schievinck 2001).

CLINICAL FEATURES OF CRANIOCERVICAL ARTERIAL DISSECTION

The clinical features of the two types of craniocervical arterial dissection, vertebral and internal carotid artery, show some distinctive features due to the different areas of the brain each vessel supplies (Thanvi, Munshi et al. 2005) (Figure 2.10). While there have been a number of studies of patients with craniocervical arterial dissection many of these are retrospective, relying heavily on information recorded in the medical files (Schievinck 2001; Haldeman, Kohlbeck et al. 2002; Arnold and Boussier 2005; Debette, Grond-Ginsbach et al. 2011). Such studies may be limited by selection bias, such as reporting more severe cases.

Reports of the clinical presentation of patients with craniocervical arterial dissection vary considerably between cases and between studies, as patients may present with pain and ischaemic signs or pain only, depending on whether the effects of the dissection are just local or may be due to distal embolisation (Baumgartner and Bogousslavsky 2005). In many cases the clinical presentation may even appear benign, particularly if there are no ischaemic signs or symptoms and the dissection may go unrecognised and heal spontaneously (Arnold and Boussier 2005; Debette and Leys 2009). Hence, published reports vary in their description of classic signs and symptoms. Importantly, limited information exists about the early presenting signs and symptoms of this condition. These details may be of particular interest to primary care practitioners to aid early recognition of this serious condition and expedite appropriate management and avoid inappropriate treatment.

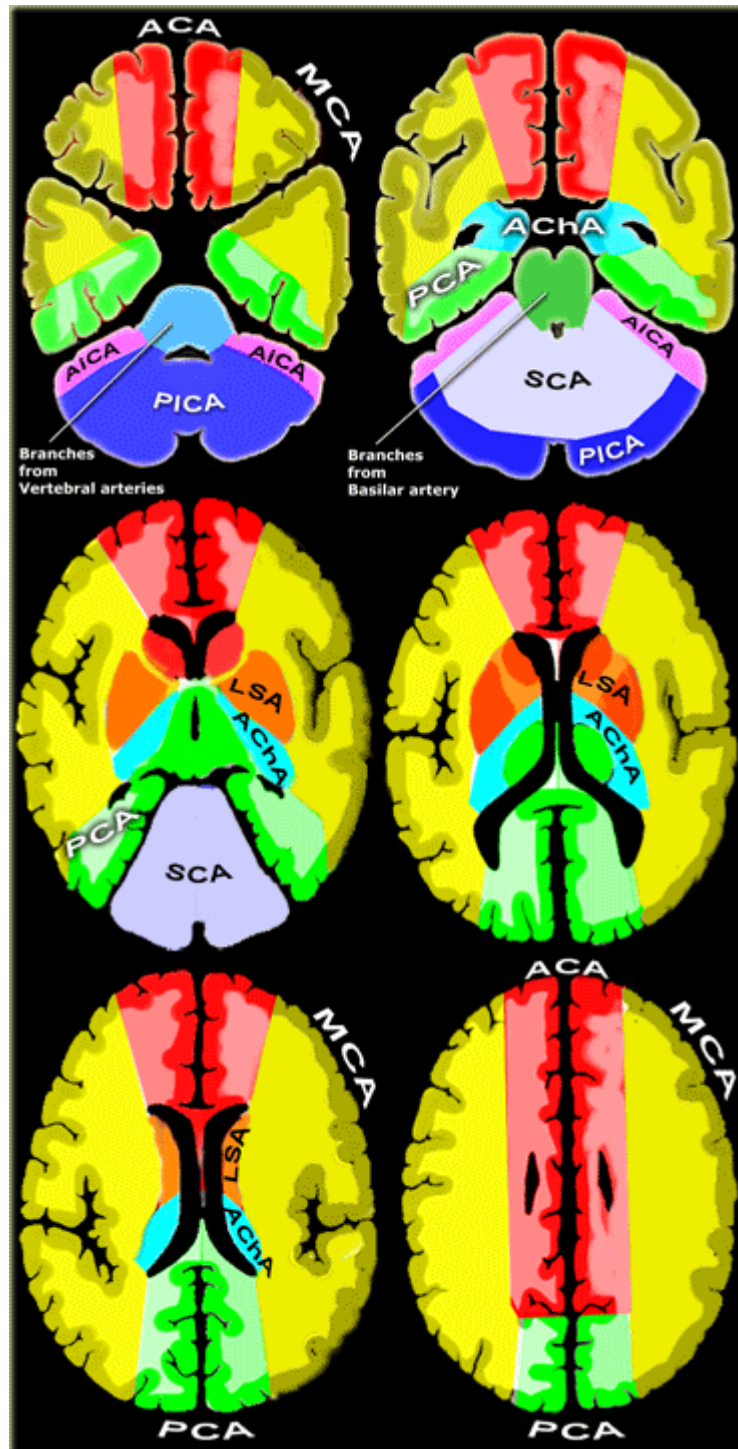


Figure 2.10 Diagram showing the different arterial territories of the brain: ACA= anterior cerebral artery (red), MCA= middle cerebral artery (yellow), and vertebral arteries: PCA= posterior cerebral artery (green), AICA=anterior inferior cerebellar artery (purple), PICA= posterior inferior cerebellar artery (blue), SCA= superior cerebellar artery (grey).

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Internal carotid artery dissection

The internal carotid arteries feed into the anterior cerebral circulation which supplies the anterior parts of the brain. Patients with internal carotid artery dissection typically present with unilateral head, neck or facial pain, which may be accompanied by a partial Horner's syndrome (oculosympathetic palsy characterised by usually ptosis and miosis) (Schievinck 2001). This may proceed to cerebral or retinal ischaemia or infarction. (Schievinck 2001; Baumgartner and Bogousslavsky 2005). All these three signs are found in one third of patients, but the presence of two of the signs should give a high index of suspicion (Schievinck 2001; Arnold and Boussier 2005).

Head and neck pain is commonly reported in patients presenting with internal carotid artery dissection and may well be the initial presenting symptom. However, the real prevalence of headache and neck pain caused by internal carotid artery dissection may not be known as not all patients presented with acute headache will be investigated for dissection (Baumgartner and Bogousslavsky 2005). Conflicting details about the nature of the headache vary considerably between studies making characteristics for internal carotid artery dissection difficult to define. In addition, dissection headache may mimic migraine or other headache types making differential diagnosis difficult (Debette and Leys 2009). Pain occurs usually on the antero-lateral side of the neck in 25% of patients and is usually accompanied by an ipsilateral headache (Schievinck 2001). The headache is typically unilateral over the frontal and temporal regions but may involve the whole head or occipital area (Arnold and Boussier 2005). Unilateral facial or peri-orbital pain has been reported in 50% of patients (Silbert, Mokri et al. 1995).

Onset of the headache is usually gradual but may be a sudden, thunderclap type, also characteristic of sub-arachnoid haemorrhage. The nature of headache is constant, a steady aching, however, in some cases it has been described as throbbing or sharp, similar to migraine (Baumgartner and Bogousslavsky 2005). Patients with migraine may report it to be similar in quality to their usual pain, however, most commonly pain is reported to be different from any other headache or facial pain previously experienced (Biousse, D'Anglejan-Chatillon et al. 1994; Silbert, Mokri et al. 1995). Pain can also mimic cluster headache, characterised by severe, repeated headache on one side of the head (Baumgartner and Bogousslavsky 2005). Pain is usually the first presenting symptom of dissection, with other features presenting within four or five days (Schievinck 2001).

Partial Horner's syndrome consists of miosis (constriction of the pupil in one eye) and ptosis (drooping of one eyelid). Facial anhidrosis (absence of facial sweating, another component of Horner's syndrome) does not usually occur as the facial sweat glands are innervated by the sympathetic plexus which surround the external carotid artery (Schievinck 2001). Unilateral Horner's syndrome has been considered to be pathognomic of internal carotid dissection even without other symptoms; however, it occurs in less than 30% of patients (Baumgartner and Bogousslavsky 2005). Pulsatile tinnitus may also occur in the presence of a distal carotid stenosis due to the propagation of a carotid bruit (a sound caused by turbulent blood flow). The bruit may be detectable on auscultation in only about a quarter of patients (Silbert, Mokri et al. 1995).

Cranial nerve palsies may also be present in internal carotid artery dissection and have been reported in 8-16% of patients (Baumgartner and Bogousslavsky 2005). Most commonly the lower cranial nerves are affected IX- XII, in particular the hypoglossal nerve (CR XII) is affected giving rise to difficulty swallowing. The oculomotor, trigeminal (CR V) and facial (CR VII) nerves may also be involved (Baumgartner and Bogousslavsky 2005). Impairment of taste (dysgeusia) is noted by approximately 10% of patients and may be a presenting symptom (Schievinck 2001), possibly due to involvement of the chorda tympani or hypoglossal nerve (Baumgartner and Bogousslavsky 2005).

Amaurosis fugax is described as 'curtains going down before the eyes' has been reported in some cases of internal carotid arterial dissection and may give rise to monocular blindness lasting less than 24 hours (Baumgartner and Bogousslavsky 2005). It is caused by retinal ischaemia and is frequently a warning symptom of ischaemic stroke (Arnold and Boussier 2005). Transient retinal ischaemia has been reported as occurring fairly frequently in patients with internal carotid artery dissection (Baumgartner and Bogousslavsky 2005). Retinal infarction presenting as monocular blindness lasting greater than 24 hours occurs infrequently in dissection (Biousse, Schaison et al. 1998; Baumgartner and Bogousslavsky 2005).

Transient ischaemic attack is defined as a neurological deficit lasting less than 24 hours and may occur as a result of internal carotid artery dissection. In more serious cases where embolisation to more distal vessels occurs from the damaged artery, ischaemic stroke i.e. cerebral infarction, usually in the territory of the middle cerebral artery may follow internal carotid artery dissection. Craniocervical arterial dissection

has been reported as a possible cause of transient ischemic attack by some authors and transient ischaemic signs and symptoms have been reported preceding internal carotid artery dissection (Biousse, D'Anglejan-Chatillon et al. 1995).

Vertebral artery dissection

The vertebral arteries feed into the posterior circulation which supplies the brainstem, cerebellum and posterior parts of the cerebral cortex (Figure 2.10). Patients with vertebral artery dissection typically present with posterior neck pain or headache followed, frequently with a time delay, by posterior circulation ischaemia. The initial presentation of vertebral arterial dissection is less distinct than that of internal carotid arterial dissection and pain is often initially interpreted as musculoskeletal in nature (Schievinck 2001; Arnold and Bousser 2005). In addition, the clinical presentation is variable and many cases of dissection may go unrecognised (Arnold and Bousser 2005).

The initial findings are usually posterior neck pain in about half of patients and occipital headache in two-thirds (Schievinck 2001; Arnold and Bousser 2005). The pain is usually unilateral and ipsilateral to the side of the dissection. However, it may involve the whole hemicranium or frontal area, and in rare cases may be bilateral. The headache may be throbbing or steady and sharp in quality making differential diagnosis from migraine difficult (Baumgartner and Bogousslavsky 2005). Only 50% of patients describe the pain as being different from any other pain ever experienced (Arnold and Bousser 2005). Migraine sufferers usually report the headache as severe but not like a migraine attack. Physical examination generally does not usually reveal any loss of cervical spine range of motion despite often severe neck pain, although

this may be confused with acute wry neck as patients may be reluctant to move their head due to the severity of the pain (Sturzenegger 1995). In rare cases there may be signs of C5-C6 nerve root involvement leading to unilateral arm pain or weakness (Crum, Mokri et al. 2000). This is thought to be due to compression by the enlarged vertebral artery (Arnold and Boussier 2005). Spinal epidural haematomas have also been rarely described as the vertebral artery supplies the cervical spinal cord (Crum, Mokri et al. 2000).

More than 80% of patients develop ischaemic signs of posterior circulation involvement. These symptoms may occur sometime after the onset of pain. If the presenting sign is neck pain, onset of neurological symptoms may not be until a median time of two weeks later (Silbert, Mokri et al. 1995; Schievink 2001). If headache is the presenting feature, onset of neurological signs is usually more rapid, with a reported median time of 15 hours (Silbert 1995, Schievink 2001).

The vertebral and basilar arteries supply blood to the pons, medulla, cerebellum, mesencephalon, thalamus, occipital lobes of the brain, and the central and peripheral vestibular system. Disturbance of blood flow to these areas may give rise to symptoms such as nausea, vertigo, dizziness, syncope or drop attacks, dysphagia, dysarthria, balance problems, auditory disturbance and visual deficits, such as diplopia or blurred vision. Differential diagnosis from migraine is important because the ischaemic features may be similar to those of basilar migraine (Arnold and Boussier 2005). If the ischaemia proceeds to infarction it frequently involves the lateral medulla and can give rise to Wallenberg's or lateral medullary syndrome. This is characterised by Horner's syndrome, altered sensation on the ipsilateral side of the

face, nystagmus, ipsilateral limb ataxia and loss of pain perception in the contralateral side of the body.

Transient ischaemic attacks are thought to be less common following vertebral artery than internal carotid artery dissection. Nonetheless, patients do not usually present with only one sign or symptom (Savitz and Caplan 2005). Dizziness may not always be present as a symptom of vertebral artery dissection but equally it may be the only symptom of dissection (Arnold and Boussier 2005). More detailed characterisation of the presenting features of vertebral artery dissection, especially the more subtle ischaemic features is needed, particularly for primary care practitioners, because of the need for differential diagnosis of musculoskeletal conditions and migraine.

DIAGNOSIS OF CRANIOCERVICAL ARTERIAL DISSECTION

The diagnosis of craniocervical arterial dissection is generally based on a suggestive history, clinical findings and radiological imaging (Vertinsky, Schwartz et al. 2008). In the absence of radiological confirmation clinical diagnosis is usually made based on a combination of presenting signs and symptoms and history. However, advances in imaging technology have considerably improved diagnosis in recent years.

RADIOLOGICAL DIAGNOSIS OF CRANIOCERVICAL ARTERIAL DISSECTION

The most common imaging modalities used to examine the craniocervical vessels are computerised tomography (CT), magnetic resonance imaging (MRI) and neuroangiography, including ultrasound (US), computerised tomography angiography (CTA) and magnetic resonance angiography (MRA) (Blumenfeld 2010). The gold standard for imaging the arterial circulation is considered to be angiography. This is

usually performed using digital subtraction (DSA) of surrounding tissues so that the blood vessels are more clearly defined. In the majority of centres however, angiography is currently most commonly performed using CTA or MRA, which have the advantage over DSA of being non-invasive procedures (Rodallec, Marteau et al. 2008). An outline of the principles of the most commonly utilised imaging modalities for the screening of patients with a potential arterial dissection is presented in the following section.

Angiography

Angiography is usually performed by introducing a catheter into the aorta via the femoral artery and injecting contrast medium, usually iodine based, into the internal carotid and vertebral arteries. The vessels are then imaged using X-rays. Limitations of angiography are that it only shows the lumen of the vessel so may miss a dissection or intramural haematoma if the contrast medium does not fill the false lumen (Rodallec, Marteau et al. 2008; Vertinsky, Schwartz et al. 2008). It also does not image the vessel wall so it may not be possible to differentiate between dissection and other causes of occlusion, such as thromboembolic or atherosclerosis (Caso, Paciaroni et al. 2005). It is helpful therefore if angiography is used in combination with CT or MR, in order to visualise the effects on the blood vessel walls and surrounding tissues. A further limitation of angiography is that it has a risk of complications due to it being an invasive procedure.

Computerised tomography (CT)

CT was developed from conventional X-ray theory and using similar principles. CT imaging examines the density of tissues in slices (from the Greek '*tomos*' referring to

a 'section') taken in the anatomical planes i.e. horizontal, sagittal or coronal. The slices (or sections) are then built up by a computer to show a detailed image of all the tissues being investigated. The re-constructed images show the detail of various tissues such as bone and soft tissue, as well as liquid and air, in differing densities.

Dense structures such as bone show up as white on CT, less dense structures such as air or water appear black. Intermediate density structures such as brain tissue appear grey, cerebrospinal fluid appears dark grey, and fat appears nearly black. Myelin contains fat, so white matter, which has high myelin content, appears darker than grey matter, which has high water content. The terms 'hyperdense' and 'hypodense' are used to describe brighter and darker areas on CT, or 'isodense' for intermediate density tissue (Blumenfeld 2010). Abnormalities of brain tissue are described using these terms. Acute haemorrhage, for example, following dissection or stroke coagulates rapidly and shows up as hyperdense areas in comparison to brain tissue, but as the clot breaks down it becomes isodense, and after 2-3 weeks hypointense. Acute cerebral infarctions cannot be seen initially on CT often until 6-12 hours when cell death and oedema cause an area of hyperdensity in the distribution of the affected artery. The oedema may also distort adjacent brain tissue; this is called 'mass effect'.

The advantages of CT are that it is usually more readily available in hospital emergency departments and images can be quickly obtained, without the need to place the patient in a narrow tunnel. This can be useful for an unstable patient and the quicker acquisition time means less time is required to restrict movement. The disadvantages are that it uses ionising radiation and the images have less detail than can be obtained through MRI.

Computed tomography angiography (CTA)

With CTA images of the brain are taken in combination with an intravenous contrast medium which highlights the blood vessels. This is not always well tolerated by the patient, however. CT images can then be reconstructed to give a 3-D image, which can considerably assist in diagnosis. Sensitivities for CTA when compared to DSA ranged between 51%-100% and specificities between 82%-95% (Provenzale and Sarikaya 2009).

Pathognomic findings of dissection on CT include double lumen and intimal flap but these are not always identifiable on imaging (Schievinck 2001). More commonly viewed are stenosis, occlusion and aneurysm formation. The stenosis generally presents as an irregular or long tapering stenosis extending along the vessel (Flis, Jäger et al. 2007; Rodallec, Marteau et al. 2008).

Craniocervical arterial dissection is a highly dynamic process which changes quickly over time (Bachmann et al 2007). Morphological changes on MRI may resolve quickly and therefore may not be detectable when MRI is performed several weeks after the neurovascular event, making definitive diagnosis difficult. CTA has been considered more sensitive for the vertebral artery, but this may depend on the stage of the dissection healing (Rodallec, Marteau et al. 2008; Provenzale 2009). The haematoma resulting from a dissection tear may be isointense to surrounding tissues in the first few days following dissection and more easily visualised on CT as it has higher spatial resolution (Vertinsky, Schwartz et al. 2008), but subsequently the dissection may appear bright on MR as it detects the breakdown products of haemoglobin as the tear heals (Vertinsky, Schwartz et al. 2008; Provenzale 2009).

Magnetic resonance imaging (MRI)

MRI was developed from nuclear magnetic resonance (NMR). It uses the properties of hydrogen nuclei. The body is largely composed of water; water molecules contain two hydrogen nuclei or protons. Protons have the property of 'spin' and 'precession'. Spin is a quantum mechanics term for movement of the proton on its own axis, precession is movement of the spinning proton like a gyroscope. In MRI the patient is placed in a static magnetic field and then a probe of electromagnetic energy is released into the field in a pulse. In the static field the protons largely line up parallel to the magnetic field. A radio frequency transmitter or coil is then turned on giving a brief pulse of electromagnetic energy. This additional magnetic field is able to flip the spinning protons so they are no longer aligned with the static field. The greater the intensity and duration, the more protons will flip out of alignment. When the additional field is turned off the protons relax back to their original alignment. The difference in energy between the static magnetic field and the introduction of the radiofrequency pulse is released as electromagnetic energy which is detected by a reception coil (often the same as the transmitting coil). Different tissues have different proton relaxation times which can be detected and used to construct an image. The proton relaxation has two components:

1. T1 relaxation - related to the longitudinal spin relaxation and depends on the net direction of alignment or non-alignment of the protons.
2. T2 relaxation – related to relaxation in the transverse plane or net effect of proton precessions.

The T1 and T2 relaxation values vary for different tissues and different radio-frequency pulse sequences are used to emphasise T1 or T2 contrast. These can be used to produce T1 weighted images or T2 weighted images. This can be useful to

enhance pathology. In T1 weighted images, water appears dark and fatty tissues bright so they look more like normal brain anatomy and are therefore useful to show anatomical detail. T2 weighted images appear like a photographic negative and thus water appears bright and fat dark. Cerebrospinal fluid, oedema and grey matter also appear bright and therefore this can be more useful for showing pathology. However, this may make it difficult to see abnormalities on the edge of structures (e.g. ventricles or dura), so most T2 scans include fluid attenuation inversion recovery imaging (FLAIR) so that the cerebrospinal fluid is dark. This allows subtle abnormalities to show up.

Another MRI sequence which may be used is diffusion weighted imaging (DWI). This measures the diffusion of water molecules in brain tissue. It can detect acute ischaemic stroke within the first 30 minutes. Areas of restricted diffusion show up as bright areas. This is useful for early detection of stroke because T2 or FLAIR MRI do not show any changes until a few hours after onset. Other factors which can be visualised on MRI are paramagnetic substances such as iron in the breakdown of blood products, methaemoglobin in subacute haemorrhage, or hemosiderin deposits in chronic haemorrhage which can assist in gauging how far the stroke pathology has developed.

MR angiography (MRA)

MR angiography (MRA) is used to evaluate the craniocervical and cerebral blood vessels. MRA uses the change in magnetic signal which occurs due to blood flow in and out of the region being assessed between the times that the radiofrequency pulse is being transmitted to when the received signal is collected. The direction and speed of blood flow being collected can be selected by the computer. To produce images

where blood is shown as bright, two methods can be used which do not require a contrast agent: time of flight (TOF) MRA and phase contrast (PC) MRA. TOF generates a positive flow contrast compared to the background stationary tissue, it can be cardiac triggered to eliminate artefact from the arterial pulse. In phase contrast (PC) MRA, the flowing blood along the magnetic field causes a shift in the phase of the MR signals which can then be cancelled from the background signal. PC MRA also allows flow or velocity quantification, because this phase shift is proportional to the velocity (Paciaroni, Caso et al. 2005). TOF and PC MRA can be performed using two dimensional (2D) or three dimensional (3D) Fourier transformation techniques for data acquisition and analysis. 3D is useful for small tortuous vessels such as the vertebral artery, because it produces thinner slices. The reported sensitivities for MR compared with DSA ranged from 50% to 100% and specificities from 29% to 100% (Provenzale and Sarikaya 2009).

Ultrasound

Ultrasound is often used as a first line radiological screening for dissection because MRI is not always available in an emergency situation. It is usually performed using colour or power Doppler or more recently using brightness mode (B-mode) imaging. Ultrasound provides direct visualisation of the vessel wall which can demonstrate a mural haematoma or a false lumen due to an intimal flap, as well as haemodynamic information which may indicate flow disturbances due to the presence of stenosis of the vessel (Provenzale 2009). However, ultrasound does not always detect the presence of dissection in comparison with a positive MRI finding (Arnold et al 2008), and follow-up imaging with MR is often clinically necessary, suggesting it may not be a highly sensitive method of imaging (Tay, King-Im et al. 2005). Indeed,

the sensitivity of colour Doppler has been reported to be high as 95-97% in detecting internal carotid arterial dissection causing cerebral ischaemia, but this decreases if the stenosis is only low grade to between 20-71% (Flis, Jäger et al. 2007; Rodallec, Marteau et al. 2008). Although, the sensitivity of ultrasound detection of vertebral artery dissection was reported as 75% in one recent study (Rodallec, Marteau et al. 2008), it is generally used only as an initial screening tool for vertebral arterial dissection due to its high operator dependency and limited visualisation of the artery in its upper segments within the foramen transversaria and along its tortuous course in the atlanto-axial region (Debette and Leys 2009) .

Diagnostic radiological features of craniocervical dissection

Diagnosis of dissection is generally made based on evidence of the presence of the following radiologic features on CT or MR imaging:

- The presence of a crescent sign, a crescentic rim of hyperintense signal seen on CT or T1 or T2 weighted MR images. The crescent represents the small true lumen left after the intramural haematoma has expanded into the lumen of the vessel
- An increase in the external diameter of the VA or ICA, due to a thickening of the wall or narrowing of the lumen
- A long tapering stenosis shown by a 'string sign' characterised by a long segment of narrowing of the artery
- A 'pearl and string sign' where the narrowing includes one or more areas of dilation of the vessel
- An intimal flap or double lumen
- An intramural thrombus

- A pseudoaneurysm or dissecting aneurysm, where the dissection has extended into the adventitial layer of the vessel wall.

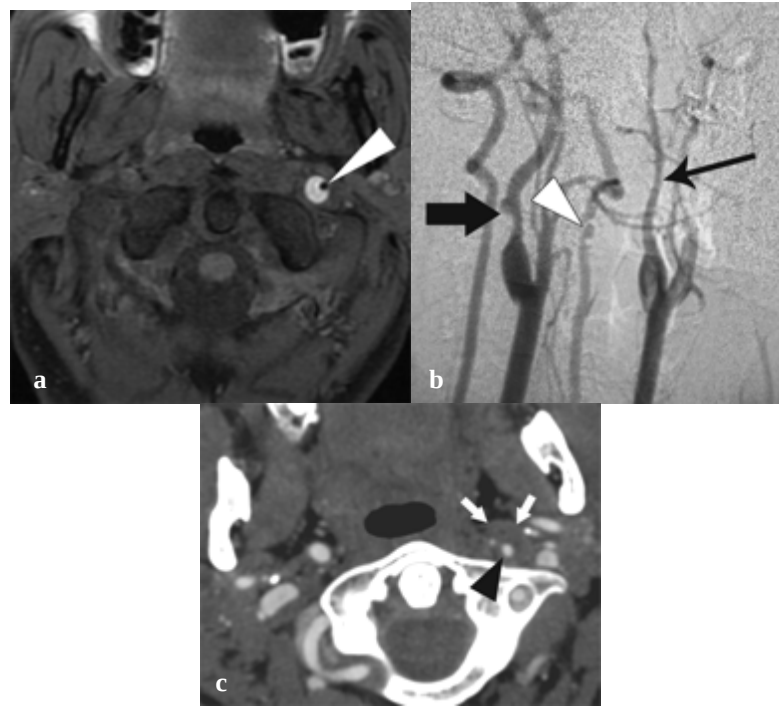


Figure 2.11 *Radiological features of dissection: a) shows a crescent sign in the left internal carotid artery on MRI, b) shows a string sign (thick black arrow) and pearl and string sign (white arrowhead) in the internal carotid artery on contrast enhanced angiography, c) shows thickening of the wall (2 small white arrows) of the left internal carotid artery on CT (Rodallec, Marteau et al. 2008)*

IDENTIFICATION OF PATIENTS AT RISK BY MANUAL THERAPISTS

Differential diagnosis by manual therapists of patients presenting with acute headache is often complicated by the fact that the presenting early signs and symptoms of dissection, notably neck pain and headache, may mimic a musculoskeletal presentation. It is possible therefore, that a patient might present to a manual therapy practitioner for treatment of symptoms which in reality are originating from a dissection in its early stages. Primary care practitioners such as

manual therapists thus need to be able to both identify patients presenting with a dissection in progress, but also those who might have other risk factors which make them unsuitable for manual therapy procedures applied to the neck. Clinical guidelines and other documents have been developed by a number of the disciplines to assist manual therapists to carefully assess any patient who presents with neck pain, headache and dizziness, or other possible symptoms of vertebro-basilar insufficiency, in whom examination or treatment of the cervical spine is planned (International Federation of Manual Medicine 1979; George, Silverstein et al. 1981; Rivett, Shirley et al. 2006; Rushton, Rivett et al. 2012).

Description of pre-manipulative screening guidelines

Concerns about the more serious neurovascular complications, such as craniocervical arterial dissection, following neck manipulation have led physiotherapists using manual techniques to introduce protocols, guidelines and other documents to aid in the identification of the patient at risk (Grant 1988; Magarey, Coughlan et al. 2000; Rivett, Shirley et al. 2006; Rushton, Rivett et al. 2012). The most recent is an information resource entitled '*International framework for examination of the cervical region for potential of cervical arterial dysfunction prior to orthopaedic manual therapy intervention*' developed by Rushton et al on behalf of the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) and in consultation with its member organisations of recognised musculoskeletal physiotherapy bodies around the world. Similar documents exist in other disciplines (International Federation of Manual Medicine 1979; George, Silverstein et al. 1981; Kleynhans and Terrett 1985)

Generally, pre-manipulative guidelines aim to determine if the patient is presenting at the time of consultation with a neurovascular event, has any pre- or currently existing signs or symptoms that suggest the patient may be at risk of a neurovascular event, and more particularly if the patient is at risk of a cerebrovascular event during a manipulative or other manual procedure.

Cervical spine positional tests intended to investigate the effects of neck position on blood flow to the brain are recommended in the Australian physiotherapy guidelines (Rivett, Shirley et al. 2006) in all patients prior to the administration of cervical spine manipulation or the use of mobilizing techniques applied at the end of physiological range. Testing is also indicated in any patient presenting with vague or unclear signs or symptoms suggestive of vertebro-basilar insufficiency.

The Australian Physiotherapy Association (APA) guidelines (Rivett, Shirley et al. 2006) recommend examining patients for the presence of signs or symptoms of vertebro-basilar insufficiency (VBI) prior to treatment of the upper quadrant, including cervical manipulation, but also during and after treatment. The key signs and symptoms identified as being potentially associated with vertebro-basilar insufficiency include the following, sometimes referred to as the 5 Ds (Conman 1986):

- Dizziness or vertigo
- Diplopia (double vision)
- Dysarthria (speech problems)
- Dysphagia (difficulty swallowing)
- Drop attacks (sudden loss of power with no loss of consciousness)

There are also the related 3 Ns of VBI:

- Nausea
- Numbness
- Nystagmus.

Other symptoms less commonly associated with vertebro-basilar insufficiency include tinnitus, blurred vision, paraesthesia in the face or tongue, vomiting and blackouts (Magarey, Coughlan et al. 2000).

The various screening guidelines typically consist of three components. Firstly, a case history is used to identify if previous or current symptoms exist that indicate that the patient is presenting with neurovascular compromise or disease, or if they have any conditions listed as absolute contra-indications to manipulation, such as inflammatory arthritides or fractures of the cervical spine (see Table 2.1). Secondly, a physical examination is performed to determine if signs of vertebro-basilar ischaemia are provoked by movement testing of the cervical spine and to assess if the patient is a suitable candidate for manipulative therapy. Finally, specific positional tests are performed to assess and challenge the vascular supply to the brain by positioning and sustaining the head in rotation and/or extension positions. A positive test would be evidenced by the provocation of any signs or symptoms of vertebro-basilar insufficiency. Commonly, dizziness is stated to be the key clinical feature elicited. The APA guidelines (Magarey, Coughlan et al. 2000) recommend the use of cervical rotation as the manoeuvre of choice because this has been shown to be the position most likely to compromise vertebral artery blood flow (Licht, Christensen et al. 1998; Haynes, Cala et al. 2002; Arnold, Bourassa et al. 2004).

The recent IFOMPT resource for cervical spine examination (Rushton, Rivett et al. 2012) recommends a more comprehensive screening of patients for 'red flags' (i.e., signs of serious pathology), contraindications to manual therapy of the cervical spine and general cardiovascular risk factors such as hypertension. Physical assessment of the cervical spine, including neurological examination for upper motor neurone dysfunction, cranial nerve examination, eye examination for Horner's syndrome, carotid palpation, measurement of blood pressure, as well as testing for cervical instability and vestibular status, are all described.

Limitations of pre-manipulative screening guidelines

Various criticisms of the validity of pre-manipulative screening have been raised in recent years including, how well the history identifies patients at risk, the focus on dizziness as a main feature of VBI, and the positional tests. Firstly, the ability of the history to consistently identify patients at risk has been questioned, as studies of patients with craniocervical arterial dissection have reported negative pre-manipulative screening by their physical therapist (Haldeman, Kohlbeck et al. 2002). It has been assumed by practitioners that neurovascular events such as vertebral artery dissections may be avoided by screening through appropriate history taking and positioning of the cervical spine to test the patency of the vertebral arteries (Haldeman, Kohlbeck et al. 2002). The history may certainly provide some information about previous ischaemic symptoms or prior vertebral artery injury, which have been proposed to be a predictor of risk of manipulative injury (Mann and Refshauge 2001).

In their review of 64 cases of neurovascular accidents related to manipulative therapy however, Haldeman et al. (2002) found that in 27 of these cases, pre-manipulative subjective history screening had been performed but was negative. Notably, this study was a retrospective study of medico-legal cases, which are arguably not representative of the complete spectrum of such cases and uses a methodology fraught with recall and other biases. The authors concluded there were no consistent risk factors identified in those in whom neurovascular accidents following manipulation had been reported. Furthermore, proposed risk factors for vertebral artery dissection, such as age, female gender, migraine, diabetes, the contraceptive pill, cervical spondylosis and smoking were found not to be supported by the literature (Haldeman, Kohlbeck et al. 1999). Haldeman et al. (1999) thus concluded that neurovascular accidents following manipulation appeared to be unpredictable and idiosyncratic. It has been suggested that the history component of a pre-manipulative screening guideline cannot not be relied upon to identify all those at risk of complication following cervical manipulation (Di Fabio 1999; Puentedura, March et al. 2012).

There is therefore a need to prospectively investigate the risk factors for adverse neurovascular events subsequent to manual treatment of the neck, as well as the early presenting clinical features of craniocervical arterial dissection, in order to overcome limitations related to retrospective methodologies such as selection bias of cases and limited data availability. This may help to generate a clearer picture of key clinical features with which to better guide manual therapists in risk assessment.

Secondly, in the past some manual therapy screening guidelines and in particular their recommended positional tests, have focused on the presence or elicitation of dizziness as being the main indicator of vertebro-basilar insufficiency or cerebral ischaemia. While dizziness may indeed be a sign of insufficiency of blood flow to the hindbrain as well as a presenting feature of craniocervical arterial dissection, there are many more benign causes of dizziness which are much more common and which need to be excluded. Such conditions include benign paroxysmal positional vertigo (BPPV), other vestibular disorders including labyrinthitis, perilymph fistula, and Menière's disease, orthostatic hypotension, hyperventilation, and cervicogenic dizziness (Asavasopon, Jankosi et al. 2005). Rather than contraindicate manual therapy, some of these conditions may actually be amenable to physical treatment notably cervicogenic dizziness and BPPV, and an incorrect diagnosis of VBI could delay potentially helpful treatment. Differential diagnosis of these conditions from VBI is therefore important.

Thirdly, the original physiotherapy pre-manipulative protocol (Grant 1988) and more recent guidelines advocated by the APA (Grant 1988; Magarey, Coughlan et al. 2000; Magarey, Rebbeck et al. 2004; Rivett, Shirley et al. 2006) have also been subjected to critical review in recent years, particularly in respect of the validity of the provocative positional tests. In particular, questions have been raised about the ability of the positional tests to predict those at risk of neurovascular insult (Dunne 2001; Refshauge 2001; Rivett 2001), the contradictory evidence supporting the validity of the provocative tests (Gross and Kay 2001), and the inability of the physical tests to predict the effects of the manipulative thrust (Dunne 2001; Refshauge 2001).

In addition, the safety of performing the positional tests which may, in and of themselves, precipitate a neurovascular event, has also been questioned (Dunne 2001; Gross and Kay 2001). Gross and Kay (2001) suggest that the pre-test likelihood ratio of vertebrobasilar insufficiency actually being present is too low to warrant implementation of the tests. As a consequence it has been argued that the positional tests actually test the adequacy of the total cerebral perfusion, rather than the patency of the vertebral arteries or their susceptibility to injury (Mann and Refshauge 2001). Furthermore, the positional tests themselves are only an indirect means of assessment of blood flow dynamics.

In an attempt to address some of these limitations, the recent international resource developed by IFOMPT (Rushton, Rivett et al. 2012) recommends a clinical reasoning approach to the evaluation of all patients presenting for treatment of the cervical spine. The document is intended to inform clinicians in considering factors in the clinical examination such as 'red flags', contraindications and precautions to treatment of the cervical spine and various other general health considerations, prior to undertaking any physical treatment. It also describes additional screening procedures for neurovascular risk factors, such as blood pressure measurement. However, while the document is an extensive information resource intended to inform manual therapy practitioners in their clinical reasoning, it outlines a number of pre-manipulative screening procedures, such as cervical spine positional testing and carotid palpation, which may not be particularly useful in informing practitioners as to the risk of dissection following cervical spine manipulation. In addition, at 37 pages practitioners may find the document too time consuming to digest and too broad to apply in day to day practice. There is therefore a need for a simple screening

recommendation for patients with neck pain and headache, which can be easily applied by manual therapy and other primary care practitioners, and which is based on research evidence from arterial dissection cases.

CLINICAL CONSIDERATIONS PRIOR TO NECK MANIPULATION

As a result of the criticisms raised about the validity of the current pre-manipulative screening recommendations, some authors have proposed additional assessment of risk should be undertaken to supplement, or indeed replace, the information obtained by the current guidelines (Haynes, Hart et al. 2000; Kerry, Taylor et al. 2008; Rushton, Rivett et al. 2012). Some authors have advocated the use of simple auditory Doppler ultrasound (velocimeter) screening of vertebral arterial flow (Haynes 2002a; Kerry, Taylor et al. 2008). The Manipulative Association of Chartered Physiotherapists in the UK, on the other hand, recommends a 'systems approach' to assessment of the cervical spine considering both the vertebral and internal carotid arterial systems and assessment of general cardiovascular risk factors (Kerry, Taylor et al. 2007). Recently, because connective tissue disorders may be associated with dissection in some cases, clinical connective tissue assessment has been suggested and indeed has been investigated by some researchers (Dittrich, Heidbreder et al. 2007; Heidbreder, Ringelstein et al. 2008). Finally, consideration as to the potential effect of manipulative techniques has led some authors to advocate the use of segmentally specific, mid-range manipulative techniques to hopefully minimise stress on the craniocervical arteries (Hing, Reid et al. 2003). The potential varying effects of differing manipulative techniques should therefore perhaps also be considered by practitioners prior to commencing manual treatment of the cervical spine.

Blood flow compromise

Over the two last decades there has been considerable interest in the evaluation of blood supply to the brain as a screening method based on the premise that compromise of blood flow to the brain such as demonstrated in neck rotation might be a risk factor for an adverse neurovascular event following neck manipulation. This is generally assessed with the positional tests. The aim of the positional tests is to examine the effects of neck position, in particular extension and contralateral rotation, on vertebral or internal carotid artery blood flow, evidenced by the provocation of any signs or symptoms of vertebro-basilar insufficiency. Some studies involving duplex ultrasound measurement of vertebral artery blood flow during the performance of positional tests have cast some doubt on the validity of positional testing (Rivett, Sharples et al. 2000; Thomas, Rivett et al. 2009). These studies have reported that changes in the patency of the vertebral arteries and impedance changes in cerebrovascular blood flow can occur in persons who do not have a positive positional test result clinically (Thiel, Wallace et al. 1994; Cote, Kreitz et al. 1996; Licht, Christensen et al. 1998; Rivett, Sharples et al. 2000). There are however, limitations with the use of ultrasound for imaging the craniocervical circulation, in particular the vertebral artery due to its small calibre and tortuous course (Haynes, Hart et al. 2000; Zwiebel 2000; Debette and Leys 2009).

It has been suggested by some authors that there is a need for a more direct method of assessing vertebro-basilar blood flow prior to neck manipulation (Rivett 2001; Kerry, Taylor et al. 2008). Several studies have investigated the use of a hand-held velocimeter (a portable Doppler ultrasound device) to evaluate blood flow in the vertebral arteries (Haynes, Hart et al. 2000; Thomas, Rivett et al. 2009) but have

reported conflicting results as to the validity and reliability of such a device. Moreover, considering studies of normal participants have shown that some individuals have marked changes in vertebral artery blood flow during neck rotation yet have no symptoms of vertebrobasilar insufficiency (Thiel, Wallace et al. 1994; Cote, Kreitz et al. 1996; Licht, Christensen et al. 1998; Rivett, Sharples et al. 2000), it would seem that asymptomatic changes in blood flow may be a normal variation and not an abnormal finding. Indeed, such findings may in fact be indicative of the presence of adequate collateral circulation (Refshauge 1994). However, critical narrowing of the artery may occur in anomalous cases and produce symptoms of vertebrobasilar insufficiency.

Cardiovascular factors

It has been suggested by some authors (Kerry and Taylor 2006) that therapists should undertake a detailed assessment of general cardiovascular risk factors for every patient for whom manual treatment for the neck is proposed, including measuring of blood pressure, auscultation for carotid bruits and possibly cranial nerve examination (Kerry, Taylor et al. 2008). However, general risk factors for cardiovascular disease are not thought to be strongly associated with dissection, as patients are in a younger age group than for general stroke, so are less likely to have developed conditions such as atherosclerosis (Schievinck 2001; Arnold and Bousser 2005; Debette and Leys 2009). Screening for these factors would add a considerable amount of time to the routine assessment of a neck patient and may not be enthusiastically adopted by practitioners in a busy clinic. Such screening also may not assist manual practitioners in their risk assessment and could in fact unnecessarily preclude some patients from potentially beneficial treatment.

Connective tissue screening

Clinical signs of a connective tissue disorder may be present in up to 20% of craniocervical dissection patients (Heidbreder, Ringelstein et al. 2008), although only 1-5% may be characterised as having a defined heritable disorder (Schievinck 2001). Ehlers-Danlos syndrome is a hereditary connective tissue disorder which affects collagen and collagen synthesis, and connective tissue abnormalities similar to those found in Ehlers-Danlos syndrome have been found in up to 60% of craniocervical dissection patients on electron microscopy (Heidbreder, Ringelstein et al. 2008). Ehlers-Danlos syndrome is characterised by joint hypermobility and skin which is hyper-extensible and easily scarred. There has been some debate as to whether these abnormalities are detectable clinically in craniocervical dissection patients, with some authors identifying them (Schievinck 2001) and others disputing their presence (Dittrich, Heidbreder et al. 2007; Heidbreder, Ringelstein et al. 2008). Studies have typically been small. If such features are present and could be reliably detected in craniocervical dissection patients by close clinical examination for joint hypermobility and skin hyper-extensibility, this might offer a useful screening test which could be performed by manual therapists prior to more vigorous treatment of the neck.

Joint hypermobility can be assessed clinically using the Beighton scale (Beighton and Horan 1969; Grahame, Bird et al. 2000) and has been shown to have good inter-rater reliability (ICC 0.72 - 0.79) (Hicks, Fritz et al. 2003; Fritz, Piva et al. 2005). The validity of the Beighton scale is the subject of some debate however, because of the lack of an appropriate reference standard with which to compare it. Skin extensibility

can be measured manually by pinching the skin on the volar aspect of the forearm. The skin is pulled up and the distance measured in centimetres or instead classified as normal, mildly hyper-extensible or severely hyper-extensible. However manual testing has not been shown to be particularly reliable and a more reliable method has been described using a suction system (Heidbreder, Ringelstein et al. 2008).

A standardised connective tissue examination (Dittrich, Heidbreder et al. 2007) has also been developed which reflects the spectrum of clinical signs found in hereditary connective tissue disorders such as Ehlers-Danlos and Marfan syndrome. It comprises 25 test items and includes signs of skin hyper-extensibility, capillary fragility and joint hypermobility (incorporating the Beighton scale), as well as physically examining for indicative physical features such as pectus excavatum, pectus carinatum, blue sclera or facial dysmorphism. It has been used by other authors investigating craniocervical dissection patients (Dittrich, Heidbreder et al. 2007), however to date, has been not found to be identify connective tissue disorders in this group.

Manual therapy procedures

Consideration should also be given to the safety of the manipulative procedures themselves. It is possible that particular manipulative procedures place the head and neck in a position which imparts too great a strain on the craniocervical arteries or, that the force of the associated manipulative thrust is potentially injurious, perhaps in the presence of some underlying vascular susceptibility. Accordingly, some authors have suggested that the use of mid-range, small amplitude, high velocity thrust techniques in the cervical spine could minimise the amount of neck rotation and

thrusting force and therefore reduce the amount of overall stress applied to the vertebral artery (Hing, Reid et al. 2003). However, while cervical manipulation has been reported as a potential risk factor for dissection, dissection may also occur spontaneously or subsequent to routine daily activities such as callisthenics, looking overhead, yoga and having hair washed in a salon basin, supporting the argument for some pre-existing weakness or susceptibility. Arguably, if cervical manipulation was a sole primary cause of dissection it would be expected that there would be a much greater number of patients experiencing dissection subsequent to manipulation than are currently reported (Rubinstein, Peerdeman et al. 2005).

BIOMECHANICAL EFFECTS OF CERVICAL MANIPULATION

Common therapeutic procedures applied to the cervical spine involve moving the head and neck into various positions. The effect of such positions as longitudinal distraction and rotational movement of the neck, common components of such manual treatments, may be to increase the mechanical strain on the craniocervical arteries, but the actual effect is unknown. It has been suggested that one factor which could contribute to adverse events following manual treatment of the neck may be positions of neck rotation close to the end of physiological range, which could potentially temporarily compromise blood flow (Haldeman, Kohlbeck et al. 1999).

It has also been suggested that in some cases of adverse neurovascular events the manipulative thrust itself may have been too forceful. The cumulative effect of repeated manipulations might also be detrimental to the integrity of the arterial wall (Symons and Westaway 2001; Symons, Leonard et al. 2002; Austin, DiFrancesco et al. 2010). Practically however, it is difficult to directly measure the effect on the

arterial wall of a manipulative procedure. However, there has been one study that has been able to indirectly measure the effect of the manipulative thrust on blood flow in an animal model (Licht, Christensen et al. 1998). This study showed a modest effect of increased blood flow volume in the contralateral vertebral artery, which lasted for approximately 40 seconds.

Positions for manual therapy procedures

It has been suggested that manual techniques performed close to the end of physiological range, particularly into contralateral rotation, may induce some biomechanical stress on the craniocervical arteries (Refshauge 1994; Haldeman, Kohlbeck et al. 1999). It may therefore be postulated that procedures performed closer to the neutral position of the neck will therefore have less effect on these arteries. However, a direct causal relationship between temporary compromise of arterial blood flow in a particular vessel and its consequent effect on brain perfusion has not been demonstrated.

Forces applied

The force of the manipulative thrust has been measured by some authors in vitro and by others using ultrasound in animal models. The findings suggested that the force required to damage a normal craniocervical artery is far greater than that normally affected by a manipulation (Licht, Christensen et al. 1999; Symons, Leonard et al. 2002; Austin, DiFrancesco et al. 2010). Similarly, the effects of the application of force on arteries with pathology have been evaluated in a few small *in-vitro* animal studies with an experimentally induced lesion in the vertebral artery, and showed the manipulative thrust had no effect on the dimensions of the lesion (Kawchuk, Jhangri

et al. 2008; Wynd, Anderson et al. 2008). Moreover, a recent MRI paper comparing dissection participants and controls used mathematical modelling to evaluate the stresses on the vertebral and internal carotid arterial walls in neck rotation and combined rotation and hyper-extension found no difference between the two groups (Callaghan, Luechinger et al. 2011).

Effect of neck movement on craniocervical arterial blood flow

It has been shown using ultrasound imaging that certain neck movements, in particular rotation or extension, can alter blood flow velocities in the craniocervical arteries (Arnetoli, Amadori et al. 1989; Weingart and Bischoff 1992; Thiel, Wallace et al. 1994; Haynes, Cala et al. 2002; Mitchell 2003; Zaina, Grant et al. 2003). It has been suggested that this might reflect biomechanical stresses on the vertebral arteries (Rivett, Sharples et al. 2003; Thomas, Rivett et al. 2009). However, the few studies examining blood flow in the internal carotid arteries generally reported that it was unchanged by neck rotation (Bowler, Shamley et al. 2011). There have been few studies evaluating the effect on blood flow in the craniocervical vessels in specific manual therapy treatment positions or when applying longitudinal force to the neck, such as used in cervical spine traction (Licht, Christensen et al. 1999; Arnold, Bourassa et al. 2004; Bowler, Shamley et al. 2011). All of these used ultrasound and two examined flow in the vertebral arteries only. Two of these studies showed a reduction in flow in the contralateral vertebral artery in a combined cervical rotation and extension position, but the other reported that flow in the internal carotid arteries was unchanged by a combined rotation and extension position. In contrast, the other study was an animal study which measured blood flow in the vertebral arteries of pigs following a manipulation of the neck, and showed a temporary increase in flow

in the contralateral artery (Licht, Christensen et al. 1999). This suggests that the effects of the neck position and the manipulative thrust on blood flow may be different and also that the vertebral arteries appear to be more susceptible to blood flow variation than the internal carotid arteries, presumably due to their smaller size. However, the use of an animal model may limit the generalisability of the findings to manipulation of a human neck.

Limitations of previous blood flow studies

There has been conflicting findings as to whether blood flow is altered by head and neck rotation, with some authors finding that blood flow velocity is increased, others that it is decreased, while yet other studies report blood flow is unchanged (Arnetoli, Amadori et al. 1989; Haynes, Hart et al. 2000; Johnson, Grant et al. 2000a; Rivett, Sharples et al. 2003; Zaina, Grant et al. 2003; Mitchell and Kramschuster 2008). All of these studies used ultrasound which is known to be highly operator dependent, particularly when sampling blood flow velocities in small diameter tortuous vessels such as the vertebral arteries in the neck (Zwiebel 2000), where most manipulative injuries have been reported to occur. This may account for some of the differences in blood flow measurements reported. In addition, as previously described, there were a number of studies in which individual participants demonstrated markedly reduced blood flow in the vertebral arteries contralateral to the direction of neck rotation, yet no signs or symptoms of VBI were reported (Thiel, Wallace et al. 1994; Rivett, Sharples et al. 2000). This would indicate adequacy of the collateral circulation and demonstrate patency of the Circle of Willis. Thus, if blood flow is reduced in one of the craniocervical vessels it should normally be compensated for by an increase in flow in another artery, in order to maintain a constant blood supply to the brain.

While many ultrasound studies measured flow in vertebral or internal carotid arteries during neck movement, none measured total inflow to the brain.

As described previously, angiography is considered to be the reference standard for imaging the craniocervical arterial system (Rodallec, Marteau et al. 2008) and currently is most commonly performed using non-invasive methods, such as MRA or CTA. A particular advantage of this approach for imaging the craniocervical vessels is that all arteries can be imaged simultaneously, thereby providing a more complete picture of total blood supply to the brain. Thus, utilising CTA or MRA to image all the craniocervical vessels during neck movement or positions used in common manual therapeutic techniques would allow direct assessment of any cerebrovascular compromise to the brain.

To date, there have been only a few small studies and case reports using MRA or CTA to examine craniocervical vessel diameter or flow in various head and neck positions (Ohsaka, Takgami et al. 2009; Callaghan, Luechinger et al. 2011) and no such studies which have examined brain perfusion. One MRA study used mathematical modelling to predict change in internal carotid artery wall stresses from neutral following neck rotation and combined rotation and extension in five patients with dissection and in five control patients, but found that wall stresses did not differ between the two groups (Callaghan, Luechinger et al. 2011).

SUMMARY

This chapter has defined cervical spine manipulation and outlined the nature of the neurovascular adverse events which may be associated with this form of therapy. It

has described the course and distribution of the craniocervical arteries, all well as detailing the aetiology and clinical presentation of craniocervical arterial dissection. The currently available pre-manipulative screening recommendations are discussed, including their limitations. The known effects of various neck positions used in vertebrobasilar provocative testing and in cervical manipulative procedures are also described.

The thesis aims to examine in detail the nature and onset of the clinical features of craniocervical arterial dissection in order to make clear recommendations to clinicians on the appropriate screening of patients both associated risk factors for adverse neurovascular events, as well to recognise a patient presenting with a dissection already in progress. This will provide a clearer picture of key relevant preceding events and clinical features based on research evidence elicited by thorough investigation of patients suffering from this serious condition. The thesis also aims to determine whether selected manipulative procedures are more or less likely than others to adversely affect craniocervical blood flow and overall brain perfusion, and from this investigation provide advice to clinicians on safe manipulative practice.

The following chapter further explores potential risk factors and the clinical presentation of patients diagnosed with craniocervical arterial dissection, using a retrospective study design. Details of the risk factors identified were compared with risk factors of a cohort of age and gender matched controls with ischaemic stroke from some other cause than dissection. The information was extracted by means of a review of medical records of the participants.

CHAPTER 3

STUDY 1: RISK FACTORS AND CLINICAL FEATURES OF CRANIOCERVICAL ARTERIAL DISSECTION: A RETROSPECTIVE STUDY

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Participants

Outcome measures

Statistical analysis

RESULTS

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Risk factors

Cardiovascular risk factors

Clinical presentation

Outcome of stroke

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Risk factors

Clinical presentation

CONCLUSION

The work presented in this chapter has been published as:

- Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. *Manual Therapy* 16: 351-356.

The work has been presented as an oral presentation at the following conferences:

- Thomas, L, Rivett, D, Levi, C (2009). Risk factors and clinical features of craniocervical arterial dissection. Third International Conference on Movement Dysfunction. Edinburgh, October 30-November 1 2009.
- Thomas, L, Rivett, D, Levi, C (2009). Risk factors and clinical features of craniocervical arterial dissection. The 16th Biennial Conference of Musculoskeletal Physiotherapy Australia. Sydney, October 1-4 2009.
- Thomas L, Levi C, Rivett D (2008). Risk factors and natural history of craniocervical arterial dissection. Poster presentation with two minute talk: International Federation of Orthopaedic Manipulative Therapists Conference. Rotterdam, June 8-13 2008.

INTRODUCTION

Cranio cervical arterial dissection is one of the most common causes of ischaemic stroke in the young to middle aged population (Touze, Gauvrit et al. 2003; Dittrich, Rohsbach et al. 2007), accounting for 10-25% of all ischaemic stroke in this age group. It is considered to often occur spontaneously, without obvious cause, with an annual incidence of 2.5-3:100,000 (Schievinck 2001; Dziewas, Konrad et al. 2003).

There is limited evidence to suggest that young persons suffering a 'spontaneous' cranio cervical dissection may actually have a pre-existing but subclinical arteriopathy, vascular anomaly or genetic predisposition (Dittrich, Rohsbach et al. 2007). Such intrinsic susceptibility may be caused by a number of different factors, such as subclinical connective tissue disorders (Brandt, Hausser et al. 1998; Schievinck 2001) or a more generalised arteriopathy (Volker, Besselman et al. 2005). In patients with such an existing intrinsic susceptibility, exposure to an extrinsic trigger such as minor mechanical trauma to the neck or a recent infection or viral illness, may initiate dissection. Cervical spine manipulation has occasionally been associated with serious adverse events (Assendelft, Bouter et al. 1996; Hurwitz, Aker et al. 1996), in particular dissection of the vertebral or internal carotid arteries (Paciaroni and Bogousslavsky 2009). Recent infection has been proposed as a possible trigger for dissection, perhaps associated with the recognised seasonal variation of spontaneous cranio cervical dissection, with a peak in autumn and winter (Schievinck 2001; Paciaroni, Georgiardi et al. 2006); dissection potentially occurring due to the presence of pro-inflammatory mediators and an immunological host response causing temporary friability of the arterial wall (Guillon, Berthet et al. 2003; Lindsberg and Grau 2003).

Traditional risk factors for cardiovascular disease are not generally thought to be contributive in dissection as cases are generally under 55 years and therefore less likely to have developed associated conditions, such as atherosclerosis (Schievinck 2001). Nonetheless, Kerry and colleagues have recommended that manual therapists should consider assessment of vascular risk factors (incorporating a system based approach) for all patients for whom manual treatment for the neck is proposed (Kerry, Taylor et al. 2008).

If individuals with intrinsic susceptibility who may be at greater risk of dissection can be more readily identified, appropriate risk management for neck manipulation may be applied. However, it is likely pre-manipulative protocols used by manual therapy practitioners, which often include provocative positional tests, do not identify all patients at risk and are not ideal for screening purposes (Refsauge 1994; Kerry, Taylor et al. 2008; Thomas, Rivett et al. 2009). Clinical screening is further complicated by the fact that signs and symptoms of craniocervical dissection may include headache and neck pain, mimicking a musculoskeletal presentation. Indeed, some patients might actually seek treatment from a manual therapy practitioner for the painful symptoms of a dissection already in progress (Haneline and Lewkovich 2005; Cassidy, Boyle et al. 2008) and differential diagnosis may be difficult. If the early signs and symptoms of craniocervical dissection can be more easily recognised, including the more subtle neurological findings, inappropriate interventions such as manipulation may be avoided and medical treatment expedited, potentially reducing the impact of the stroke.

Previous research has identified patients with craniocervical dissection from hospital or stroke data banks, individual clinic records and medico-legal reports. Often these studies were uncontrolled and age limitations not always applied (Haldeman, Kohlbeck et al. 2002; Haneline and Lewkovich 2005; Arnold, Pannier et al. 2009). Findings are commonly inconsistent between studies and consensus has yet to be reached on definitive risk factors for dissection

The aim of the current study was to retrospectively investigate young patients, under 55 years, with radiologically confirmed or clinically suspected vertebral or internal carotid artery dissection presenting to hospital in the Hunter and Manning regions of New South Wales, Australia. Specifically, the aims were to identify risk factors for dissection from the patient history, examine and describe the presenting clinical features, and gain an understanding of the natural history and outcome for patients following craniocervical dissection. The upper age was chosen as craniocervical dissection occurs most commonly in the fourth and fifth decade before more traditional cardiovascular risk factors are likely to have developed.

METHOD

Design

Cases of vertebral or internal carotid artery dissection were identified via the medical record coding system of the John Hunter Hospital between 1998 and 2009. This hospital is a large tertiary referral hospital of 550 beds servicing the Hunter and Manning regions with a population of approximately 617,000 (Australian Bureau of Statistics 2009). The medical records database was searched using the international

diagnostic coding system ICD-10 (World Health Organisation 2007) for patients with radiologically confirmed or suspected vertebral or internal carotid arterial dissection.

Participants

The database was searched in the following diagnostic categories:

- 1670 dissection of cerebral arteries non ruptured;
- 1630-1639 cerebral infarction unspecified;
- 1640 stroke not specified as haemorrhage or infection;
- 1660-1669 occlusion and stenosis of unspecified cerebral artery;
- 1650-1659 occlusion and stenosis of carotid artery.

Although some of these codes do not directly identify vertebral or internal carotid dissection, in case of possible miscoding it was expected that dissection cases would at least be coded under one of these categories. An additional search was also made of the hospital electronic discharge referral system using keywords of vertebral or internal carotid artery dissection. Throughout the course of the study regular communication with research and clinical staff of the neurology unit was made to identify any new dissection cases.

Inclusion criteria were all patients under 55 years with radiologically confirmed or suspected vertebral or internal carotid artery dissection. Control participants were age and sex matched patients with a clinico-radiological diagnosis of stroke from some cause other than arterial dissection. Patients diagnosed with sub-arachnoid haemorrhage were excluded as this is a rare condition with a distinctively different presentation.

Outcome measures

Once the medical record numbers of patients were identified, medical notes were retrieved and data extracted using a standardised data extraction proforma administered by the lead author. Information was sought in the medical notes of both dissection and control participants about the presenting signs and symptoms of the stroke, the history of preceding events, in particular minor mechanical trauma and specifically manual treatment of the neck, pre-existing medical status including reports of any recent infection or febrile illness, and pre-existing cardiovascular risk factors. Details of any radiological and haematological investigations were also recorded.

Brain and vascular imaging was accessible through the John Hunter Hospital Picture Archiving Communication System (PACS) and was reviewed using a standardised proforma. The brain imaging was evaluated on-line by two experienced stroke neurologists (CL and MP) blinded to the case or control status. The imaging diagnosis of confirmed craniocervical dissection was made by consensus.

The outcome of the stroke was recorded as a modified Rankin score (mRS) (van Swieten, Koudstaal et al. 1988). The mRS is widely used for assessing global outcomes following stroke. It has been demonstrated to have acceptable inter-rater reliability ($\kappa=0.71-0.95$) (van Swieten, Koudstaal et al. 1988; Wolfe, Taub et al. 1991; Wilson, Hareendran et al. 2005). The project was approved by the Hunter New England Area Human Ethics Committee.

Statistical analysis

Descriptive statistics were used to summarise the demographic data, outcomes and risk factors. Simple logistic regression was performed for the major risk factors identified. All factors with a p-value of 0.2 or less were included in a multiple logistic regression model; outcomes were expressed as odds ratios with 95% confidence intervals. Statistical analysis was performed using the STATA statistical /data analysis software (version 11, Statacorp, Texas, USA).

RESULTS

Characteristics of participants

The medical records of 47 dissection participants and 43 age and sex matched controls were reviewed. Of the dissection participants, 27 (57%) had sustained a dissection of the vertebral artery or basilar artery (VBAD) and 20 (43%) participants had sustained a dissection of the internal carotid artery (ICAD). Participant demographics and characteristics are reported in Table 3.1. Of the participants, 36 (77%) had radiographic confirmation of their dissection arrived at by consensus between the two reviewing neurologists (CL and MP). The neurologists were in agreement on all cases. For the remaining 11 participants, diagnosis of dissection was based on suggestive history and clinical examination at the time of admission as well as radiological suspicion of dissection.

Table 3.1 Characteristics of participants

Characteristic	Dissection N=47	Control N=43
Vertebrobasilar artery territory, n (%)	27 (57)	5 (12)
Radiological confirmation	20 (74)	5 (100)
Clinical diagnosis but no imaging confirmation	7 (26)	0
Internal carotid artery territory, n (%)	20 (43)	38 (88)
Radiological confirmation	16 (80)	38 (100)
Clinical diagnosis but no imaging confirmation	4 (20)	0
Age (yr), mean (SD)	37.6 (10)	43.6 (7.3)
Gender, n males (%)	27 (57)	22 (51)

Risk factors

Thirty (64%) of the dissection participants (17 VBAD, 13 ICAD) had a history of minor mechanical trauma to the neck (i.e. no evidence of fracture or dislocation) within the preceding three weeks, of which 11 (23%) participants (8 VBAD, 3 ICAD) had a report of recent manual therapy to their neck (Table 3.2a and b). An additional three (6%) participants had a history of head trauma within the past several years. In contrast, only three (7%) control participants had a history of recent mechanical trauma to the head or neck, and only one of these cases involved manual therapy to the cervical spine. This equates to an odds ratio (95% CIs) of 23.53 (6.31, 87.7) for mechanical neck trauma ($p<0001$) and 12.8 (1.58, 104.28) for neck manual therapy ($p=0.009$), both of which remain significant in the adjusted model (adjusted for age and gender). The types of trauma are shown in Table 3.3.

Table 3.2a Risk factors identified in dissection and control participants.

Risk factor	Dissection participants N=47	Control participants N=43	Odds ratio (95%CI)	Adjusted odds ratio* (95%CI)	P value
Recent head or neck trauma	30 (64%) (17 VBA, 13 ICA)	3 (7%)	23.53 (6.31, 87.70)	23.51 (5.71, 96.89)	<0.000
Neck manual therapy	11 (23%) (8 VBA, 3 ICA)	1 (2%)	12.8 (1.58, 104.28)	12.67 (1.43,112.0)	0.009
Recent infection	12 (26%) (6 VBA, 6 ICA)	4 (9%)	3.34 (0.99, 11.32)	3.77 (1.07,13.24)	0.040
§ Craniocervical vascular anomaly	17 (36%) (17 VBA)	7 (16%)	2.62 (0.90, 7.60)	3.0 (0.99, 9.02)	0.068

*Multiple regression analysis with odds ratios adjusted for age and gender

§ anomalies involving the posterior circulation such as ectatic or hypoplastic VA or VA ending in posterior inferior cerebellar artery (PICA)

Table 3.2b Risk factors identified in dissection and control participants: subgroup analysis of radiologically confirmed dissection participants

Risk factor	Confirmed dissection participants N=36	Control participants N=43	Odds ratio (95%CI)	Adjusted odds ratio* (95%CI)	P value
Recent head or neck trauma	23 (64%) (13 VBA, 10 ICA)	3 (7%)	26.67 (6.83, 104.17)	25.29 (6.04, 105.82)	<0.000
Neck manual therapy	8 (22%) (7 VBA, 1 ICA)	1 (2%)	12.0 (1.42, 101.30)	12.67 (1.43,112.0)	0.022
Recent infection	8 (22%) (4 VBA, 4 ICA)	4 (9%)	1.94 (0.62,6.08)	1.90 (0.58,6.22)	0.287
§ Craniocervical vascular anomaly	14 (39%) (9 VBA, 5 ICA)	7 (16%)	3.27 (1.14, 9.36)	4.46 (1.37, 14.60)	0.013

*Multiple regression analysis with odds ratios adjusted for age and gender

§ anomalies involving the posterior circulation such as ectatic or hypoplastic VA or VA ending in posterior inferior cerebellar artery (PICA)

Table 3.3 Types of minor mechanical trauma described in participant history. (Note that trauma may have been categorised under more than one type)

Minor mechanical trauma	Dissection participants n=30	Control participants n=3
Manual therapy	11 (6 chiro, 2 massage, 1 osteo, 2 physio)	1 (osteo)
Sport with direct trauma to head/neck	9 (1 martial arts, 4 fall from horse/ bike/ wakeboard, 1 rugby, 1 netball, 1 gymnastics, 1 head clash)	0
Heavy lifting	3 (1 boxes, 2 gym work)	0
Motor vehicle accident	2	1
Direct trauma to neck	2 (1 twisting, 1 attempted hanging)	0
Indirect trauma to neck	3 (1 show ride, 1 horse riding, wisdom teeth extraction)	1 (playing squash)

Seventeen (36%) of the dissection participants had radiological evidence of vessel abnormalities involving the posterior circulation, such as an ectatic or hypoplastic vertebral artery or one ending in the posterior inferior cerebellar artery. On the other hand, only seven (16%) control participants had a report of vessel abnormalities within the cerebral circulation. The adjusted odds ratio of 3.0 (95% CI 0.99, 9.02) narrowly missed significance in the adjusted model.

Twelve (26%) of the dissection participants had a history of recent infection or viral illness prior to their admission to hospital compared with just four (9%) of the control participants, for an adjusted odds ratio of 3.77 (95% CI 1.07, 13.24).

Dissections occurred most frequently during autumn and winter (30 participants, 64%), whereas 53% (23 participants) of strokes in the control group occurred during these seasons. Blood investigations were inconsistently reported in the medical notes so no meaningful comparisons could be made between groups.

Cardiovascular risk factors

The occurrence of cardiovascular risk factors is reported in Table 3.4a. Statistically significant risk factors were hypertension (OR 0.23, 95% CI 0.09, 0.58), smoking (OR 0.22, 95% CI 0.13, 0.73) and elevated cholesterol (OR 0.27, 95% CI 0.11, 0.66). Notably, these were more likely to occur in controls. In general, the controls had considerably more cardiovascular risk factors than the dissection participants; an average of 3.23 (SD 1.6) or more risk factors and other co-morbidities, in contrast to the dissection participants who were generally without other co-morbidities until their dissection and had an average of 1.4 (SD 1.3) cardiovascular risk factors.

Subgroup analysis of risk factors was performed for the radiologically confirmed cases (i.e. excluding the 11 unconfirmed) and findings were similar except that recent infection was no longer significant ($p=0.29$) and vascular anomaly became significant ($p=0.13$) (Table 3.2b and 3.4b).

Table 3.4a Cardiovascular risk factors identified in dissection and control participants

Risk factor	Dissection participants N=47	Control participants N=43	Odds ratio (95%CI)	Adjusted odds ratio* (95%CI)	P value
Hypertension	9 (19%)	23 (53%)	0.23 (0.09, 0.58)	0.29 (0.11, 0.79)	0.001
Current or past smoker	14 (30%)	28 (65%)	0.31 (0.13, 0.73)	0.31 (0.13, 0.78)	0.001
High cholesterol	11 (23%)	23 (53%)	0.27 (0.11, 0.66)	0.33 (0.12, 0.85)	0.001
Family history of stroke	4 (9%)	6 (14%)	0.40 (0.13, 1.29)	0.55 (0.16, 1.88)	0.126
Oral contraception	5 (11%)	4 (9%)	1.46 (0.38, 5.58)	1.32 (0.31, 5.69)	0.578
Migraine	11 (23%)	8 (19%)	1.62 (0.56, 4.64)	1.54 (0.51, 4.67)	0.373

*Multiple regression analysis with odds ratios adjusted for age and gender

Table 3.4b Cardiovascular risk factors for dissection and control participants: Subgroup analysis of confirmed dissection cases

Risk factor	Confirmed dissection participants N=36	Control participants N=43	Odds ratio (95%CI)	Adjusted odds ratio* (95%CI)	P value
Hypertension	7 (19%)	23 (53%)	0.23 (0.83, 0.64)	0.28 (0.09, 0.85)	0.005
Current or past smoker	12 (33%)	28 (65%)	0.33 (0.13, 0.83)	0.33 (0.13, 0.89)	0.018
High cholesterol	8 (22%)	23 (53%)	0.25 (0.92, 0.67)	0.28 (0.10, 0.82)	0.006
Family history of stroke	4 (11%)	6 (14%)	1.86 (0.69, 4.98)	2.18 (0.76, 6.26)	0.213
Oral contraception	5 (14%)	4 (9%)	1.53 (0.38, 6.36)	1.69 (0.38, 7.63)	0.525
Migraine	10 (28%)	8 (19%)	1.98 (0.66, 5.88)	1.99 (0.64, 6.27)	0.220

*Multiple regression analysis with odds ratios adjusted for age and gender

Clinical presentation

The most commonly presenting feature in the dissection group was headache; reported by 38 (81%) participants compared with 22 (51%) controls. The frequency and distribution of reported signs and symptoms are shown in Tables 3.5a and b.

Table 3.5a Reported symptoms (n, %) in the dissection and control participants. (UL=upper limb, LL=lower limb) VBAD = vertebrobasilar arterial dissection, ICAD = internal carotid artery dissection

Symptoms, n (%)	VBAD N=27	ICAD N=20	Total Dissection participants N=47	Control participants N=43
Headache	23 (85%)	15 (75%)	38 (81%)	22 (51%)
Neck pain	18 (67%)	9 (45%)	27 (57%)	6 (14%)
Dizziness	14 (52%)	1 (0.5%)	15 (32%)	3 (7%)
Visual disturbance	9 (33%)	7 (35%)	16 (34%)	12 (28%)
Paraesthesia (face)	8 (30%)	6 (30%)	14 (30%)	8 (19%)
Paraesthesia (UL)	9 (33%)	7 (35%)	16 (34%)	20 (47%)
Paraesthesia (LL)	4 (15%)	5 (25%)	9 (19%)	14 (33%)

Table 3.5b Reported clinical signs (n, %) in dissection and control participants

Signs, n (%)	VBAD N=27	ICAD N=20	Total dissection participants N=47	Control participants N=43
Unsteadiness/ataxia	18 (67%)	8 (40%)	26 (55%)	15 (35%)
Weakness (UL)	9 (33%)	13 (65%)	22 (47%)	32 (74%)
Weakness (LL)	11 (41%)	10 (50%)	21 (45%)	26 (60%)
Dysphasia/dysarthria/ aphasia	12 (44%)	9 (45%)	21 (45%)	30 (70%)
Facial palsy	6 (22%)	12 (60%)	18 (38%)	20 (47%)
Ptosis	5 (19%)	12 (60%)	17 (36%)	2 (5%)
Nausea/vomiting	7 (26%)	6 (30%)	13 (28%)	6 (14%)
Dysphagia	7 (26%)	1 (0.5%)	8 (17%)	2 (5%)
Drowsiness	1 (4%)	4 (20%)	5 (11%)	1 (2%)
Confusion	2 (7%)	3 (15%)	5 (11%)	6 (14%)
Loss of consciousness	4 (15%)	4 (20%)	8 (17%)	2 (5%)

In participants with vertebrobasilar arterial dissection, the most common signs and symptoms were headache, neck pain, dizziness and unsteadiness. Headache was present in 23 (85%) participants, commonly in the occipital region (65% VBAD participants), but notably was not present in all participants and was not always severe. Dizziness was experienced by 14 (52%) participants. Unsteadiness or ataxia was present in 18 (67%) participants.

In participants with internal carotid dissection, the most common signs and symptoms were headache, ptosis, facial palsy, and upper and lower limb weakness. Headache occurred in 15 (75%) participants and was commonly reported in the retro-orbital (47%) or temporal (47%) regions. Ptosis and facial palsy each occurred in twelve (60%) participants, upper limb weakness in 13 (65%) cases and lower limb weakness in ten (50%).

In the control group, which comprised largely anterior circulation stroke, headache was a presenting feature in only 22 (51%) of participants and was not localised to any particular region. Dysphasia (30 participants, 70%), upper (32 participants, 74%), and lower limb weakness (26 participants, 60%), upper limb paraesthesia (20 participants, 47%) and facial palsy (20 participants, 47%) were much more commonly reported in controls.

Outcome of stroke

The majority (72%) of patients in both the dissection and control groups had a favourable outcome i.e. modified Rankin score (mRS) ≤ 2 . Table 3.6 shows the outcome in terms of disability expressed as a (mRS). A modified Rankin score of 2 means a patient is able to walk and manage their own affairs (van Swieten, Koudstaal et al. 1988).

Table 3.6 Stroke outcome in terms of disability - modified Rankin Score (mRS) n (%) for dissection and control participants.

mRS	Dissection participants N=47	Control participants N=43
Favourable ≤ 2	34 (72)	31 (72)
Unfavourable >2	10 (21)	8 (19)
Ungraded	3 (7)	4 (9)

DISCUSSION

The present investigation is the first retrospective study of craniocervical dissection patients from a manual therapy perspective. It is one of few case controlled studies of dissections and importantly used a representative sample of young strokes rather than those potentially more severe cases who might undertake medico-legal action. The

overarching aim was to identify key findings which may be of use to manual therapy practitioners in the management of patients presenting with neck pain or headache, and specifically to help therapists identify those patients in whom manual therapy may be inappropriate.

Risk factors

The main finding of our study in the identification of risk factors was that there was a statistically significant association of recent minor mechanical trauma, including manual therapy to the neck, and craniocervical dissection, in comparison to a control group. This finding is consistent with that of other authors investigating craniocervical dissection, though not all previous studies used a control group (Dziewas, Konrad et al. 2003; Touze, Gauthier et al. 2003; Dittrich, Rohsach et al. 2007). It is therefore important for manual therapy practitioners to be aware of the possibility of arterial dissection in a patient presenting with headache or neck pain and reporting a recent history of even minor head or neck trauma. In such cases, manual therapy practitioners should be particularly alert to the presence of other more subtle neurological signs and symptoms such as balance impairments, ptosis or visual disturbances. Moreover, the results of the study serve to caution practitioners to use minimal force when treating the cervical spine and to be alert to the potential dangers of a patient suddenly developing neck pain or headache following manual treatment to the neck (Smith, Johnston et al. 2003).

All presenting young stroke patients are routinely questioned about previous manual therapy to the neck in our neurology unit, so it was possible to compare this factor between the groups. Therefore the potential limitation of this question not having

being asked of the control patients was less likely in our study, although it is acknowledged that a negative response may not have always been recorded. However, when patients had reported prior manual treatment, no detail of the type or procedure was recorded. It was thus not possible to determine the relative risk of one type of manual therapy (e.g. manipulation), let alone specific technique, over another. Although therapists may feel safer in using gentler manual techniques, it should be borne in mind that the condition they are treating could in fact be a dissection mimicking a musculoskeletal presentation. Therapists must therefore be able to recognise a possible dissecting artery and expedite onward medical referral, rather than risk being implicated in the cause or potentially progressing the pathology (Cassidy, Boyle et al. 2008).

Although recent infections occurred more frequently in the dissection group and dissections were more common in autumn and winter compared to the control group, this factor was of borderline statistical significance in this study ($p=0.04$). This may have been due to low numbers of participants or reporting bias of minor conditions. Similarly information on blood results, which may have helped identify any inflammatory factors, was limited. Although information about recent infections or viral illness was reported as part of the normal history taken on admission to hospital, data were not available on their temporal relationship to the participant's stroke. Despite this, it may be prudent for clinicians to question patients about recent infection or viral illness and be cautious of more vigorous techniques in such cases.

Recently Kerry et al (2008) have recommended that manual therapists should consider vascular risk assessment (incorporating a system based approach) of patients

prior to treatment of the neck. However cardiovascular risk factors commonly associated with stroke were not strongly represented in this dissection group in comparison to the non-dissection controls. Data on cardiovascular risk factors in a similar age general population in Australia is not available except for smoking (20%). Smoking is reported as being slightly higher in the dissection group (33%) but this is about half the rate of the non-dissection group (65%) (Australian Institute of Health and Welfare 2005; Australian Bureau of Statistics 2009). Indeed, this study there was a mean of 1.4 cardiovascular risk factors per dissection participant compared with 3.23 in the non-dissection group. This suggests that in younger patients, routine assessment of such factors in the patient examination (e.g. taking of blood pressure) may not be particularly useful for manual therapists in determining the risk of adverse neurovascular events following manual therapy to the cervical spine.

Clinical presentation

Considering some current clinical recommendations and pre-manipulative guidelines for practitioners employing manual therapy for neck disorders (George, Silverstein et al. 1981; Rivett, Shirley et al. 2006; Kerry, Taylor et al. 2007), it is important to note that headache was not always present and not always severe in either vertebrobasilar or internal carotid artery dissection participants, although it was more common in vertebrobasilar (85%) and internal carotid artery dissection (75%) participants than controls (51%). Similarly, neck pain and dizziness were more likely to occur in vertebrobasilar than internal carotid artery dissection participants or controls. It was particularly surprising to find that dizziness was present in only 52% of the vertebrobasilar dissection participants, yet this symptom has often been stressed as

the primary clinical indicator of vertebrobasilar flow insufficiency (Grant 1988; Maitland 2005; Petty 2006). The presence or absence of nystagmus was rarely recorded, although other visual disturbances were reported. Ataxia or balance problems were also a fairly common finding in the vertebrobasilar dissection group (67%), so manual therapists should be alert to this finding in an assessment of a patient with neck pain or headache and perhaps consider formal testing of balance more routinely. Similarly findings for the internal carotid artery dissection participants suggest it may be appropriate to perform a focused cranial nerve examination (e.g. for facial palsy or ptosis) if specific symptoms are reported in the history or signs are evident on casual observation.

One of the main limitations of retrospective studies is that medical records are not always detailed and it is acknowledged that negative responses to questions in the history may not always be recorded. Details of blood results and radiological imaging were sometimes limited. Radiological imaging such as magnetic resonance angiography (MRA) and computerised tomographic angiography (CTA) are not always sensitive enough to detect the more subtle signs of dissection, in particular vertebral artery dissection (Levy, Laissy et al. 1994; Vertinsky, Schwartz et al. 2008). Furthermore, if imaging is not performed within a few days of the onset of symptoms it may not provide evidence of a dissection, despite an initial clinical diagnosis of dissection. Radiographic findings may change in a matter of days or even hours (Schievinck 2001). Indeed, in our study radiological confirmation of dissection was not possible in all participants; 11 participants did not have clear radiological evidence at the time the imaging was performed and in some cases this was a few weeks or even months after the onset of their symptoms. A further limitation of the

current study is that the sample size is modest, reflecting the relative rarity of craniocervical dissection and despite electronic records at a large tertiary teaching hospital being searched over a 12 year period. Finally, although the study was limited to participants under 55 years, as this is the sub-group in whom craniocervical dissection complications are most commonly reported, it is possible that other serious neurovascular complications may occur in older people.

Future studies should ideally be undertaken prospectively to ensure all relevant clinical information can be collected for both dissection and control cases, including timely imaging. Ideally future studies should also be multi-centre to ensure a greater number of participants are captured so that more meaningful analysis of associations can be made between groups for different factors.

Considering the results, there is clearly a significant association between recent minor mechanical trauma, including manual therapy, to the cervical spine and craniocervical dissection. Manual therapists should therefore be alert to such a history in patients presenting with head and neck pain and be prepared to perform a focused neurological examination, where indicated, for subtle neurological signs and symptoms. Practitioners should also be aware that these patients may present complaining of severe headache or neck pain, but not always, and that dizziness which has traditionally been associated with vertebrobasilar arterial dissection is only present in about half of the cases. It is anticipated that the results of this study will enable clinicians to better recognise a dissection in progress and the factors potentially associated with an increased risk of an adverse neurovascular event from manual therapy to the neck.

CONCLUSION

Recent minor mechanical trauma, including manual therapy to the cervical spine, is significantly associated with craniocervical dissection. General cardiovascular risk factors do not appear to be strongly represented in craniocervical dissection patients, suggesting they may not be useful indicators of the risk of adverse neurovascular complication associated with manual treatment of the neck. However, there may be other types of serious neurovascular complications which could indeed exhibit such factors. The utility of assessing for cardiovascular risk factors should therefore not be dismissed on these data alone. Manual therapists need to be aware of the more common symptoms of a dissection in progress, some of which may mimic a mechanical neck disorder, and be prepared to test for subtle neurological signs, such as imbalance or cranial nerve impairment.

The following chapter outlines the radiological findings in the cohort of radiologically confirmed craniocervical arterial dissection patients described in this chapter. The radiological features of the dissection on which diagnosis was based are reported and the topography of any resulting infarct described. These radiological features are then discussed in relation to the risk factors reported in the present chapter.

CHAPTER 4

STUDY 2: RADIOLOGICAL FEATURES OF CRANIOCERVICAL ARTERIAL DISSECTION AND THE TOPOGRAPHY OF THE RESULTANT INFARCT: RELATION TO RISK FACTORS

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METHOD

Design

Participants

Measurement of radiological features of craniocervical arterial dissection

Measurement of infarct topography

Measurement of risk factors

Statistical analysis

RESULTS

Characteristics of participants

Radiological features of craniocervical arterial dissection

Infarct topography

Relation between arterial wall deficits and risk factors

Relation between the occurrence of infarct and risk factors

DISCUSSION

Strengths and limitations of the study

CONCLUSION

The work presented in this chapter has been accepted for publication as:

- Thomas, L, Rivett, D, Levi, C (2012) Risk factors, radiological features and infarct topography of craniocervical arterial dissection. International Journal of Stroke. DOI:10.1111/j.1747-4949.2012.00912.x.

The definitive version is available at www.wileyonlinelibrary.com

The work has been presented as an oral presentation at the following conference:

- Thomas, L, Rivett, D, Levi, C. Radiological features of craniocervical arterial dissection and topography of the resultant infarct: Relation with risk factors. Stroke Society of Australasia meeting, Sydney, August 29-31 2012. International Journal of Stroke. September 2012 Volume 7, Issue Supplement S1, p 14.

INTRODUCTION

The diagnosis of craniocervical arterial dissection is generally based on history, clinical findings and radiological imaging (Vertinsky, Schwartz et al. 2008). Risk factors such as minor neck trauma, recent infection, vascular anomaly and connective tissue disease such as fibromuscular dysplasia have been identified (Schievinck 2001; Dittrich, Rohsbach et al. 2007; Thomas, Rivett et al. 2011). The standard reference for imaging the craniocervical vessels is catheter angiography but most centres usually use computed tomography (CT) and CT angiography or magnetic resonance (MR) and MR angiography as they are less invasive (Paciaroni, Caso et al. 2005).

There has been some debate in the literature as to the advantages of CT or MR in imaging the craniocervical vessels but it is generally considered that both are useful (Rodallec, Marteau et al. 2008; Provenzale 2009). (Vertinsky, Schwartz et al. 2008; Provenzale 2009). Limitations of angiography are that it only shows the lumen of the vessel so may miss a dissection or intramural haematoma if the contrast medium does not fill the false lumen (Rodallec, Marteau et al. 2008; Vertinsky, Schwartz et al. 2008). CT angiography has been considered more sensitive for imaging the vertebral artery but this may depend on the stage of the dissection healing (Rodallec, Marteau et al. 2008; Provenzale 2009). The haematoma resulting from a dissection tear may be isointense to surrounding tissues in the first few days following dissection and more easily visualised on CT as it has higher spatial resolution (Vertinsky, Schwartz et al. 2008) but subsequently the dissection may appear bright on MR as it detects the breakdown products of haemoglobin as the tear heals. Pathognomic findings of dissection on CT or MR include the presence of an intimal flap, double lumen, or a narrowed lumen surrounded by a crescent shaped hyperintense area of mural

thickening indicative of a mural haematoma but these are not always easily identifiable on imaging .

Cerebral infarcts are reported in 40-60% of patients with craniocervical arterial dissection. In internal carotid artery dissections infarcts are thought to be mainly embolic in origin and are commonly located in the cortex or sub cortically (Flis, Jäger et al. 2007) in the territory of the middle cerebral artery. Infarcts associated with vertebral artery dissection affect the posterior circulation and are commonly located in the cerebellum.

Previous research has generally identified case series of patients with craniocervical arterial dissection from hospitals stroke data banks or individual case studies. There have been a number of recent studies of the radiological features and risk factors for craniocervical arterial dissection. However, these were often limited by the lack of comparison with a control group and the inclusion of older patients in whom cardiovascular risk factors for stroke were more likely to be present (Haldeman, Kohlbeck et al. 2002; Haneline and Lewkovich 2005; Rizzo, Greco Crasto et al. 2006; Arnold, Pannier et al. 2009). There have been a number of studies where the pathological features of dissection have been described (Kumral, Bayulkem et al. 2004; Pelkonen, Tikkakoski et al. 2004; Schwartz, Vertinsky et al. 2009; Pfefferkorn, Saam et al. 2011). Studies have often focussed more on the comparison of MR, CT and conventional angiography in the natural history of craniocervical arterial dissection (Vertinsky, Schwartz et al. 2008). There have been few studies in which detailed description or mapping of the resultant infarct topography have been performed (Kumral, Bayulkem et al. 2004) to identify any distinctive features which

might make it more recognisable. There have been no studies where arterial wall findings present in craniocervical arterial dissection have been compared with reported risk factors, which might alert practitioners to inspect imaging more closely for such features in the presence of particular risk factors. The present study was therefore undertaken to investigate whether there was any association between particular risk factors for craniocervical arterial dissection and the nature of the radiological features and occurrence of cerebral infarct.

The aims of the current study were to identify patients under 55 years with radiologically confirmed or clinically suspected craniocervical arterial dissection, to describe the arterial wall abnormalities and topography of any associated infarction and to identify any association between previously reported risk factors and the site and radiological features of the dissection. The specific research questions were:

1. What are the radiological features including arterial wall abnormalities resulting from craniocervical arterial dissection?
2. What is the infarct topography resulting from cervical arterial dissection?
3. What is the relationship between radiological features including arterial wall abnormalities and risk factors for craniocervical arterial dissection?
4. What is the relationship between the occurrence of cerebral infarct and risk factors for arterial dissection?

METHOD

Design

The study was a retrospective case control study. The study formed a secondary subgroup analysis of the dissection group described in the previous chapter, Study 1. The

design is outlined in Figure 4.1. Participants were identified via the medical record system of the John Hunter Hospital between 1998 and 2009. The John Hunter is a large tertiary referral hospital of 550 beds which services the Hunter and Manning regions. These encompass a population of approximately 617,000 (Australian Bureau of Statistics 2009). The medical records database was searched for patients with radiologically confirmed or suspected vertebral or internal carotid arterial dissection using the international diagnostic coding system ICD-10 (World Health Organisation 2007). The following ICD-10 codes were used. :

- 1670 dissection of cerebral arteries non ruptured;
- 1630-1639 cerebral infarction unspecified;
- 1640 stroke not specified as haemorrhage or infection;
- 1660-1669 occlusion and stenosis of unspecified cerebral artery;
- 1650-1659 occlusion and stenosis of carotid artery.

As vertebral or internal carotid arterial dissection is a relatively uncommon diagnosis it is possible some dissection cases may have been miscoded and recorded as general stroke. So these categories were also searched as it was expected that dissection cases would at least be coded under one of these categories. An additional search strategy was also employed to interrogate the hospital electronic discharge referral system using keywords of vertebral or internal carotid artery dissection.

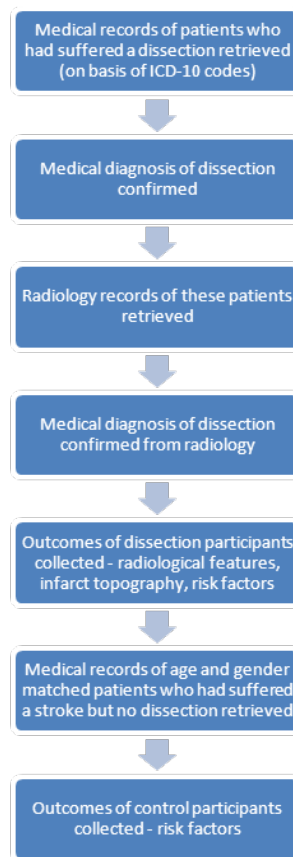


Figure 4.1 *Design of the study*

Medical records were retrieved from the database on the basis of the ICD-10 codes. As for Study one, the records were reviewed for a reported medical diagnosis of vertebral or internal carotid arterial dissection. The radiological imaging and reports were reviewed and only participants with a radiologically confirmed diagnosis of craniocervical arterial dissection were admitted to this study. Outcome measures for the dissection participants, specifically radiological features, infarct topography, demographic details and risk factors were collected from the medical records. The medical records of age and gender matched patients with stroke but not dissection were retrieved. Outcome measures for these control participants were collected,

specifically the presence of risk factors were identified. Data were recorded on a standardised proforma (see Appendix B).

In accordance with the local stroke management protocol, all cases with clinically suspected craniocervical arterial dissection had undergone both extracranial and intracranial vascular imaging with either CT or MR. All participants with suspected stroke related to craniocervical arterial dissection had undergone brain MRI. Imaging was performed on a 1.5T MRI system (Magnetom Vision; Siemens, Erlangen, Germany). Brain and vascular imaging was reviewed using a standardised proforma. The brain imaging was evaluated on-line by two experienced stroke neurologists (CL and MP) blinded to the case or control status. In the case of the imaging being unavailable on line, the descriptive details in the radiology report were used. The imaging diagnosis of confirmed craniocervical arterial dissection was made by consensus. The radiologic criteria applied were:

- The presence of a crescent sign, a crescentic rim of hyperintense signal seen on CT or T1 or T2 weighted MR images
- An increase in the external diameter of the vertebral or internal carotid artery, due to a thickening of the wall or narrowing of the lumen
- A long tapering stenosis shown by a ‘string sign’ characterised by a long segment of narrowing of the artery
- A “pearl and string sign” where the narrowing included one or more areas of dilation
- An intimal flap or double lumen
- An intramural thrombus

- A pseudoaneurysm or dissecting aneurysm, where the dissection has extended into the adventitial layer

Participants

Inclusion criteria for dissection participants were patients 55 years or less with a discharge diagnosis of radiologically confirmed vertebral or internal carotid artery dissection. The upper age limit was chosen as craniocervical arterial dissection occurs most commonly in the fourth and fifth decade before more traditional cardiovascular risk factors are likely to have developed. Patients were excluded if they had subarachnoid haemorrhage or dissection from iatrogenic causes.

Control participants were age and sex matched patients randomly selected from the hospital database with a clinico-radiological diagnosis of ischaemic stroke without dissection. Control participants were chosen so that the mean age and gender of the group matched that of the dissection group.

The following demographic information was collected for each participant: age, gender and arterial territory involved, and in the case of the dissection which side (right or left) vessel was involved. The type of imaging performed: CT or MR was recorded.

Measurement of radiological features of craniocervical arterial dissection

Radiological features of the cervical arterial dissection such as location and arterial wall abnormalities were recorded as present/absent and reported as frequency. The location of the dissection was defined as being in the intra or extra-cranial portion of

the artery and the specific site of the extra-cranial dissections was identified (e.g. skull base, axial loop or vertebral level). The arterial wall abnormalities were defined as the presence of a dissection or intimal flap or double lumen, a pseudoaneurysm or dissecting aneurysm, an intramural thrombus, a mural haematoma or a long tapering stenosis. Stenosis of the vertebral or internal carotid arteries was defined as a percentage reduction of the lumen of the artery; graded as <30%, 30-70%, 70% or occlusion >2cm.

Measurement of infarct topography

Infarct was defined in the acute phase of stroke as high signal on diffusion weighted imaging (B=1,000) and in the subacute phase as high signal intensity on FLAIR T2 weighted imaging. Location of the infarct was defined as either in the cerebellum, mid-brain, medulla, pons, occipital lobe, pons, brainstem or middle cerebral artery territory. Topography of the infarct was mapped schematically to show the frequency of infarct in the different locations.

Measurement of risk factors

Risk factors were recorded as recent head or neck trauma (in particular from manual therapy) or recent infection (ie, febrile illness) as well as the presence of vascular variant/anomaly or connective tissue disease such as fibromuscular dysplasia. Recent head or neck trauma was defined based on the work of Dittrich et al (Dittrich, Rohsbach et al. 2007) as heavy lifting, direct or indirect trauma to the head or neck, jerky or abrupt movements of the head, sexual intercourse, sporting activities or manual treatment of the neck in the preceding four weeks. Recent infection was defined as upper respiratory tract infection, gastroenteritis or urinary tract infection

diagnosed by a doctor or requiring antibiotic medication in the preceding four weeks. Vascular variant or anomaly of the posterior or anterior cerebral circulation was defined as aplasty of a vessel or vertebral artery ending in posterior inferior cerebellar artery.

Statistical analysis

Descriptive statistics were used to summarise demographic data, radiological features and risk factors. Simple logistic regression was performed for the major risk factors identified. All factors with a p-value ≤ 0.2 were included in a multiple logistic regression model; outcomes expressed as odds ratios 95% confidence intervals (CI). Statistical analysis was performed using STATA statistical/data analysis software (version 11, Statacorp, Texas, USA).

The study was approved by the local ethics committee.

RESULTS

Characteristics of participants

Thirty-six dissection participants and 43 control participants entered the study. Eleven suspected dissections were excluded due to lack of radiological confirmation of their diagnosis. The demographic characteristics of the 36 confirmed dissection participants and the 43 control participants are reported in Table 4.1. In the dissection group, the mean age was 36.9 years (SD 10) and 20 participants were male (56%). In the control group, the mean age was 42.6 years (SD 7.3) and 22 participants were male (51%).

Table 4.1 Characteristics of dissection and control participants

Characteristic	Dissection N=36	Control N=43	Difference between participants (P value)
Vertebral artery territory, n (%)	20 (56)	5 (12)	<0.0001
Internal carotid artery territory, n(%)	16 (44)	38 (88)	<0.0001
Age (yr), mean (SD)	37 (10)	43 (7.3)	=0.42
Gender, n males (%)	20 (56)	22 (51)	=0.70

Of the vertebral artery dissections, 12 were of the left vertebral artery, eight of the right. Of the internal carotid artery dissections, three were left sided, 12 right, and one bilateral. In the control group, 38 (88%) participants had sustained a stroke in the anterior cerebral circulation (i.e. carotid territory) and five (12%) participants had suffered a posterior circulation stroke (i.e. vertebrobasilar territory).

The majority (62%) of dissection participants had both CT and MR imaging. Twenty vertebral artery dissection and 15 internal carotid artery dissections were confirmed on MR, one internal carotid on CT. Five vertebral artery dissection participants had normal findings on CT but positive signs for dissection on MR.

Radiological features of craniocervical arterial dissection

Location of dissection

In the dissection group, dissection was identified in the extracranial vertebral artery in 20 (56%) participants and in the extracranial internal carotid artery in 16 (44%) participants. In six vertebral artery and four internal carotid artery participants, the dissection extended intracranially. Locations of dissections are shown in Table 4.2.

In the vertebral artery, the majority of dissections 14 (70%) occurred at the atlas loop or skull base (V3 segment) and one at the origin (V1 segment) (see Table 4.2). Six (30%) vertebral artery dissections extended intracranially (V4 segment) to involve the basilar artery. One participant had two sites of dissection (C2, C5). In the internal carotid artery, the majority of dissections (56%) occurred at the skull base or C2 level (cervical segment). Four (20%) of these extended intracranially within the skull base, one leading to sub-arachnoid haemorrhage (SAH). Interestingly, of the 13 vertebral artery dissection participants with a history of trauma, ten (77%) were at the atlas loop, and only 2 (33%) of these extended intracranially.

Table 4.2 Location of dissection in dissection participants (n, %)

Location of dissection	Vertebral artery N=20	Internal carotid artery N=16	All N=36
Extra-cranial	20 (100)	16 (100)	36 (100)
Atlas loop	12 (60)	4 (25)	16 (44)
Skull base	2 (10)	5 (31)	7 (19)
C3	2 (10)	3 (19)	5 (14)
C5/origin	1 (5)	0 (0)	1 (3)
Intra-cranial	6 (30)	4 (25)	10 (28)
Unspecified	3 (15)	3 (19)	6 (17)

Arterial wall abnormalities

Arterial wall abnormalities were evident in both vertebral and internal carotid artery dissections, characteristics are described in Table 4.3. Most commonly seen in vertebral artery dissections was a dissection or intimal flap, visible in twelve (60%), with five (25%) also showing a double lumen. The finding of a dissection flap was slightly less common in internal carotid artery dissections with only seven (44%) participants, six (38%) having evidence of a double lumen. All vertebral artery dissection and four of the internal carotid artery dissection participants with a dissection or intimal flap had a history of trauma.

Table 4.3 Arterial wall abnormalities in dissection participants (n, %)

Arterial wall abnormality	Vertebral artery N=20	Internal carotid artery N=16	All N=36
Dissection/intimal flap	12 (60)	7 (44)	19 (53)
Double lumen	5 (25)	6 (38)	11 (31)
Pseudoaneurysm	1 (5)	0 (0)	1 (3)
Dissecting aneurysm	2 (10)	3 (19)	5 (14)
Intraluminal thrombus	1 (5)	3 (19)	4 (11)
Mural haematoma	4 (20)	3 (19)	7 (19)
Long tapering stenosis	4 (20)	7 (44)	11 (31)
Stenosis	15 (75)	10 (63)	23 (64)
Occlusion	5 (25)	6 (38)	10 (28)
>70%	2 (10)	2 (13)	4 (11)
30-70%	4 (20)	2 (13)	6 (17)
<30%	2 (10)	0 (0)	2 (6)

Dissecting aneurysm (2 vertebral [10%], 3 internal carotid [19%]) and pseudoaneurysm (1 vertebral, 5%) were uncommon in both groups. Stenosis was present in 15 (75%) vertebral artery dissections and ten (63%) internal carotid artery dissections, and a long and tapering stenosis was identified in four vertebral artery dissections and seven internal carotid artery dissections. Most commonly in both types of dissection there was total occlusion of the vessel. Intraluminal thrombus and mural haematoma were much less commonly identified. Two internal carotid artery dissections had a subarachnoid haemorrhage secondary to dissection. Seven (70%) internal carotid artery dissections with stenosis <70% or occlusion also had infarction. Ten (75%) of the vertebral artery dissections also had infarcts but only 50% were <70% or occlusion.

Infarct topography

Infarction on MR was demonstrated in 23 (64%) participants. Of the vertebral artery dissections, 13 (65%) were in the cerebellum or medulla. Three participants had two different sites of infarction. Nine (56%) of the internal carotid artery dissection

participants showed infarction, mainly in the middle cerebral artery territory (see Table 4.4).

Table 4.4 Location of infarct in dissection participants (n, %)

Location*	Vertebral artery N=20	Internal carotid artery N=16
Infarct on MRI	14 (70)	9 (52)
Cerebellum	8 (57)	0 (0)
Mid-brain	2 (14)	0 (0)
Medulla	7 (50)	0 (0)
Occipital lobe	2 (14)	0 (0)
Pons	1 (7)	0 (0)
MCA territory	0 (0)	8 (89)
Brainstem	0 (0)	1 (11)

*some participants had infarct in more than one location. MCA= middle cerebral artery

Figure 4.2 shows the topography and frequency of infarction in the different topographies of the posterior cerebral circulation and Figure 4.3 shows the anterior circulation.

Interestingly, six (67%) vertebral artery dissection participants with infarction also had vascular anomalies. Thirty (70%) control participants had infarcts, the majority of which were in the middle cerebral artery territory.

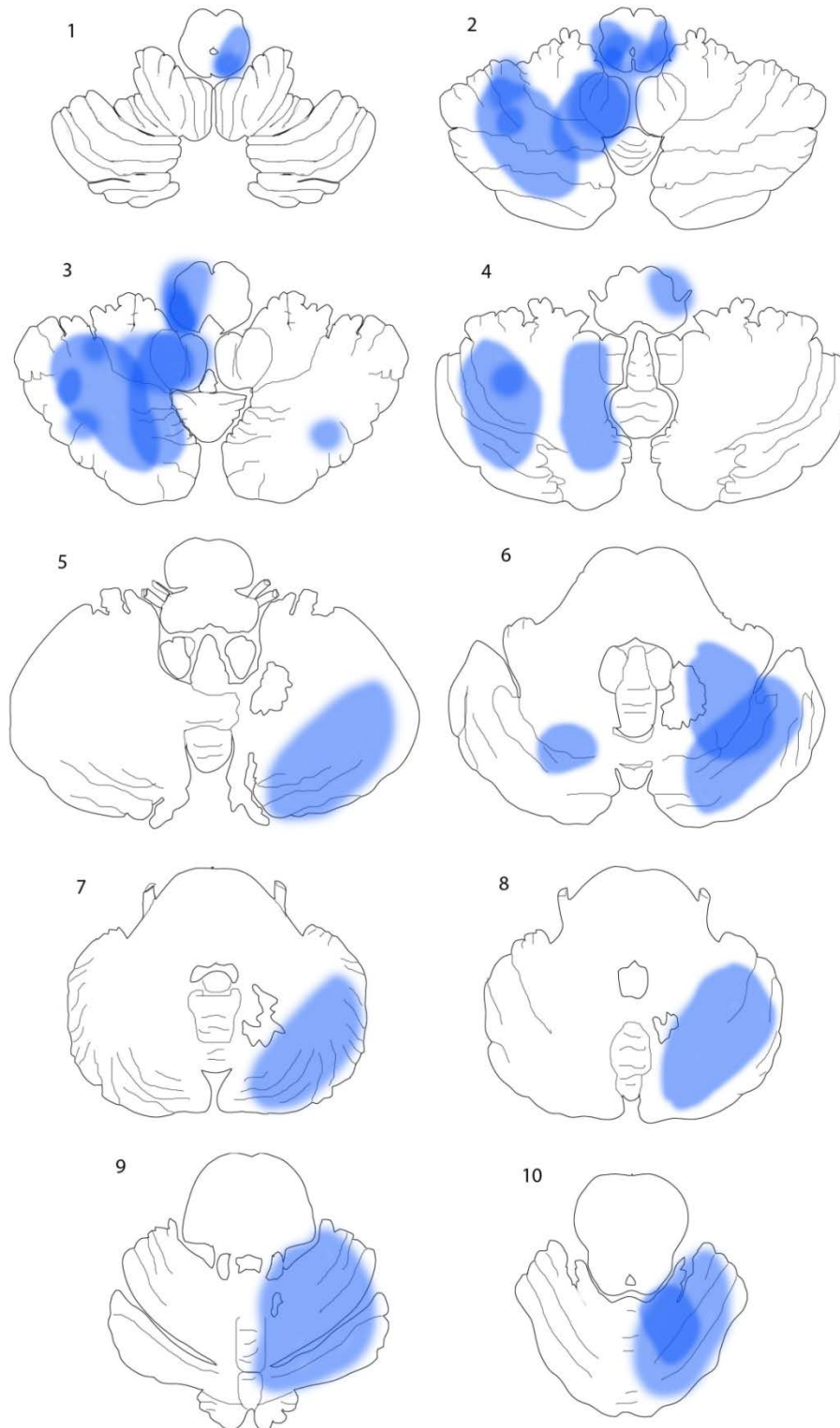


Figure 4.2 *Schematic representation of brain showing pooled topography of brainstem and hemispheric infarction of posterior circulation dissections (vertebral artery dissections). Pooled mapping of infarct topography performed by layering of individual topography using Adobe Photoshop CS5. An increase in colour density implies an increased frequency of infarction in a specific region.*

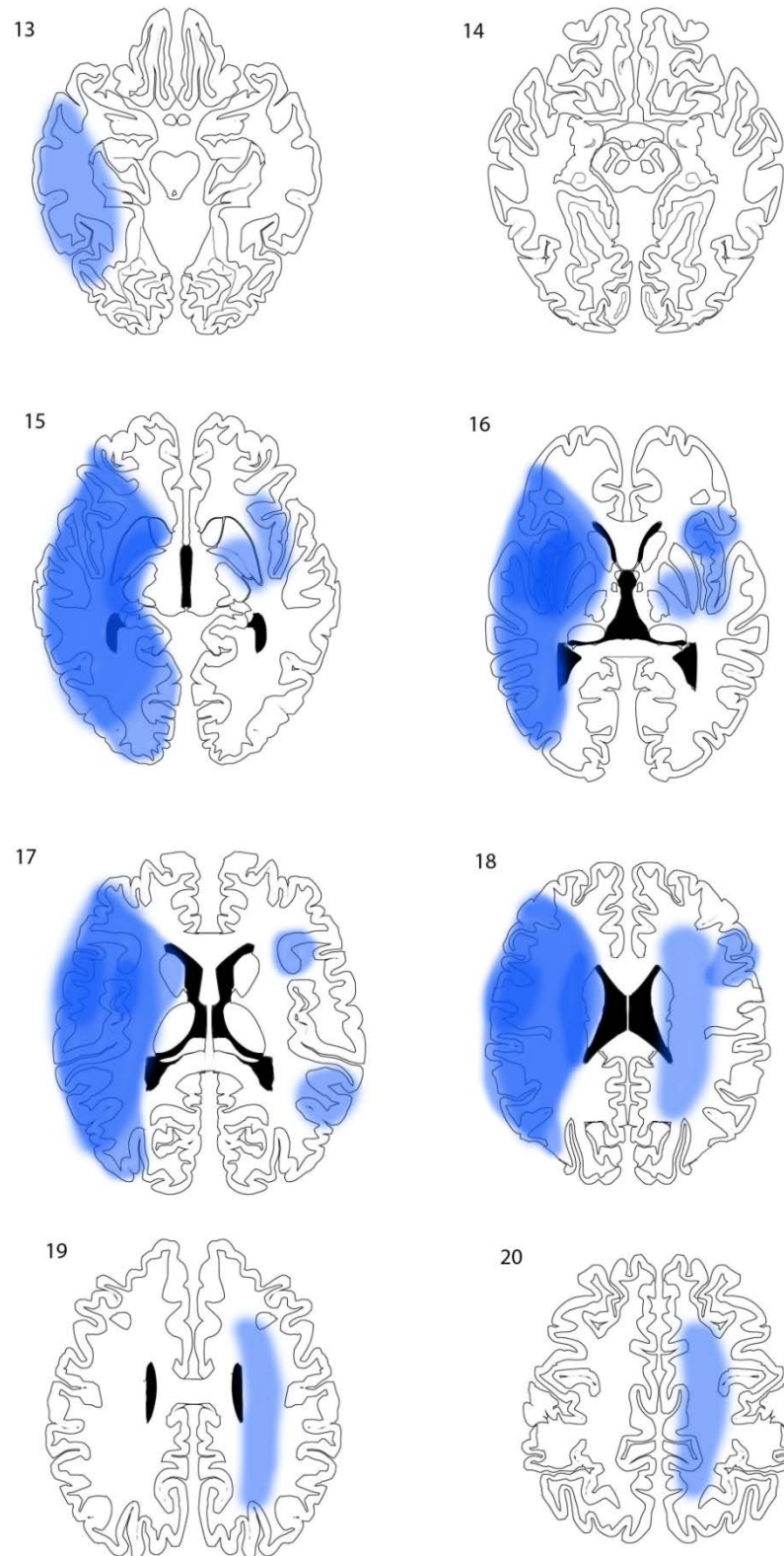


Figure 4.3 Schematic representation of brain showing topography of brainstem and hemispheric infarction of anterior circulation dissections (internal carotid artery dissections). An increase in colour density implies an increased frequency of infarction in a specific region.

Relation between arterial wall deficits and risk factors

The risk factors for the dissection and control participants are shown in Table 4.5.

Table 4.5 Risk factors for dissection and control participants (n, %)

Risk factor	Dissection			Control N=43	Difference between participants		
	Vertebra l artery N=20	Internal carotid artery N=16	All N=36		Odds ratio (95%CI)	Adjusted odds ratio* (95%CI)	P value
Recent head or neck trauma	13 (65)	10 (50)	23 (64)	3 (7)	26.67 (6.83,104.17)	25.29 (6.04,105.82)	<0.00
Recent manual therapy	6 (30)	1 (6)	7 (30)	1 (3)	12.0 (1.42,101.30)	12.67 (1.43,112.0)	0.02
Recent infection	4 (20)	4 (25)	8 (22)	4 (9)	1.94 (0.62, 6.08)	1.90 (0.58, 6.22)	0.29
† vascular variant/ anomaly	9 (45)	4 (25)	13 (36)	7 (16) (7 VA)	3.27 (1.14, 9.36)	4.46 (1.37, 4.6)	0.01
Fibromuscular dysplasia	1 (5)	1 (6)	2 (6)	0 (0)	N/A	N/A	N/A

* multiple regression analysis adjusted for age and sex

† Anomalies involving the posterior circulation such as ectatic or hypoplastic VA or VA ending in posterior inferior cerebellar artery

Recent head or neck trauma

Thirteen (65%) of the participants with vertebral artery dissection and 10 (50%)

internal carotid artery dissection had a history of minor mechanical trauma within the preceding three weeks, of these; seven (30%) participants (6 vertebral, 1 internal carotid) reported recent manual treatment of their neck by a chiropractor,

physiotherapist or masseur. In contrast, only three (7%) control participants had a history of recent mechanical trauma to the head or neck, and only one of these cases involved manual treatment of the cervical spine. Dissection participants were 26.67 (95% CI 6.83-104.17) times more likely to have been exposed to mechanical trauma than control participants. Nine (69%) vertebral artery and five (50%) internal carotid artery dissections with a history of trauma also had a cerebral infarct and all were extracranial. Vertebral artery dissection participants were more likely to have a

dissection flap (7 [54%]) or mural haematoma (4 [30%]), internal carotid artery dissections most commonly had a dissection flap (4 [75%]).

Recent infection

Eight (22%) of the dissection participants (4 vertebral, 4 internal carotid) had a recorded history of recent infection or viral illness prior to their admission to hospital, compared with just four (9%) of the control participants. Dissection participants were 1.94 (CI 0.62-6.01) times more likely to have been exposed to a recent infection than controls.

Vascular variant/anomaly

Thirteen (36%) of the dissection participants had radiological evidence of vessel anomalies mainly involving the posterior circulation, such as an ectatic or hypoplastic vertebral artery, or one ending in the posterior inferior cerebellar artery. One internal carotid artery dissection participant had an anterior circulation variant with an absent anterior cerebral artery. On the other hand, only seven (16%) control participants had a report of vessel abnormalities, these were all posterior circulation. Two participants (6%) had evidence of fibromuscular dysplasia. Dissection participants were 4.46 (CI 1.37, 14.6) times more likely to have a vascular anomaly ($p=0.13$) than control participants

Relation between the occurrence of infarct and risk factors

Nine (69%) vertebral artery dissections and five (50%) internal carotid artery dissections with a history of trauma also had a resultant cerebral infarct. For the vertebral artery dissections this was mainly in the cerebellum or medulla. Six (67%)

vertebral artery dissections with vascular anomalies also had infarction, mainly (4/6) in the medulla.

DISCUSSION

This study examined a group of young patients with craniocervical arterial dissection and reported in detail the arterial wall abnormalities and pooled mapping of the topography of the resultant infarct in the brain. Understanding of the particular radiological features of this condition is important as its recognition can sometimes be difficult (Provenzale, Sarikaya et al. 2011). The study found that the majority of dissections occurred extracranially, usually as a result of a tear of the intima of the artery. Infarction was present in 64% of dissection participants and most commonly involved the lateral medulla or cerebellum or middle cerebral artery territory in the case of internal carotid arterial dissection. Dissection participants were more likely than controls to have a history of mechanical trauma to the head or neck, particularly in the case of vertebral artery dissection, to have an intimal tear and show evidence of infarction. Dissection participants were more likely to have a vascular anomaly or anatomical variant and those with evidence of vascular anomaly were also more likely to show evidence of infarction.

The dissections most commonly occurred extracranially in the upper cervical spine, in the atlanto-axial (V3) segment of the vertebral artery and at the skull base or C2 level of the internal carotid artery. This is in agreement with other authors describing the location of craniocervical arterial dissection (Schievinck 2001; Provenzale 2009). Dissections where there was a history of trauma were more likely to be extracranial, 92% vertebral and 50% internal carotid artery dissections had a history of trauma to

the head or neck. Knowledge about common sites of dissection should prompt radiologists to explore these areas in particular when a dissection is suspected from the patient history. The site of dissection is also important given the current interest in drug therapies for dissection i.e. antithrombotic or endovascular treatment. For example, 28% of patients had an intracranial extension of their dissection, raising issues with the use of heparin, due to the risk of haemorrhage from the thinner intracranial portions of the artery.

The most common radiological feature was a dissection or intimal flap and stenosis of the vessel. This is in contrast with some recent studies suggesting that the dissection more commonly involves an intramural haematoma and is visualised as an increased external diameter and mural thickening of the artery (Lanczik, Szabo et al. 2005; Rodallec, Marteau et al. 2008). All vertebral arterial dissection participants with a history of trauma had evidence of an intimal tear. In patients with a history of mechanical trauma to the head or neck, it may be useful for radiologists to more closely inspect the upper cervical portions of the craniocervical arteries, in particular the vertebral artery, for features such as an intimal tear.

Cerebral infarction occurred in 64% of dissection participants, similar to previous findings (Pelkonen, Tikkakoski et al. 2004; Flis, Jäger et al. 2007). With pooled topographical mapping of the infarct territory in the dissection participants, it can be seen that for the posterior circulation, infarcts were most commonly located in the lateral medulla and relatively common in the anterior and posterior inferior cerebellar artery (AICA and PICA) territories. They were less common in the superior cerebellar artery territory and rare in the pons and mid-brain. Two participants also

had infarction in the occipital lobe indicating additional posterior cerebral artery involvement. Anterior circulation infarction was a mix of embolic and potential haemodynamic causes. Infarction involving the middle cerebral artery territory considered likely to be of embolic cause (Szabo, Kern et al. 2001; Pelkonen, Tikkakoski et al. 2004) were much more common, watershed infarctions involving the internal and external watershed, considered to be haemodynamic (Szabo, Kern et al. 2001; Pelkonen, Tikkakoski et al. 2004) were less frequently observed. This suggests that the lateral medulla and anterior and posterior inferior cerebellar artery territories should be closely inspected in the case of suspected vertebral artery dissection, for the presence of small areas of infarction. Similarly, where infarction is seen in these areas it may be useful to inspect the V3 segment of the vertebral artery for evidence of dissection.

Infarction was more commonly demonstrated in vertebral artery dissection than internal carotid artery dissection. Interestingly a high proportion of vertebral artery dissection participants with infarction also had evidence of a vascular anomaly or anatomical variant, mainly in the posterior circulation. It is possible that the presence of such vascular anomaly limited the potential for collateral flow to develop to compensate for flow deficits in another vessel and so infarction occurred more readily. Similarly, cerebral infarction in vertebral artery dissection participants tended to occur with a lesser degree of stenosis than in internal carotid artery participants, who tended to have stenosis < 70% for infarction to occur. This perhaps reflects the efficiency of collateral flow in the posterior circulation. Clinically, radiologists could consider that there may be a greater likelihood of infarction developing in a patient with dissection if they also have a vascular anomaly.

Exposure to an environmental trigger such as minor mechanical trauma to the head or neck certainly appeared to increase the risk of infarction. Fourteen (61%) dissection subjects with infarction had a history of trauma, in comparison with only three (7%) control participants. Participants with infarction from vertebral artery dissection were much more likely to have a history of trauma (85%) compared with internal carotid artery dissection (50%). This may be due to the greater tortuosity of the vertebral artery and its relative fixation within the cervical spine making it more vulnerable to insult, so that trauma in this situation applying greater stress to the arterial wall. Radiologists and neurologists should be particularly alert to the possibility of arterial dissection in a patient presenting with a history of minor head and neck trauma, particularly if there is no other more obvious mechanism or cardiovascular risk factors.

Strengths and limitations of the study

Strengths of this study are that it investigated a young group of participants so cardiovascular risk factors are less likely to have developed. Other studies may be confounded by the inclusion of older patients in whom atherosclerosis is more likely. In addition, radiology was reviewed post hoc by two reviewers until consensus and in most cases multimodal imaging was available. This made it less likely that subtle radiological features would have been missed. Detailed topographical mapping of the infarct territory was also performed which has not been previously undertaken, and this allowed a clear demonstration of the most commonly infarcted areas in dissection. This may be useful to prompt further radiological investigation for other features of dissection when infarcts are identified in areas such as the lateral medulla

or posterior inferior cerebellum. All young stroke patients in our unit are routinely questioned about trauma in addition to other risk factors for stroke. This allows for comparison of similar risk factors between dissection participants and controls.

One of the limitations of the study was that it was undertaken retrospectively and relied on the information available in the medical records. Radiological confirmation was possible in 77% dissections. Of the unconfirmed participants, imaging was performed at varying times after the onset of symptoms, in some cases several months. In other cases dissection was strongly suspected due to the history and clinical signs but pathognomic signs such as intimal flap or mural haematoma were not identifiable. It is possible that radiological confirmation may have been limited by late imaging and resolution of dissection signs, (Flis, Jäger et al. 2007). Vertebral artery dissection involving the posterior cerebral circulation was slightly more common (57%) than internal carotid artery dissection in this group, which is in contrast with other authors (Schievinck 2001; Flis, Jäger et al. 2007). However the size of the dissection group sample was modest and therefore may not reflect a true distribution of craniocervical arterial dissection. Finally, reporting bias may be present since young people presenting with posterior circulation strokes may be more likely to be questioned about neck trauma, if other more obvious causes of stroke cannot be identified.

CONCLUSION

Participants with craniocervical arterial dissection are more likely to have an extracranial dissection tear in the atlas loop region in the case of vertebral artery dissection or at C2 or the skull base in internal carotid artery dissection. It may be

useful for radiologists to thoroughly examine these regions for features such as an intimal tear where dissection is suspected. Intracranial extension was identified in about one in four participants prompting consideration of the choice of drug therapy because of the risk of intracranial haemorrhage. The majority of dissection participants demonstrate an intimal tear. The infarct topography of vertebral artery dissection typically involves the anterior and posterior inferior cerebellar territory and lateral medulla. A recent history of trauma to the head or neck was common in participants with dissection, particularly of the vertebral artery and clinicians should be alert to the possibility of this diagnosis in such patients where other more obvious causes of stroke cannot be identified. The presence of vascular anomaly was also high in dissection participants and was commonly associated with infarction. This suggests that infarction may be more likely to develop in patients who already have a vascular anomaly, so particular attention should be paid to identifying areas of infarction in such patients.

In Chapters 3 and 4 the results of retrospective studies of participants with craniocervical arterial dissection were presented and discussed. However as discussed, there are limitations as to the amount and quality of clinical information which can be ascertained, as well as the conclusions which can be drawn, from a retrospective review of medical records. In order to address the limitations of this methodology, the following chapter presents the preliminary results of a prospective study of participants with craniocervical arterial dissection. The prospective study design will allow validation of these earlier findings as well as enabling clinical information to be explored in greater detail and from a perspective which might be particularly pertinent to a manual therapy or primary care practitioner

CHAPTER 5

STUDY 3: RISK FACTORS AND CLINICAL PRESENTATION OF CRANIOCERVICAL ARTERIAL DISSECTION: PRELIMINARY RESULTS OF A PROSPECTIVE STUDY

INTRODUCTION

METHOD

Design

Participants

Measurement of risk factors for craniocervical arterial dissection

**Measurement of presenting clinical features of craniocervical arterial
dissection**

Measurement of early warning signs

Statistical analysis

RESULTS

Characteristics of participants

Risk factors

Presenting clinical features of craniocervical arterial dissection

Early warning signs

DISCUSSION

Risk factors

Clinical presentation

Early warning signs of dissection

CONCLUSION

Some of the work in this chapter has been published as:

- Thomas, L, Rivett, D, Levi, C (2012). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Study protocol. BMC Musculoskeletal Disorders. 13:164 - 169.

The work has been presented as oral presentations at the following conferences:

- Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. Oral presentation. International Federation of Orthopaedic Manipulative Physical Therapists 2012. Quebec City, Canada October 1-5 2012.
- Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. Oral presentation. Australian Physiotherapy Association. Brisbane. October 27-30 2011.
- Thomas, L, Rivett, D, Levi, C (2011). Risk factors and clinical features of craniocervical arterial dissection. A prospective study: Preliminary results. Oral presentation. World Confederation of Physical Therapy Congress: World Physical Therapy 2011. Amsterdam, Netherlands June 20-23 2011.

INTRODUCTION

The complex nature of the aetiology of craniocervical arterial dissection was introduced in chapter three and is explored in greater detail in the following chapter. The aetiology of craniocervical arterial dissection is not fully understood and many cases have been described as occurring spontaneously when no obvious mechanism can be identified (Norris, Beletsky et al. 2000). However, craniocervical arterial dissection is generally considered to include contribution from both intrinsic and extrinsic factors. It has been suggested that the mechanism involves a pre-existing intrinsic susceptibility (such as an underlying arteriopathy) and a precipitating event (Schievinck 2001; Arnold, Cumurciuc et al. 2006; Debette and Leys 2009; Schievink and Debette 2011). The underlying arteriopathy may be in the form of a vascular anomaly, a genetic pre-disposition (Brandt, Hausser et al. 1998) such as a subclinical connective tissue disease, or may be a transient situation, perhaps caused by an infection or pro-inflammatory state, giving rise to a temporary friability of the vessel wall (Volker, Besselman et al. 2005; Pfefferkorn, Saam et al. 2011). In patients with an existing susceptibility, exposure to a precipitating event, such as minor mechanical trauma or activities imparting some stress to the neck, may trigger a dissection of the artery (Dittrich, Rohsbach et al. 2007). Such trauma is usually fairly innocuous such as might occur during the course of normal daily activities. Frank trauma, such as motor vehicle accident, has not usually been reported (Norris, Beletsky et al. 2000; Debette, Grond-Ginsbach et al. 2011).

Cervical spine manipulation has been hypothesised to be one type of minor trauma or stress on the neck which may cause craniocervical arterial dissection. This has raised concerns amongst manual practitioners as to whether the nature of a manipulative

technique is responsible for reported cases of craniocervical arterial dissection or inadequate differential diagnosis of the patient's condition has been made. Notably, the clinical presentation of craniocervical arterial dissection typically includes neck pain or headache which may in many cases mimic a migraine or a musculoskeletal disorder (Schievinck 2001; Arnold, Cumurciuc et al. 2006; Debette and Leys 2009). It is possible therefore, that a dissection might not be recognised, particularly in the absence of clear ischaemic (or neurological) features, and the patient may present for treatment from their primary care practitioner or manual therapist for the painful symptoms which are in reality from a dissection in progress (Cassidy, Boyle et al. 2008).

Previous research has primarily involved retrospective studies of craniocervical arterial dissection (Schievinck 2001; Rubinstein, Peerdeman et al. 2005; Debette and Leys 2009) which have shown conflicting findings in respect of the presence of particular risk factors, such as cardiovascular factors (Debette and Leys 2009). Exposure to minor mechanical trauma of the neck has been shown to be associated with dissection by a number of studies (Haldeman, Kohlbeck et al. 1999; Dziewas, Konrad et al. 2003; Haneline and Lewkovich 2005; Dittrich, Rohsbach et al. 2007). However, detailed characterisation of the types of trauma and direction of force application has been limited. Retrospective studies are often limited and biased by the information available in medical records, highlighting the need for prospective studies which include interviews of patients close to the time of their dissection.

Previous prospective studies which have been undertaken have tended to be from large hospital series and were therefore medically focussed, relying on information

collected routinely in the medical records and did not use a physical interview (Dittrich, Rohsbach et al. 2007; Arnold, Pannier et al. 2009). Importantly, they may also have been subject to selection bias if inclusion was at the discretion of the investigators based on the information available in the records. Some studies have also lacked age limitations so may have included patients with atherosclerosis or other age-related conditions, and did not always include a control group for comparison. In particular, studies generally report limited historical details about activities, events, or the occurrence of any transient ischaemic features in the weeks preceding hospitalisation which might facilitate early recognition of dissection. These details are of particular interest to primary care practitioners to assist them to more readily identify patients at risk of dissection or those who may be presenting with early signs and symptoms.

The recognition of potential risk factors for craniocervical arterial dissection is problematic, particularly for manual therapists in the clinical situation. Arteriopathy and vascular anomaly can only be identified by radiological imaging which is not readily available for screening purposes in the clinical situation. It has been suggested by some authors that therapists should consider assessment of vascular risk factors for all patients for whom manual treatment for the neck is proposed (Kerry, Taylor et al. 2008). Typical risk factors for cardiovascular disease such as hypertension or elevated blood cholesterol are not thought to be strongly associated with dissection, since patients are in a younger age group so less likely to have developed conditions such as atherosclerosis (Schievinck 2001). However, some studies have shown that cardiovascular risk factors are similar between craniocervical

arterial dissection cases and controls (Pezzini, Caso et al. 2006; Arnold, Pannier et al. 2009).

It has been argued that the timely recognition of potential risk factors and subtle early presenting neurological signs or symptoms of craniocervical arterial dissection is critical (Debette and Leys 2009) so that the patient is not exposed to inappropriate manual treatment of the neck. Early recognition is also critical in the case of a patient presenting with a dissection in progress, so that referral for appropriate medical management can be made promptly. There is also a need to characterise the presenting features of vertebral and internal carotid artery dissection, in particular ischaemic features, with more descriptive detail so as to aid recognition of the significance of early signs and symptoms. These features have only been documented in a limited way in previous studies, such as might be collected in a medical interview, with little descriptive detail or appreciation of the patient's interpretation of these signs and symptoms. More detailed information might be useful to assist primary care practitioners such as manual therapists in the recognition of such features.

In manual therapy texts and guidelines on the safety of manual therapy in the cervical spine much emphasis has been placed on the identification of vertebrobasilar insufficiency, an insufficiency of blood flow to the hindbrain, as an indicator of risk of dissection (Rivett, Shirley et al. 2006). Pre-manipulative screening protocols have often focussed on the dizziness as a warning sign of vertebro-basilar insufficiency, and severe, unusual headache or neck pain as the main presenting features of arterial dissection (George, Silverstein et al. 1981; Schievinck 2001; Rivett, Shirley et al.

2006). However, it is possible that other clinical features may be earlier and more useful indicators of the presence of dissection and associated vertebrobasilar insufficiency. Identification of early clinical features related to dissection of the craniocervical arteries may help in the prompt recognition of these conditions in patients presenting to physiotherapists and other primary care practitioners.

In chapter three, the risk factors and clinical features of craniocervical arterial dissection were described retrospectively. The medical records of 47 patients ≤ 55 years who had suffered a vertebral or internal carotid dissection were examined, and it was found that 64% had a recent history of minor mechanical trauma to the neck (Thomas, Rivett et al. 2011). Other preceding events and proposed risk factors such as recent infection and hypertension were less well documented. This study was limited by inconsistent recording of data in the medical records. Hence the current study was designed to investigate the risk factors identified by the retrospective study and to describe in greater detail the nature of presenting clinical features of craniocervical arterial dissection in a prospective group of patients. This will help improve recognition of this serious pathology and identify those patients at risk from neurovascular adverse event subsequent to manual therapy of the neck.

The aim of the current study were to identify patients 55 years or less with radiologically confirmed vertebral or internal carotid arterial dissection and prospectively investigate putative risk factors compared with a control group and report presenting clinical features of dissection. The specific research questions were:

1. Are the following putative risk factors associated more with vertebral or internal carotid arterial dissection than stroke from another cause?
 - Recent minor mechanical trauma to the head or neck
 - cervical spine manual therapy, specifically high velocity or end range rotational techniques or deep upper cervical soft tissue massage
 - recent infection, febrile illness or clinical markers of pro-inflammatory states
 - vascular anomaly or anatomical variant
 - connective tissue disease
 - cardiovascular risk factors
2. What are the presenting clinical features of craniocervical arterial dissection?
3. Are there early warning signs (such as antecedent ischaemic neurological features) for craniocervical arterial dissection?

METHOD

Design

The study was a prospective case-control design examining patients with craniocervical arterial dissection and age- and gender-matched controls with ischaemic stroke but without dissection. The flow of participants through the study is shown in Figure 5.1. People with a radiological diagnosis of dissection of the vertebral or internal carotid artery were identified on admission to hospital and approached by the treating neurologist to participate in the study. The treating neurologist was blind to the specific study aims and investigators were blind to participant medical history prior to their entry into the study. Following admission to the study, one of the investigators interviewed the participants and reviewed their

medical records using a standardised data extraction proforma, to collect information about presenting features, risk factors, preceding activities and medical history. Dissection participants were then matched by one of the investigators for age and gender with control participants who were admitted to hospital with stroke from another cause than dissection, identified on radiological imaging. The investigator was blind to the details of their medical history other than their stroke diagnosis prior to matching. Information about presenting features, risk factors, preceding activities and medical history was collected for the control participants in the same way as for the dissection participants. Ethics approval was obtained from the Hunter New England Human Ethics Committee and all participants gave their informed consent before data was collected.

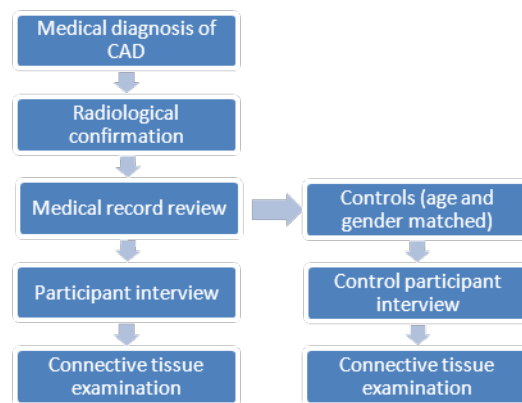


Figure 5.1 *Design of the study*

Participants

Patients presenting to hospital in the Hunter region of New South Wales, Australia were included if they were aged 55 years or less, had a radiological diagnosis of extracranial vertebral or internal carotid arterial dissection (with or without stroke) and gave their informed consent to be included in the study. Participants were excluded if they had craniocervical arterial dissection of iatrogenic origin or presented with subarachnoid haemorrhage, because this is a rare condition with distinctively different presenting features from dissection. Patients with primary intracranial dissection were also excluded as this is commonly associated with subarachnoid haemorrhage.

The diagnosis of craniocervical arterial dissection was confirmed by radiological review. Imaging was performed using computed tomography (CT) or magnetic resonance imaging (MRI), as ordered by the admitting neurologist. Radiological imaging was reviewed online by two neurologists to describe the radiological features. Similarly to the retrospective study in Chapter 4, the radiologic criteria (Rodallec, Marteau et al. 2008) applied were visualisation of the following typical features of dissection:

- The presence of a crescent sign, a crescentic rim of hyperintense signal seen on CT or T1 or T2 weighted magnetic resonance images
- An increase in the external diameter of the vertebral or internal carotid artery, due to a thickening of the wall or narrowing of the lumen
- A long tapering stenosis shown by a ‘string sign’ characterised by a long segment of narrowing of the artery

- A “pearl and string sign” where the narrowing included one or more areas of dilation
- An intimal flap or double lumen
- An intramural thrombus
- A pseudoaneurysm or dissecting aneurysm, where the dissection has extended into the adventitial layer

Cerebral infarction was defined as high signal on diffusion weighted imaging (B=1,000) in the acute phase and as high signal on FLAIR T2 weighted imaging in the subacute phase.

Control participants were recruited from age- and gender-matched patients who had a stroke from some other cause than dissection. Stroke (cerebral infarction) was identified on radiological imaging as described previously

In order to describe the sample, we collected the following information from the medical records: age, gender, burden of stroke, location of the dissection and stroke arterial territory, ie, vertebral or internal carotid artery and the number of participants with dissection but without stroke. Burden of stroke was collected from the discharge summary; details of residual signs and symptoms and by the Modified Rankin Score (mRS) (van Swieten, Koudstaal et al. 1988) and National Institute of Health Stroke Score (NIHSS) (Brott, Adams et al. 1989). The mRS is widely used for assessing global outcomes following stroke. The score is out of six where zero denotes full recovery, six denotes death and a score of two or less means a patient is able to walk and manage their own affairs (van Swieten, Koudstaal et al. 1988). The mRS has

been demonstrated to have acceptable inter-rater reliability ($\kappa = 0.71-0.95$) (van Swieten, Koudstaal et al. 1988; Wolfe, Taub et al. 1991; Wilson, Hareendran et al. 2005). The NIHSS is a well validated tool used in the evaluation of neurological deficit in stroke patients (Kasner 1999). It has moderate to excellent inter-rater reliability (ICC 0.82), and high validity ($r=0.68$) when compared to infarct volume on CT imaging (Lyden and Grau 1991; Kasner 1999).

Measurement of risk factors for craniocervical arterial dissection

The following putative risk factors for craniocervical arterial dissection were sought, based on the findings of the retrospective study: minor mechanical trauma to the neck, recent infection, vascular anomaly, connective tissue disorder and cardiovascular risk factors. Factors were compared between cases and controls. Risk factors were identified by a review of the medical records of dissection and control participants and further details and clarification were obtained by a structured interview when the participant was medically stable. The interview was undertaken by the student researcher who is a registered physiotherapist with post-graduate qualifications in manual therapy and 28 years of clinical experience. All details were recorded on a data extraction proforma (see Appendix B).

Minor mechanical trauma

Minor mechanical trauma was defined based on the work of Dittrich et al (Dittrich, Rohsbach et al. 2007) as :

- Heavy lifting >25 kg or with activation of maximum effort
- Sexual intercourse
- Mild direct trauma to the neck such as a direct blow

- Indirect trauma to the neck such as a mild whiplash injury
- Jerky head movement with abrupt deviation of the head >30°
- Sports activity with greater than usual effort e.g. jogging >45 minutes
- Cervical spine manipulation or manual treatment of the neck

Participants were specifically questioned about exposure to minor mechanical trauma or stress to the neck during the preceding month. This information was collected during the patient interview and from the medical notes on admission. If any trauma was reported, specific descriptive details of the amount of force involved and direction of movement of the head and neck were sought from the patient.

If the participant had undergone recent manual therapy in the preceding month, descriptive details of the therapeutic procedure received were sought from the participant during the interview in order to identify any potentially hazardous practices such as high-velocity thrust manipulation, end-range rotational mobilisation techniques or deep upper cervical soft tissue massage.

Recent infection

Recent infection was defined as any infection or febrile illness such as upper respiratory tract infection, gastroenteritis or urinary tract infection, reported by the patient within the last month. Details of the type and severity of the condition, whether it was confirmed by a health professional and the need for medical intervention, such as antibiotic treatment were recorded. Details of haematological results at time of admission; specifically full blood count, erythrocyte sedimentation rate, C-reactive protein, immunological studies and coagulation times were collected

from the medical records. These were examined for the presence of existing clinical markers of pro-inflammatory factors. These details were collected from the medical notes and from the patient interview

Vascular anomaly

Vascular anomaly or anatomical variant was defined as radiological evidence of a hypoplastic or aplastic cerebral artery or an anomalous course or termination of a cerebral artery e.g. a vertebral artery ending in posterior inferior cerebellar artery.

Evidence of vascular anomaly or anatomical variant was identified from the review of radiological imaging of the participants.

Connective tissue disorder

Connective tissue disorder was defined as a medical diagnosis of a known connective tissue disease such as Ehler's Danlos or Marfan's syndrome or fibromuscular dysplasia. Mild connective disorder was defined as the presence of joint hypermobility, skin hyperextensibility or skin fragility. These features were measured using a 25-item scale (Dittrich, Heidbreder et al. 2007) (see Appendix B). A sum score of all positive items was calculated, where 0 = no disorder and scores >10 = strong disorder. The cut off used for the presence of connective tissue disorder was eight, based on the work of Dittrich (Dittrich, Heidbreder et al. 2007). The examination included tests for joint hypermobility and skin fragility and extensibility. Also included were additional questions about prior tendency to bruising or scarring, a reported history of hypermobile joints and the ability to contort the body as a child. Measurement of joint hypermobility included items comprising the Beighton scale (Beighton and Horan 1969). This has been shown to have good inter-rater reliability

(ICC 0.72, 0.79) (Hicks, Fritz et al. 2003; Fritz, Piva et al. 2005). Skin extensibility was measured manually by pinching the skin on the volar aspect of the forearm one third of the distance from the elbow to the wrist with the elbow at 90° or in extension. Skin was pulled up and the distance measured and quantified as $\leq 1\text{cm}$, $>1\text{cm}$, $>2\text{cm}$, $>3\text{cm}$, $>4\text{cm}$, $>5\text{cm}$, with the pathological level determined as $> 2\text{cm}$ (Remvig, Duhn et al. 2009).

Cardiovascular factors

The presence of cardiovascular factors were defined as a reported medical diagnosis of hypertension, hypercholesterolemia, history of smoking, diabetes, migraine, family history of young stroke and contraceptive pill use. The type and number of cardiovascular risk factors was recorded.

- Hypertension was defined as a systolic pressure $>140\text{ mmHg}$ and diastolic pressure >90 according to National Heart Foundation guidelines (Heart Foundation 2004).
- Smoking (yes/no)
- Hypercholesterolemia was defined as a total cholesterol level $> 200\text{ mg/dL}$ (PubMed Health 2011).
- Oral contraceptive pill use (yes/no)
- Family history of young stroke $< 55\text{ years}$ (yes/no)
- Migraine (medical diagnosis of migraine, on medication for migraine, self-report of migraine) (yes/no)
- Diabetes (medical diagnosis of type one or type two diabetes)

Details of cardiovascular risk factors were collected from the medical notes and patient interview.

Measurement of presenting clinical features of craniocervical arterial dissection

Detailed characterisation of the features that commonly present during the process of both vertebral and internal carotid artery dissections was made. Clinical features were categorised into headache, neck pain and ischaemic features for both vertebral and internal carotid artery dissection, and were investigated under the following headings:

- Headache (presence, location, severity)
- Neck pain (presence, location, severity)
- Facial palsy (presence of ptosis/ Horner's syndrome)
- Visual disturbance (presence of blurred/diplopia/hemianopia,)
- Speech disturbance (presence of dysarthria/dysphasia such as expressive/receptive, dysphonia)
- Balance disturbance (presence of dizziness/imbalance/unsteadiness/falls)
- Paraesthesia (presence, location such as upper limb/lower limb, face/tongue)
- Weakness (presence, location such as upper limb/lower limb)

Questions about clinical features not expected to be present were also included as distractors (e.g. presence of chest pain and altered cognition). In the case of headache or neck pain, the location of the pain was recorded on a body chart and the severity of the pain was defined as mild moderate or severe. Information was initially sought in the medical notes and additional details, including the time frame of onset of signs and symptoms, were obtained from a patient interview.

Measurement of early warning signs

Early warning signs of dissection were defined as any transient headache, neck pain and in particular ischaemic signs and symptoms which may have occurred at any

time during the month preceding their admission to hospital. This information was obtained as part of the medical records review and participant interview

Statistical analysis

The projected sample size was 40 patients and 40 controls, based on ten participants per prognostic indicator (Peduzzi, Concato et al. 1995). Indicators evaluated include: mechanical trauma, recent infection, vascular anomaly and cardiovascular factors, based on a review of the literature (Haldeman, Kohlbeck et al. 1999; Debette and Leys 2009; Thomas, Rivett et al. 2011). Preliminary results are presented for 20 participants that took three years to collect. Due to the relative infrequency of craniocervical arterial dissection cases, it is estimated that it will take a minimum of three more years to collect the full sample.

Descriptive and comparative statistics were used to summarise and analyse the demographic data, burden of stroke and risk factors. Comparative statistics were used to compare risk factors between dissection and control participants. Simple logistic regression was performed for all the major risk factors identified, with outcomes expressed as odds ratios and 95% confidence intervals (95% CI), alpha was set at 0.05. Clinical features including early warning signs or symptoms were reported using descriptive statistics. Statistical analysis was performed with STATA statistical analysis software (version 11, Statacorp, Texas, USA)

RESULTS

Characteristics of participants

Twenty participants with craniocervical arterial dissection and twenty control participants with ischaemic stroke, but not dissection, were recruited to the study. The demographic characteristics of the participants are presented in Table 5.1. The mean age of the dissection group was 43.7 years (SD 7.6) and eleven participants (55%) were male, while the mean age of the control group was 39.6 years (SD 11.6) and eleven participants (55%) were male. Nine (45%) dissection participants had sustained vertebral artery dissection and eleven (55%) an internal carotid artery dissection. In general, the burden of stroke in the study was not high for either dissection or control groups (mRS <2), however one dissection participant died and two were left substantially incapacitated.

Table 5.1 **Characteristics of participants**

Characteristic	Dissection N=20	Controls N=20
Age (yr), mean (SD)	43.7 (7.6)	39.6 (11.6)
Gender, n male (%)	11 (55)	11 (55)
Burden of stroke		
Mod Rankin Score (0 to 6), mean (SD)	1.3 (1.6)	1.2 (1.3)
Location of stroke, n (%)		
vertebral artery territory	9 (45)	4 (20)
internal carotid artery territory	11 (55)	16 (80)
Dissection without stroke, n (%)	2 (10)	0 (0)

Risk factors

Risk factors identified for craniocervical arterial dissection and control participants are presented in Table 5.2. The odds ratios for differences between the two groups are also shown.

Table 5.2 Risk factors for dissection and control participants (n, %) and difference between groups expressed as odds ratios (95% CI) and p values

Risk factor	Dissection			Control	Difference between groups
	Vertebral artery N=9	Internal carotid artery N=11	All N=20	N=20	Dissection group relative to control group
Minor mechanical trauma	8 (89)	6 (55)	14 (70)	0 (0)	53.40 (7.5 to inf) p<0.001
neck manual therapy	2 (22)	1 (9)	3 (15)	0 (0)	4.19 (0.43 to inf) p=0.23
Recent infection	1 (11)	3 (27)	4 (20)	2 (10)	2.21 (0.27 to 27.5) p=0.66
Vascular anomaly	1 (11)	3 (27)	4 (20)	2 (10)	2.21 (0.27 to 27.5) p=0.66
Connective tissue disorder					
diagnosed	0 (0)	2 (18)	2 (10)	1 (5)	2.07 (0.10 to 131.0) p=1.0
mild > 8 points*	0 (0)	0 (0)	0 (0)	0 (0)	-
Cardiovascular					
hypertension	1 (11)	3 (27)	4 (20)	6 (30)	1.0 (0.21 to 4.8) p=1.0
smoking	3 (33)	2 (18)	5 (25)	9 (45)	0.42 (0.08 to 1.9) p=0.32
cholesterol	0 (0)	0 (0)	0 (0)	9 (45)	0.05 (0 to 0.4) p=0.001
oral contraception	0 (0)	2 (18)	2 (10)	7 (35)	0.34 (0.05 to 1.9) p=0.27
family history	1 (11)	0 (0)	1 (5)	1 (5)	1.0 (0.01 to 82.6) p=1.0
migraine	4 (44)	4 (36)	8 (40)	2 (10)	5.74 (0.92 to 64.6) p=0.06
diabetes	0 (0)	0 (0)	0 (0)	3 (15)	0.24 (0 to 2.3) p = 0.23

* Using scale described by Dittrich et al (2007)

Mechanical trauma

Fourteen (70%) dissection participants reported a recent history of minor mechanical trauma to their neck. This was more common for vertebral artery dissection participants (89%) than for internal carotid artery dissection participants (55%). The details of the type of trauma are summarised in Table 5.3. The reported mechanism

of trauma largely fell into three main categories: jerky or abrupt head movement, intensive physical effort, and sustained extreme positions of the neck. The most commonly reported jerky or abrupt head movements included sporting activities involving hyper-extension or lateral deviation of the neck, such as catching a volley ball overhead or playing a Wii™ rugby game, and during other vigorous pursuits such as racing a go-kart over rough ground. Five participants reported this type of trauma. Another five participants reported a recent history of undertaking activity involving extreme or unusual physical effort: three of these participants reported a history of lifting and carrying heavy objects on one shoulder, while two participants reported a history of recent extreme forced expiratory effort, one during childbirth with her head sustained in full cervical flexion for an extended period, the other weight lifting (> 50 kg) at the gym. Two further participants had undertaken intensive exercise at the gym; one a daily 30 minute high impact/explosive type cardiovascular exercise, the other running for over 45 minutes on a treadmill whilst partially supporting their bodyweight through the arms. The final two participants had sustained a dissection following an activity involving prolonged straining of the neck into hyper-extension; in one case through a difficult dental extraction, the other while undertaking overhead painting of his house over three days.

Interestingly, eight dissection patients also reported a past history of head trauma in the last five years, which included previous motor vehicle accidents, hitting the head causing fracture of the T1 vertebral body, and wearing a heavy helmet at work. None of the control participants reported any history of trauma. Dissection participants were 53.4 (95% CI 7.5 to inf) times more likely to have been exposed to recent

mechanical trauma to the neck than control participants, and this was statistically significant ($p < 0.001$).

Table 5.3 **Types of mechanical trauma experienced by dissection participants (n, %)**

Type of mechanical trauma	Dissection group		All N= 20	Control group N=20
	Vertebral artery N=9	Internal carotid artery N=11		
Jerky or abrupt head movement (hyperextension or lateral deviation)	5 (56)	0	5 (25)	0
Intensive effort during exercise or activity	2 (22)	3 (27)	5 (25)	0
Manual therapy	2 (22)	1 (9)	3 (15)	0
Prolonged strain of neck into hyperextension	0	2 (18)	2 (10)	0

One participant reported two types of trauma

Cervical spine manual therapy

Three participants had undergone recent chiropractic treatment of their neck in the month prior to their dissection; in one case this had reportedly involved deep massage to the sub-occipital region and in two cases treatment had involved rotary high velocity thrust manipulation to the cervical spine. Dissection participants were 4.19 (95% CI 0.43 to inf) times more likely to have undergone recent manual therapy to the neck than control participants. This was not statistically significant.

Recent infection

Four (20%) craniocervical arterial dissection participants reported having had a recent infection. This was more common in participants with internal carotid artery dissection (27%) than those with vertebral artery dissection (11%). In three cases this was an upper respiratory tract infection requiring antibiotics, with one participant reporting a recent gastroenterological infection. Two control participants reported a

recent infection; one had a tooth abscess, the other pneumonia. Blood testing did not identify any consistently abnormal clinical markers suggestive of a prior infective process in either the craniocervical arterial dissection or control group. Dissection participants were 2.21 (95% CI 0.27 to 27.5) times more likely to have had a recent infection than controls but this was not statistically significant.

Vascular anomaly or anatomical variant

Four (20%) dissection participants and two (10%) control participants had a vascular anomaly or anatomical variant. One vertebral artery dissection participant had an anomalous vertebral artery connection to the basilar artery; two internal carotid artery dissection participants had an anomalous origin of their left vertebral artery; and two participants with internal carotid artery dissection had a beaded appearance of their arteries consistent with fibromuscular dysplasia. One dissection participant had two anomalies. Dissection participants were 2.21 (95% CI 0.27 to 27.5) times more likely to have had a vascular anomaly or anatomical variant than control participants but this again was not statistically significant.

Connective tissue disorder

Two (10%) dissection participants and one (5%) control participant had a diagnosed connective tissue disorder. The two internal carotid artery dissection participants had fibromuscular dysplasia and the control participant had Marfan's syndrome and had recently undergone surgery for an anomalous cardiac valve. No participants demonstrated any evidence of a mild connective tissue disorder on physical examination. Dissection participants were 2.07 (95% CI 0.10 to 131.0) times more likely to have a connective tissue disorder, but this was not statistically significant.

Cardiovascular factors

Cardiovascular risk factors were not strongly represented in the dissection group with the exception of migraine. Eight (40%) dissection participants had a medically diagnosed past history of migraine and were 5.74 (95% CI 0.92 to 64.6) times more likely to suffer from migraine than control participants ($p=0.06$). Four (20%) dissection participants had hypertension during their admission and five (25%) dissection participants were current smokers. In contrast, all control participants had at least one cardiovascular risk factor (average 2.3 factors, compared with 0.9 for dissection participants); the most commonly reported factors were cholesterol (45%), smoking (45%), oral contraception (35%) and hypertension (30%). Control participants were statistically more likely to have elevated cholesterol levels than dissection participants ($p = 0.001$). In addition, control participants were more represented in co-morbidities compared with dissection participants, such as diabetes (15%). Dissection participants were otherwise generally healthy with no major health concerns.

Presenting clinical features of craniocervical arterial dissection

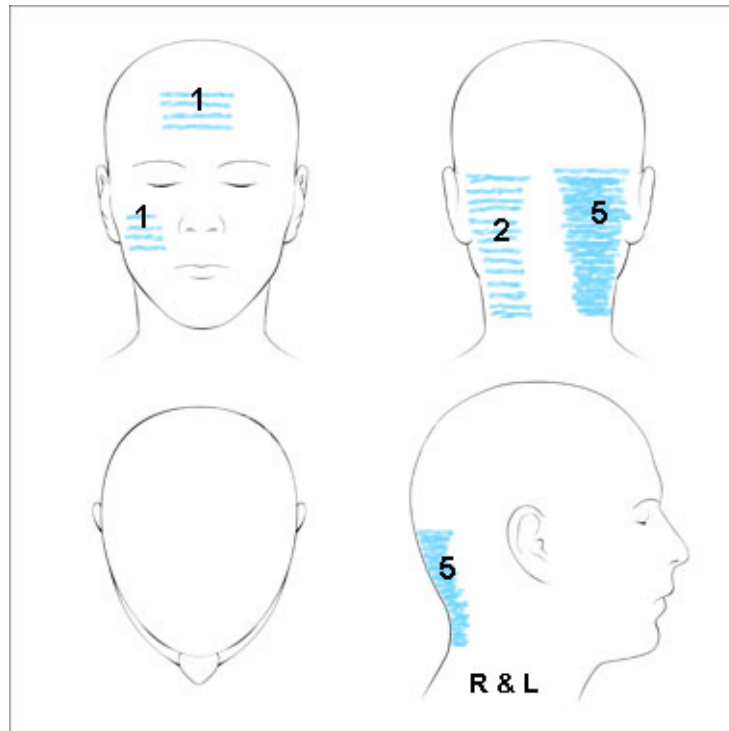
The presenting clinical features of the dissection group are reported in Table 5.4.

Table 5.4 Number of participants (%) presenting with each clinical feature

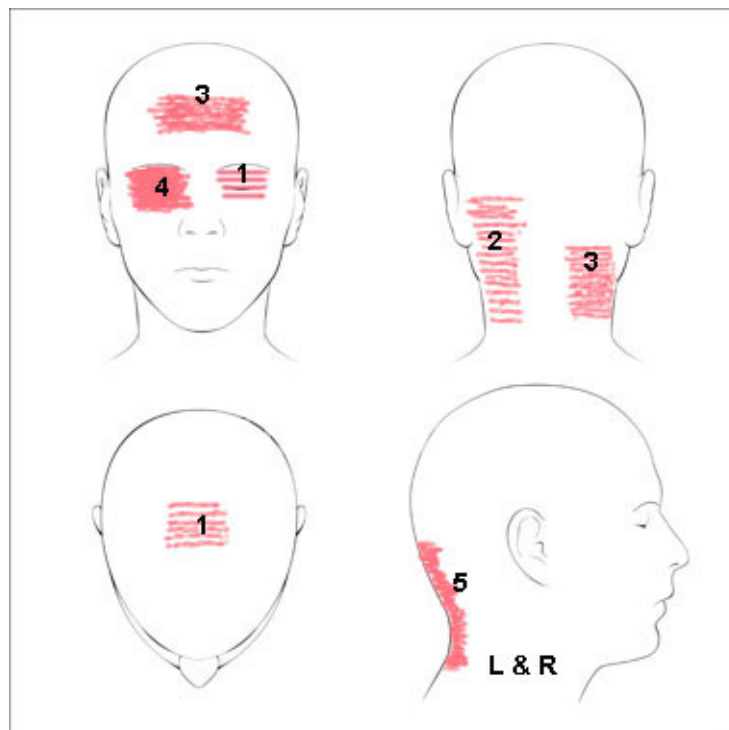
Clinical features	All N=20	Vertebral artery dissection N=9	Internal carotid artery dissection N=11
Headache	16 (80)	8 (89)	8 (73)
Neck pain	12 (60)	7 (78)	5 (45)
Facial palsy	7 (35)	2 (22)	5 (45)
ptosis	6 (30)	1 (11)	5 (45)
Visual disturbance	8 (40)	5 (56)	3 (27)
Speech disturbance	14 (70)	7 (78)	7 (64)
Balance disturbance	9 (45)	8 (89)	1 (9)
Dizziness	9 (45)	7 (78)	2 (18)
imbalance	9 (45)	7 (78)	2 (18)
Paraesthesia	9 (45)	5 (56)	4 (36)
facial/tongue	5 (25)	3 (33)	2 (18)
limb	8 (40)	4 (44)	4 (36)
Limb weakness	13 (65)	7 (78)	6 (55)

All dissection participants

In most dissection participants (80%), headache was a presenting feature of their dissection, but in only thirteen participants (65%) was this described as moderate or severe. Some participants described the headache as ‘unusual’, but this was not the case for all participants, particularly if they had a history of migraine. Ten participants (50%) presented with both neck pain and headache, and two participants presented with neck pain only, though one later developed headache in hospital. In vertebral artery dissection participants, the headache was mainly located in the occipital region (78%), but two participants had frontal or facial pain (Figure 5.2a). In the internal carotid artery dissection participants, headache location was mainly frontal or retro-orbital (64%) (Figure 5.2b), but two participants reported occipital and neck pain.



a)



b)

Figure 5.2 *Distribution of headache and neck pain in participants with a) vertebral artery dissection, and b) internal carotid artery dissection*

The most commonly presenting ischaemic features were speech disturbance (70%), limb weakness (65%), paraesthesia (40%), visual deficit (40%), and dizziness and imbalance (45%), but these features were distributed variably according to the vascular territory involved.

Presenting clinical features of vertebral artery dissection

The specific presenting features of vertebral artery dissection in comparison to internal carotid artery dissection are shown in Table 5.4. Six (67%) participants presented with both headache and neck pain. Two (22%) participants presented with headache only, and one with neck pain only. Pain intensity was reported as moderate or severe by six participants and only mild by three participants. Most commonly, in those reporting neck pain or headache, the pain was in the occipital region (78%) and in the neck (78%) ipsilateral to the side of the dissection. Two (22%) participants reported frontal or facial pain; the facial pain was ipsilateral to the dissection, the frontal pain was bilateral. The most common ischaemic feature was balance deficit. Eight (89%) participants reported balance problems; most commonly this was described as a generalised unsteadiness but three participants presented with ataxia and four reported veering to one side. Seven (78%) participants reported dizziness; in one case this was rotational in nature but most participants described the dizziness as light headedness or a feeling of imbalance. Seven (78%) participants reported speech impairment as a presenting feature of their dissection, and this was dysarthria (difficulty with talking), but two participants also reported dysphasia (difficulty finding or losing words). Visual disturbance was present in five (56%) participants, who mainly described blurred vision or difficulty focussing.

Presenting clinical features of internal carotid artery dissection

The specific presenting features of internal carotid artery dissection in comparison to vertebral artery dissection are shown in Table 5.4. Eight (73%) participants presented with headache and in six of these the pain intensity was described as severe. Four (36%) participants reported headache and neck pain. Headache was mainly located in the retro-orbital (36%) area ipsilateral to the dissection or in the frontal area (27%) where it was distributed bilaterally in all cases. However, two (18%) participants had ipsilateral occipital pain and one described headache on the top of the head. One participant reported neck pain only. The most frequent ischaemic features for participants with internal carotid artery dissection were ptosis, speech disturbance and limb weakness. Seven (64%) participants presented with speech disturbance, most commonly this presented as dysarthria (55%), but three (27%) participants experienced dysphasia and one (9%) was aphasic. Five (45%) participants presented with facial palsy and ptosis, and six (55%) presented with limb weakness. Visual deficit and dizziness or balance problems were not major presenting features of internal carotid artery dissection in this sample.

Early warning signs

Fourteen (70%) dissection participants reported early warning signs demonstrated by antecedent ischaemic neurological features or unusual headache or neck pain in the preceding five weeks. Headache or neck pain appeared to have presented similarly frequently in both the vertebral and internal carotid artery dissection groups, but neurological features, in particular dizziness and visual disturbance appeared more frequently in the vertebral artery dissection group, however the results need to be interpreted with caution due to the small sample to date. These early warning signs

are reported in Table 5.5. In most cases participants had interpreted these clinical features as being due to other more benign causes.

Table 5.5 Number of participants (%) with ‘early warning’ signs and symptoms

Warning signs and symptoms	All N=20	Vertebral artery dissection N=9	Internal carotid artery dissection N=11
Unusual headache or neck pain	9 (45)	4 (44)	5 (45)
Facial paraesthesia	1 (5)	1 (11)	0 (0)
Visual disturbance	4 (20)	3 (33)	1 (9)
Speech disturbance	2 (10)	1 (11)	1 (9)
Dizziness	4 (20)	3 (33)	1 (9)
Imbalance	3 (15)	2 (22)	1 (9)
Upper limb paraesthesia	3 (15)	2 (22)	1 (9)
Upper limb weakness	2 (10)	1 (11)	1 (9)

DISCUSSION

This prospective study examined young patients with craniocervical arterial dissection with the aim of improving the early identification of this often difficult to diagnose condition. Detailed clinical information was collected from participants via an interview and medical record review to identify putative features which might be useful to identify those at risk from manual therapy applied to the neck, or those who may be presenting in the early stages of a dissection. A prospective study of this nature has not previously been undertaken with such a primary care focus. The preliminary results of the study suggest that minor mechanical trauma to the head or neck may be associated with dissection. This is consistent with the findings of our retrospective study (Chapter 3). General cardiovascular risk factors, with the

possible exception of migraine, do not seem to be important risk factors for dissection, which also reflects the findings of our retrospective study, and suggests these factors may not generally be useful as indicators of risk. Moreover, the findings indicate that headache and neck pain, speech disturbance, limb weakness, and to a lesser degree dizziness and imbalance and paraesthesia were the main presenting features of dissection. Importantly, 70% of dissection participants reported antecedent transient ischaemic features prior to their admission to hospital, which is considerably higher than reported rates of transient ischaemic episodes prior to general stroke which are reported as being between 3.8 and 15.7% (Deitelzweig, Ogbonnaya et al. 2010). This finding has not been identified in previous studies.

The preliminary findings of this prospective study highlight some important points for consideration by primary care practitioners, and those using manual therapy, when assessing a patient presenting with head or neck pain and a recent past history of trauma to the head or neck. The findings may also help expedite medical management for patients presenting with this serious condition.

Risk factors

The main results of this study are consistent with the findings demonstrated in Chapter 3 and with other reports (Haldeman, Kohlbeck et al. 1999; Rubinstein, Peerdeman et al. 2005; Debette and Leys 2009) that recent minor mechanical trauma or strain to the neck appears to be associated with craniocervical arterial dissection ($p < 0.001$). All control participants were questioned but none reported recent exposure to minor trauma or stress to the head or neck. None of the trauma reported by dissection participants was frank or extreme as found by other authors (Norris,

Beletsky et al. 2000), but did involve some stress to the neck sufficient to be discernible by the participant. Only a small proportion of dissection participants (20%) had had recent manual therapy to the neck, including manipulation but also arguably less vigorous manual techniques such as deep sub-occipital massage. However, one participant suffered a dissection during chiropractic manipulation and subsequently died. The type of minor trauma seemed to fall into three main categories: activities involving abrupt or jerky movements of the head particularly into extension or laterally, activities involving extremes of physical effort such as Valsalva type manoeuvres or intensive gym exercise, and activities involving sustained extreme positions of the neck such as hyperextension. This is similar to the categories identified by Dittrich and colleagues (Dittrich, Rohsbach et al. 2007) requiring some unusual effort such as heavy lifting > 25 kg, sporting activity > 45 min, jerky head movements or forced expiratory effort. It could be useful, therefore, for practitioners to question patients about recent experience of this type of minor trauma or any other stress of the neck.

A history of recent infection was present in 20% of dissection participants but this was not significantly different from control participants in this study ($p=0.66$). This is in contrast to our retrospective study and some other studies (Guillon, Berthet et al. 2003; Lindsberg and Grau 2003; Caso, Paciaroni et al. 2005) so the non-significance of this finding in the present study may perhaps be due to the small sample to date. Recent infection was, however, reported more frequently in participants with internal carotid arterial dissection (27%) than vertebral (11%). Despite the non-significance of our preliminary results, a finding of recent infection in 20% of all dissections and 27% in participants with internal carotid artery dissection, suggests that it may still be

useful for practitioners to specifically question patients about recent infection prior to manual treatment of the neck. Further results of our study may confirm whether this factor is indeed a useful indicator of risk. It is important to note that in this study a history of recent infection was not always recorded in the medical notes and was sometimes discovered during the interview, so may be under-reported in studies relying only on data retrieval from medical records.

Vascular anomaly similarly, was present in 20% of dissection participants and occurred more frequently in participants with internal carotid artery dissection, but this was not significant in this study ($p=0.66$). This was in contrast with our retrospective study (Chapter 3) and other studies (Debette and Leys 2009) where vascular anomaly has been more frequently reported, but our study sample is modest to date. Clinical signs of mild connective tissue disorder were not identified in this group of dissection participants, though 10% had a diagnosed disorder. This suggests that examination for joint hypermobility or skin elasticity may not be particularly useful to pursue in pre-manipulative screening or patient assessment prior to manual treatment of the cervical spine.

Cardiovascular risk factors, with the possible exception of migraine, were not strongly represented in the craniocervical arterial dissection group, which suggests that they may not be useful indicators of risk of dissection. This is consistent with the findings of our retrospective study but would seem not to support recommendations of other authors who have advocated general cardiovascular screening should be undertaken by practitioners prior to any manual treatment of the cervical spine (Kerry, Taylor et al. 2008). Despite a bare non-significant finding in this study, 30%

more dissection participants were migraine sufferers than control participants, which is consistent with previously reported findings (Tzourio, Benslamia et al. 2002; Metzo, Tatlisumak et al. 2012). Twenty-five percent of craniocervical arterial dissection participants were smokers, which is similar to general population figures for this age group (Australian Bureau of Statistics 2009). Smoking has been shown to be associated with higher blood levels of inflammatory mediators (Wannamethee, Lowe et al. 2005; Csiszar, Podlutzky et al. 2009), which may have implications for vessel wall friability. However, the present study did not identify elevated blood levels of any particular clinical inflammatory markers amongst participants. In summary, given the relatively high rate of migraine in the dissection group this should be considered by clinicians as a potential risk factor for dissection. However, it may be difficult clinically to differentially diagnose a headache caused by dissection from migraine in such patients.

Clinical features

The initial presenting clinical features of craniocervical arterial dissection were commonly headache and neck pain, which can make differential diagnosis from a musculoskeletal disorder difficult. In the dissection group, the reported headache or neck pain was not always severe as often reported in other studies (Arnold and Bousser 2005; Thanvi, Munshi et al. 2005), although it was commonly described by participants as being different from any previous or usual pain (Arnold and Bousser 2005). In addition, the site of the headache did not always equate to typically reported sites of pain for vertebral artery dissection and internal carotid artery dissection, for example some vertebral artery dissection participants experienced retro-orbital pain and some internal carotid artery dissection participants experienced

occipital pain. Thus, location and severity of pain may not be particularly helpful features to assist in the differential diagnosis of dissection from other more benign causes of headache and neck pain.

Of the most commonly reported ischaemic features for vertebral artery dissection, speech disturbance (mainly dysarthria) and balance disturbance (including dizziness and imbalance), weakness, paraesthesia and visual disturbance also occurred relatively frequently in participants. Interestingly however, only 45% of all dissection participants reported dizziness and imbalance which seems lower than the common understanding of the importance of such features in craniocervical arterial dissection, for example in pre-manipulative guidelines (Rivett, Shirley et al. 2006; Kerry, Taylor et al. 2007) where dizziness is highlighted as a key feature, although dizziness was somewhat higher in the vertebral artery dissection group (78%). It is suggested practitioners take care to question patients presenting with headache and neck pain about other ischaemic features and not to overlook mild or transient signs, such as visual and speech disturbances. The commonly reported presenting ischaemic features in participants with internal carotid artery dissection were less definitive, but included signs such as facial palsy, limb weakness and speech disturbance.

‘Early warning signs’ of dissection

An important finding in terms of early identification of craniocervical arterial dissection is that a high proportion (70%) of dissection participants did report transient antecedent ischaemic neurological features in the month previous to their dissection. It should be noted that to date the sample is modest, so such high rates may not be sustained in the full sample. However, this is considerably higher than the

recognised occurrence of transient ischaemic symptoms prior to general stroke, which is around 10% (Deitelzweig, Ogbonnaya et al. 2010). This finding of antecedent ischaemic features in dissection has not been reported by other authors, perhaps because most studies are retrospective and therefore biased against collecting a true sample of antecedent signs and symptoms as they generally only rely on available information in medical records. Our study is one of only a few prospective studies of dissection participants and it is possible that we were able to identify this finding because we utilised a participant interview close to the time of dissection.

Of the most common antecedent features, visual deficit (usually blurred vision, although one patient reported transient hemianopia), dizziness/imbalance and speech disturbance (usually dysphasia) were most frequent. These features were typically of short duration, up to half an hour. Interestingly, one of these participants continued to attend a chiropractic clinic for treatment whilst experiencing dizziness and imbalance, yet no action was taken by the chiropractor to investigate the participant further and manual treatment was continued. This suggests that perhaps such ischaemic features are not well recognised by manual therapy practitioners. This is perhaps not surprising given they are uncommonly seen in manual therapy practice. In most cases, the participants themselves had disregarded the significance of these features and had written them off as being due to other causes such as aging. For example, in explanation of the report of transient blurred vision one participant said “I had turned 40 so I thought I was getting old and might need glasses”, and to his reports of transient dysphasia and dizziness, “I thought I was just was tired and stressed”. This perhaps highlights the need for practitioners to specifically interrogate patients when they present with unusual neck pain or headache, particularly when

there is a recent history of minor trauma to the neck, migraine or perhaps infection. Specifically, it may be useful for practitioners to question such patients about changes in vision, speech, balance or muscle power in the last month.

Limitations of the study include the small sample size, and data collection is continuing to address this. The findings to date however have largely reflected the findings of the retrospective study while providing additional detail about preceding events and clinical features. The prospective study design with a patient interview does still rely on participant recall and information in the medical records. However, this potential limitation is addressed by interviewing participants close to the time of their stroke to minimise problems with recall as far as possible. In addition, as the participant is generally still in hospital at the time of interview, further information could be sought from the medical staff if required to limit the problem of missing data in medical files inherent in retrospective studies.

CONCLUSION

Minor mechanical neck trauma appears to be an important feature in craniocervical arterial dissection and patients should be carefully questioned about this when they present with moderate to severe or unusual neck pain or headache. While cervical manual therapy was not often reported prior to dissection, one participant suffered a dissection during chiropractic treatment and subsequently died. It is therefore important that practitioners consider the possibility that patients may present for treatment of the headache or neck pain arising from a dissection in progress. Less vigorous manual therapy techniques such as deep upper cervical massage may also be implicated. General cardiovascular risk factors appear not to be associated with

dissection so may be less useful predictors of risk prior to manual treatment of the neck, with the possible exception of migraine. There may be transient ischaemic signs and symptoms as ‘warning signs’ in the preceding few weeks prior to dissection, and these may be important clinical findings for practitioners to specifically seek out to assist them with early identification of dissection. Primary care practitioners should question patients for any signs of visual disturbance, dizziness and balance, arm paraesthesia or speech deficits if they present with unusual headache or neck pain with recent history of minor neck trauma or possibly migraine.

These previous three studies (Chapters 3, 4 and 5) have described and evaluated the risk factors for dissection and its early clinical features in both a retrospective and prospective group of participants with craniocervical arterial dissection. The following chapter investigates the other aspect of risk associated with manual therapy to the neck, that of the safety of the manual procedures themselves. This chapter reports the final study which investigates blood flow in the craniocervical arteries during common manual therapy procedures, to assess the relative safety of neck positions utilised in particular therapeutic techniques. This study aimed to identify any neck positions which were potentially more hazardous than others in terms of blood flow in the craniocervical arteries or which compromised blood flow to the brain. The flow findings in these therapeutic neck positions may help inform safety decision-making in manual therapy practice.

CHAPTER 6

STUDY 4: THE EFFECT OF SELECTED MANUAL THERAPY INTERVENTIONS FOR MECHANICAL NECK PAIN ON VERTEBRAL AND INTERNAL CAROTID ARTERIAL BLOOD FLOW AND CEREBRAL PERFUSION: AN EXPERIMENTAL STUDY

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Measurement of total blood supply to the brain

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DISCUSSION

Strengths and limitations of the study

Future research

CONCLUSION

The work in this chapter has been submitted for publication as:

- Thomas, L, Rivett, D, Bateman, G, Levi, C (2013). The effect of selected manual therapy interventions for mechanical neck pain on vertebral and internal carotid arterial blood flow and total cerebral perfusion. *Physical Therapy*. Published ahead of print June 27, 2013, doi:10.2522/ptj.20120477.

The work has been presented as an oral presentation at the following conference:

- Thomas, L, Rivett, D, Bateman, G, Levi, C. The effect of selected manual therapy interventions for mechanical neck pain on vertebral and internal carotid arterial blood flow and total cerebral perfusion. International Federation of Orthopaedic Manipulative Therapists. Quebec City, Canada, October 1-5, 2012.

INTRODUCTION

Manual therapy including high velocity manipulation is commonly used for the treatment of neck pain and associated headache but has in rare cases been associated with serious adverse events (Haldeman, Kohlbeck et al. 1999; Thiel, Bolton et al. 2007; Cassidy, Boyle et al. 2008) as discussed previously. As seen in the retrospective and prospective studies, Chapters 3, 4 and 5, these events most commonly involve compromise of the craniocervical arteries i.e. the vertebral or internal carotid arteries in the neck (Frisoni and Anzola 1991; Assendelft, Bouter et al. 1996; Hurwitz, Aker et al. 1996; Haldeman, Kohlbeck et al. 1999; Caso, Paciaroni et al. 2005; Paciaroni and Bogousslavsky 2009). Compromise of these arteries may directly alter blood flow to the brain causing insufficiency of blood flow to the hind brain (vertebro-basilar insufficiency) or cause a tear or dissection of the intimal or medial layer of one of the arteries (Caso, Paciaroni et al. 2005; Paciaroni and Bogousslavsky 2009). Alteration in blood flow in the craniocervical arteries may trigger embolus formation, potentially causing a stroke (Mitchell and Kramschuster 2008; Ohsaka, Takgami et al. 2009). Arterial dissection may cause an intramural thrombus to develop compromising blood flow or part of the thrombus may break off and propagate to the brain in the form of an embolus, also causing brain ischemia i.e. ischaemic stroke (Schievinck 2001). Most injuries have been reported to occur in the atlanto-axial portion of the vertebral artery and upper cervical portion of the internal carotid artery.

Concern has been raised widely both in the media and in parts of the medical profession about the safety of neck manipulation (Lee, Carlini et al. 1995; Norris, Beletsky et al. 2000). It has been suggested that manual therapy may cause alteration

in blood flow in the craniocervical arteries or a dissection in the arterial wall due to the force of the thrust and the rotated positions of the head in which this manoeuvre is commonly performed (Haldeman, Kohlbeck et al. 1999; Mitchell and Kramschuster 2008).

It has been shown using ultrasound imaging that certain neck movements, in particular cervical rotation, a common component of many therapeutic manoeuvres, can alter blood flow velocities in the craniocervical arteries in some individuals (Stevens 1991; Licht, Christensen et al. 1998; Li, Zhang et al. 1999; Johnson, Grant et al. 2000a; Mitchell 2003; Zaina, Grant et al. 2003; Arnold, Bourassa et al. 2004). There have been a number of studies which examined blood flow in different positions of the neck using duplex or transcranial Doppler ultrasound, but results have been conflicting (Arnetoli, Amadori et al. 1989; Weingart and Bischoff 1992; Thiel, Wallace et al. 1994; Haynes, Cala et al. 2002; Mitchell 2003; Zaina, Grant et al. 2003). Some authors found that blood flow was changed in contralateral cervical rotation and others reported that it was unchanged. The reason for this disagreement may relate to a number of methodological considerations between studies, such as the type of ultrasound used, the site of sampling, the position of subjects and operator reliability (Magarey, Rebbeck et al. 2004; Thiel and Rix 2005). Most notably, ultrasound is known to be highly operator dependent, particularly when sampling blood flow parameters such as velocity in small diameter tortuous vessels such as the vertebral artery in its atlanto-axial portion, where most injuries have been reported to occur (Zwiebel 2000; Paciaroni and Bogousslavsky 2009). Studies have also commonly measured parameters involving flow velocity which is subject to wide fluctuation, particularly if sampled close to the vessel wall (Freed, Brown et al. 1998;

Zwiebel 2000). Moreover, most studies typically examined blood flow in a single vessel, usually the vertebral artery. However, examination of blood flow in one vessel cannot provide a complete picture of blood flow to the brain.

The reference standard for evaluating cerebral blood vessels is digital subtraction angiography. However, in most centres angiography is now performed using computed tomography or magnetic resonance angiography which has the advantage of being less invasive. The advantages of magnetic resonance angiography in contrast to ultrasound, is that it can be used to generate a much clearer image of the craniocervical vessels using Time of Flight imaging to better visualise the anatomy and check for any vascular anomaly. Magnetic resonance imaging can also measure blood flow simultaneously in all four vessels (i.e. internal carotid and vertebral arteries), and has the advantage of being able to produce a high resolution image of the vessels in an axial or sagittal slice while allowing simultaneous blood flow quantification. Magnetic resonance imaging blood flow quantification is a robust technique with measured errors of less than $\pm 5\%$ (Evans, Iwai et al. 1993; Laffon, Valli et al. 1998; Power, Maier et al. 2000). Unlike ultrasound, magnetic resonance imaging does not require the operator to track the vessel of interest and thus avoids many of the problems of measurement error inherent in ultrasound. Magnetic resonance angiography also provides more detailed imaging and evaluation of blood flow characteristics and cerebral perfusion than can be achieved using ultrasound.

Common cervical spine manual therapeutic procedures involve moving the head and neck into various positions. It has been suggested that one factor which may contribute to adverse events following manual treatment of the neck may be positions

of neck rotation close to the end of physiological range, which could temporarily compromise blood flow (Haldeman, Kohlbeck et al. 1999). These flow changes may be an indication of increased biomechanical stress of the arterial wall (Refshauge 1994). It is possible that rotation combined with longitudinal distraction, a common component of techniques employed by Cyriax (Cyriax and Cyriax 2000) may further increase the mechanical stress on the arteries. In contrast, it may be considered that manual techniques performed closer to the overall neutral position of the neck, perhaps involving localised segmental rotation, such as those advocated by Maitland (Maitland 2005) and Hing et al (Hing, Reid et al. 2003) will have less effect on the arteries. It is important for manual therapy practitioners to be aware of the effects their treatments may have on the craniocervical blood vessels and brain perfusion in order to avoid or minimise the use of any techniques which may have a greater effect on blood supply to the brain.

While there have been a number of studies looking at vertebral and internal carotid arterial blood flow in positions of neck rotation using duplex ultrasound and transcranial Doppler (Johnson, Grant et al. 2000a; Zaina, Grant et al. 2003; Olszewski, Majak et al. 2006; Mitchell and Kramschuster 2008), few have evaluated the effect on blood flow in these vessels during specific manual therapy procedures or when applying longitudinal force to the neck, such as used in cervical traction (Licht, Christensen et al. 1999; Bowler, Shamley et al. 2011) and all utilised ultrasound. Notably, to date, no studies were identified which have investigated craniocervical arterial blood flow using magnetic resonance imaging during manual treatment of the neck. We were only able to find a few individual clinical case reports using magnetic resonance imaging to examine blood vessel diameter or flow

during head and neck rotation (Ohsaka, Takgami et al. 2009), and none which involved specific therapeutic techniques

Where adverse neurovascular incidents have been reported in relation to neck manipulation, these have most commonly involved the C1-2 or atlanto-axial portion of the vertebral artery (Provenzale 2009). So, it is possible that this portion of the vertebral artery might be particularly subject to biomechanical stress in different neck positions and flow changes might be more easily detectable with imaging in this region.

The purpose of this study was to examine the effect of common manual therapy procedures on blood flow in the craniocervical arteries and blood supply to the brain in healthy participants, using magnetic resonance imaging. The objective was to determine if there were any differences in craniocervical arterial flow or total blood supply to the brain between the positions involved in selected manual therapy techniques, which may help inform risk assessment by manual therapy practitioners.

The specific research questions were:

1. Do certain neck positions used in common manual therapy procedures cause greater difference in blood flow in the craniocervical arteries compared with the neutral position than others?
2. Do certain neck positions used in common manual therapy procedures cause greater difference in total blood supply to the brain compared with the neutral position than others?

METHOD

Design

The study was an experimental magnetic resonance imaging study examining blood flow in the vertebral and internal carotid arteries in the neutral neck position and comparing these measurements with blood flow measurements in seven other neck positions used in common manual therapy procedures. The design of the study is shown in Figure 6.1. Informed consent was gained from all participants and the study protocol was approved by the University of Newcastle Human Research Ethics Committee.

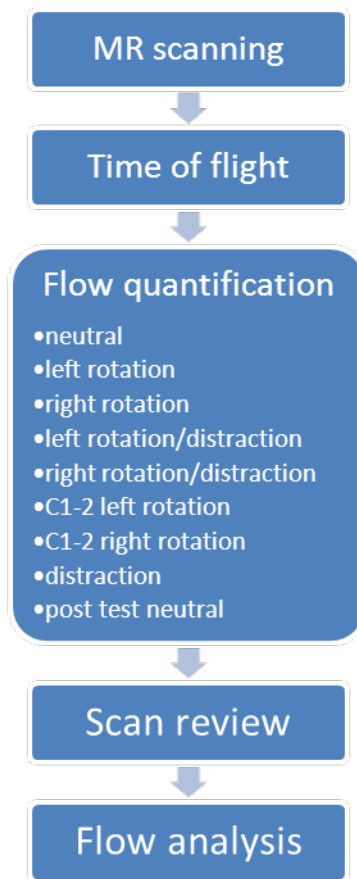


Figure 6.1 *Design of the study*

Participants

Inclusion criteria were healthy volunteers between 18-65 years, with no reported mechanical neck pain or headache. Potential participants were excluded if they reported any of the following (1-4 are standard contraindications for manual therapy to the neck):

1. Diagnosed inflammatory joint disease
2. Any history of serious cervical spine trauma, such as fractures
3. Any congenital disorder recognised as being associated with hypermobility or instability of the upper cervical spine
4. Diagnosed vertebrobasilar artery insufficiency (VBI)
5. Claustrophobia or discomfort in confined spaces (standard contraindication for MRI)
6. Any contraindication identified by the Hunter New England Health MRI safety screening questionnaire.

Demographic data were collected for all participants including age and gender. In addition, information on the normality of the anatomy of the cerebral circulation was collected, as well as any dominance of an artery. Time of flight MR angiography was performed in the neutral neck position to give an image of the anatomy of the cerebral circulation. This allowed visual inspection of the course of both vertebral and internal carotid arteries as well as the Circle of Willis. The time of flight angiography was reviewed post hoc from images saved onto a disc. The anatomy of the cerebral circulation was reviewed by the student researcher for the presence of any vascular anomalies such as hypoplasia or aplasia of a vessel or anatomical variants such as the vertebral artery ending in the posterior inferior cerebellar artery,

suggestive of an incomplete Circle of Willis. The presence of dominance of either vertebral or internal carotid artery was identified. Dominance of an artery was determined by visual inspection of its relative size compared to the contralateral vessel and a marked difference in the average flow in millilitres per second (ml/s).

Experimental conditions

The following sequence of neck positions was used:

1. Neutral
2. Left rotation – the participant was asked to turn their neck as far as possible to the left.
3. Right rotation – same as above with different direction
4. Left rotation with distraction – a strong longitudinal stretch was applied to the neck by the student researcher (an experienced musculoskeletal physiotherapist), the head was then fully rotated to the left side and held in the rotated position while the distraction was maintained (Cyriax and Cyriax 2000)
5. Right rotation with distraction– same as above with different direction
6. Left rotation localised to C1-2 – the C2 spinous process was stabilised in the neutral position by the thumb and index finger of the student researcher and the head was rotated to the left until end-range was perceived, localising rotation to the C1-2 segment (Maitland 1986)
7. Right rotation localised to C1-2 – same as above with different direction

8. Distraction – a longitudinal stretch of the neck with the head in neutral was then applied by the investigator, with one hand under the occiput and the other under the chin.
9. Post-test neutral

The experimental neck positions were selected to replicate as closely as possible common manual therapy procedures without the application of the thrust component. Neck rotation is a common component of a number of manual therapy procedures. Neck distraction with rotation, is a position described by Cyriax (Cyriax and Cyriax 2000). This manual therapy procedure involves a longitudinal stretch (distraction) being applied to the neck by the practitioner and the neck then being taken to the limit of rotation (Figure 2a). A high velocity thrust (manipulation) is then applied into further rotation. The present study did not include the thrust but examined the position in which it would be performed. The pre-manipulative position for this procedure was chosen as it might be expected to apply some degree of stress particularly to the contralateral craniocervical arteries, as highlighted by recently published international guidelines (Rushton, Rivett et al. 2012). Localised rotation of the C1-2 segment was chosen to simulate the pre-manipulative position for a procedure described by Maitland (Maitland 1986) in which the C2 vertebra is fixed by the operator's thumb and index finger and the neck rotated by the other hand (Figure 2b). The manipulation is a high velocity thrust applied to increase rotation at the C1-2 segment. Again, the thrust was not performed. The pre-manipulative position for this procedure was chosen because it was a localised technique to one vertebral segment only and therefore might be expected to impart less stress to the arteries. The atlanto-axial (C1-2) segment was chosen because this is the region

where most dissections attributed to manipulation have been reported. A second post-test neutral measurement was taken to assess the variability of blood flow volume.



Figure 6.2 *Participant position for a) right rotation with distraction, b) left rotation localised to C1-2*

Participants lay supine on the scanner bed with their head in a phased array head coil. This is a rigid plastic box which encloses the head above and on either side, with a bar which passes anterior to the chin. There is a space of approximately four centimetres separating the box from the participant's head on all sides (Figure 6.3). Participants were monitored closely throughout and immediately following the procedure for any symptoms or signs of discomfort, claustrophobia or vertebrobasilar insufficiency, in the case of which the examination would have been terminated.

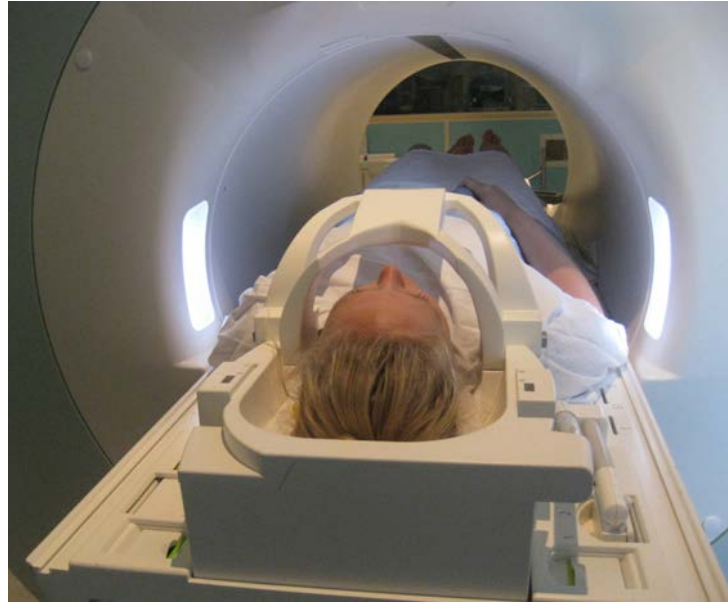


Figure 6.3 *Participant positioned in scanner showing head and neck coil*

Measurement of blood flow in the craniocervical arteries

Blood flow in each of the four craniocervical arteries (right internal carotid, left internal carotid, right vertebral and left vertebral artery) was measured in each of the experimental positions with magnetic resonance imaging, using a phase-contrast flow quantification sequence. All participants were imaged on a 3Tesla superconducting magnet - Siemens Magnetom Verio (Siemens AG, Erlangen, Germany). Participants were scanned with T1 weighted sagittal and axial images and 2-D time of flight angiography. A retrospective cardiac-gated phase-contrast flow quantification sequence was used (TR 29 msec, TE 7 msec, flip angle 30°, slice thickness 6mm, matrix 192 × 512, field of view 200, and number of excitations 1: This is a standard sequence available on this imaging unit) (Bateman 2008). A velocity encoding value of 100 cm/s was used. The arterial plane of section was selected to intersect the top of the atlas loop of the vertebral arteries at the level of the C1 vertebral body. Imaging included a short segment extending to just below the atlas loop. The atlas

loop segment was chosen as this is the site where most manipulative injuries have been reported and therefore where most changes in flow might be expected to occur. The acquisition time was approximately two minutes.

Blood flow measurements were analysed post hoc using the proprietary software syngo Argus (Siemens AG, Erlangen, Germany). In order to analyse blood flow using the Argus system, a region of interest was placed around each artery for each of the neck positions. In order to assess the effect of neck position on blood flow, average blood flow volume measured in ml/s was used as the primary test variable and was analysed in neutral and each of the neck positions for each artery. Average blood flow volume in each artery was then compared between the neutral position and each of the experimental neck positions to determine whether blood flow volume changed from neutral. Velocity was not used for comparison because it is subject to wide variation depending on the area of sampling (Freed, Brown et al. 1998; Zwiebel 2000).

Measurement of total blood supply to the brain

Total blood supply to the brain was determined from the sum of average flow volume (ml/s) in both vertebral and both internal carotid arteries. The addition of the flow from the four arteries gave the total supratentorial blood supply. The total blood supply for each of the neck positions was then compared with neutral. A difference in average total supply (increase or decrease) of $\geq 10\%$ compared with the neutral position was considered to be clinically important (Kreiger, Streicher et al. 2012).

Statistical analysis

Descriptive statistics were used to summarise the demographic data. Average blood flow in all four arteries for the neutral position and each of the experimental neck positions was analysed with descriptive statistics and tested for normal distribution. A linear mixed effects model was fit for each artery (L, R) using a single effect variable (neck position) to assess if there were any differences between positions. The models were fitted using SAS (SAS 2008, proc mixed) (SAS Institute Inc, V9.2 (TS2M2), 2008, Cary, NC, USA) with restricted maximum likelihood estimation and with the Kenward-Roger adjustment for downward bias in the variance-covariance matrix. Compound symmetry was used. If the effect of a neck position was significant, follow-up testing of pairs of means was undertaken in two ways using Dunnett's adjustment to compare the neutral position with the other neck positions and to examine all pairs of means using a Bonferroni adjustment to the significance level.

For post hoc power analysis, the variabilities were determined using a random effects mixed model for each artery, combining data for all four arteries, to determine standard deviations due only to measurement and neck position sources of variation.

RESULTS

Participant characteristics

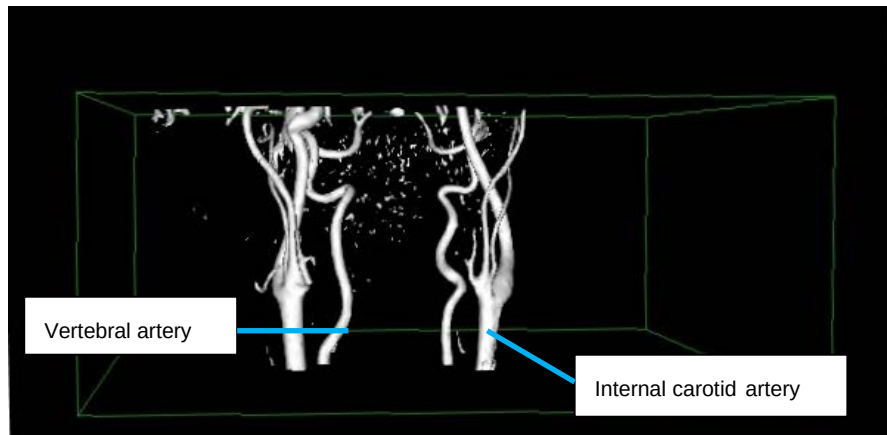
Twenty-one people were screened for eligibility. One participant was excluded due to previously unknown claustrophobia on lying in the scanner. Therefore, 20 participants were recruited into the study. The mean age was 33.1 years (SD 11.9) and 10 (50%) participants were male (Table 6.1). No participants experienced any

signs or symptoms of vertebrobasilar insufficiency while having their head held in any of the neck positions.

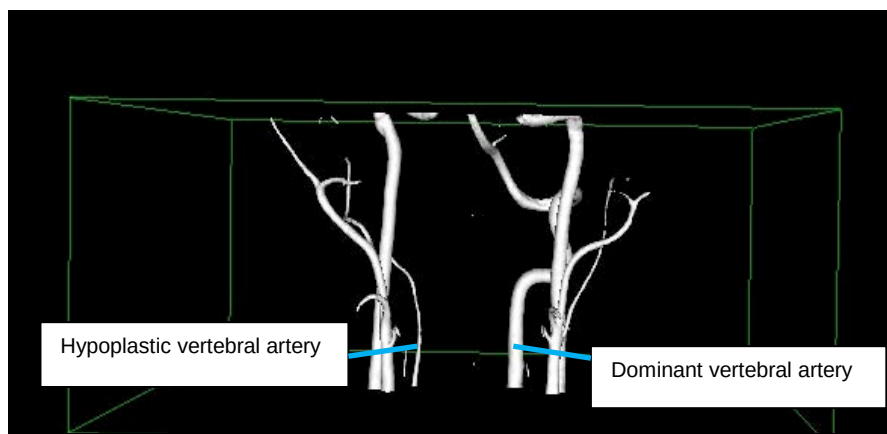
Table 6.1 Participant characteristics

Characteristic	N=20
Age, yrs, (SD)	33 (11.9)
Gender male (%)	10 (50)
Normality of artery n (%)	20 (100)
Dominance of one vessel n (%)	3 (15)

All participants had a normal anatomy of the craniocervical arterial circulation (Figure 6.4a). Three (15%) of participants had hypoplasia of one vertebral artery and dominance of the other vertebral artery (Figure 6.4b).



a)



b)

Figure 6.4 *Surface rendered 3-D multi-planar reformatted image of the carotid and vertebral arteries of a participant showing a) normal anatomy and no dominance of any vessel b) hypoplastic right vertebral artery and dominance of left vertebral artery*

Effect of neck position on blood flow

Average blood flow volume in ml/s for the internal carotid and vertebral arteries in the neutral and each of the experimental conditions is presented in Table 6.2 and show that blood flow volume varied from the neutral position in the majority of the experimental neck positions.

Table 6.2 Mean (SD) average blood flow volume (ml/s) in the craniocervical arteries for each neck position and the mean difference between each neck position and neutral. Linear mixed model testing by artery (p value) is shown below.

Neck position	Craniocervical arteries				Difference between neck position and neutral			
	RICA	LICA	RVA	LVA	RICA	LICA	RVA	LVA
					Neck position minus neutral	Neck position minus neutral	Neck position minus neutral	Neck position minus neutral
Neutral	2.57 (0.86)	2.71 (1.03)	0.73 (0.62)	0.98 (0.64)	N/A	N/A	N/A	N/A
Left rotation	2.22 (0.76)	2.66 (0.97)	0.53 (0.72)	1.12 (0.71)	-0.4	-0.1	-0.2	0.14
Right rotation	2.61 (1.0)	2.56 (0.96)	0.80 (0.70)	0.87 (0.59)	0.04	-0.2	0.1	-0.1
Left rotation/distractio	2.79 (1.19)	3.01 (1.29)	0.65 (0.87)	0.87 (0.50)	0.2	0.3	-0.1	-0.1
Right rotation/distractio	2.98 (1.01)	2.61 (1.19)	0.73 (0.79)	0.86 (0.61)	0.4	-0.1	0.0	-0.1
C1-2 Left rotation	2.84 (1.53)	3.01 (0.97)	0.66 (0.74)	1.03 (1.10)	0.3	0.3	-0.1	0.1
CI-2 Right rotation	2.76 (0.87)	2.86 (0.96)	0.74 (0.69)	1.04 (0.71)	0.2	0.2	0.0	0.1
Distractio	2.83 (1.10)	2.68 (1.08)	0.55 (0.64)	0.88 (0.68)	0.3	-0.0	-0.2	-0.1
Post-test neutral	2.94 (1.0)	2.85 (0.91)	0.64 (0.55)	1.14 (1.0)	0.4	0.1	-0.1	-0.2
P* value	<0.001	0.01	0.28	0.47				

*Linear mixed model p value for test of difference among the nine position means
RICA=right internal carotid artery, LICA=left internal carotid artery
RVA=right vertebral artery, LVA=left vertebral artery

In general, rotation tended to reduce flow in the contralateral internal carotid and vertebral arteries (Figure 6.5). For example, manoeuvres involving end range rotation to the left generally decreased blood flow volume in the contralateral vessels although this was statistically significant only for the right internal carotid ($p < 0.001$) artery. End range rotation to the right produced a trend towards a reduction in flow in the left internal carotid and left vertebral arteries (LICA - 0.2, LVA - 0.1) but this was not significant. In comparison, the addition of distraction to contralateral rotation resulted in a small reduction in flow in the vertebral arteries (RVA - 0.1, LVA - 0.1) and a small increase in flow in the internal carotid arteries (RICA 1.19, LICA 1.19) but again this was not significant. Ipsilateral rotation appeared to increase flow in both vertebral arteries and the right internal carotid artery (RVA 0.1, LVA 0.14, RICA 1.0). Localised (C1-2) ipsilateral rotation appeared to increase flow in the internal carotid arteries (RICA 0.87, LICA 0.97). Distraction in neutral tended to reduce flow in the vertebral arteries (RVA -0.1). Interestingly, this was accompanied by a concurrent significant increase in flow in the right internal carotid artery (0.4).

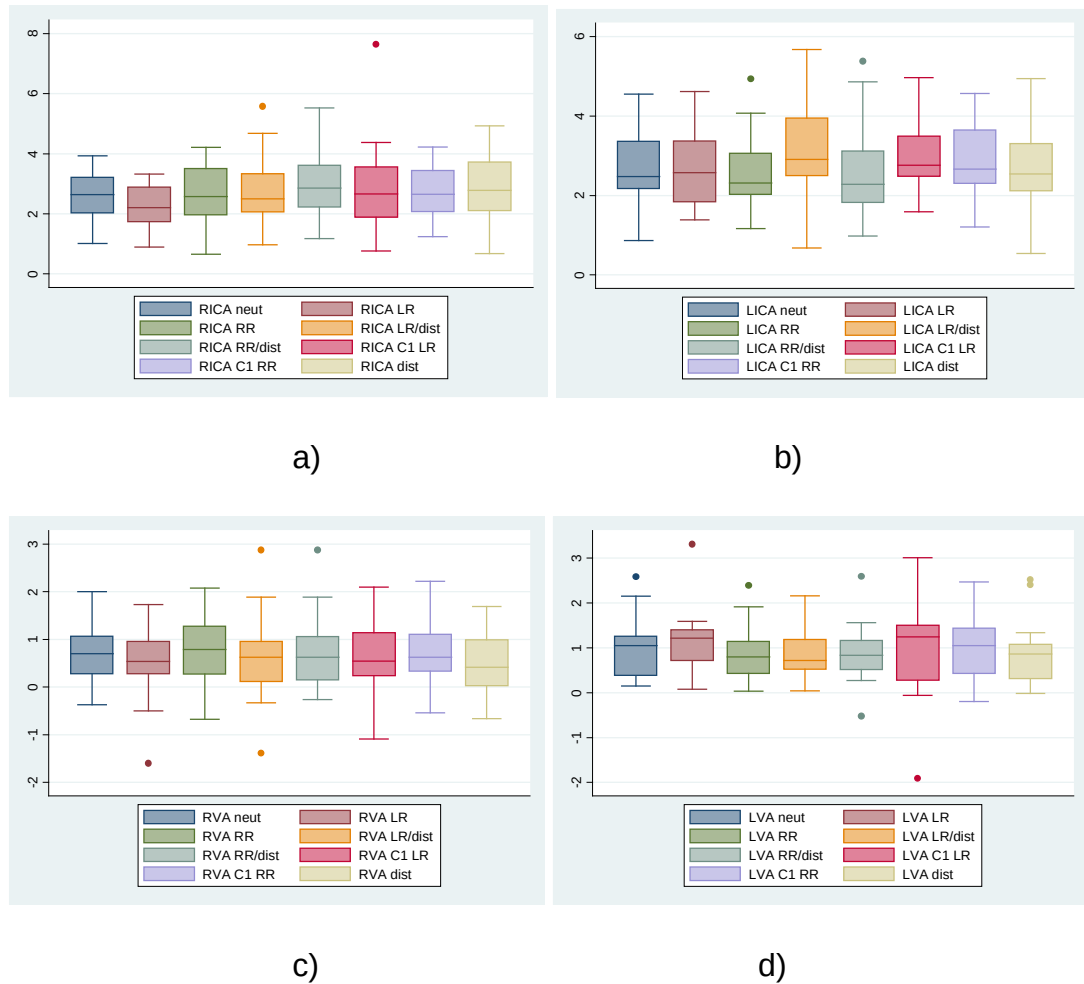


Figure 6.5 Box plots showing average flow volume (ml/sec) for experimental neck positions a) right internal carotid artery (RICA), b) left internal carotid artery (LICA), c) right vertebral artery (RVA), d) left vertebral artery (LVA). Outliers (values > 2 SD) shown by circles ●. Note the values for VA cross zero but ICA do not.

In order to compare differences in average volume flow for all arteries and all nine positions, to see if any of the neck positions had greater effect on any artery than another, we analysed flow volume using a linear mixed effects model. For each of the four arteries we assessed one treatment variable with nine levels (neutral, left rotation, right rotation, left rotation/distraction, right rotation/distraction, C1-2 left rotation, C1-2 right rotation, distraction and a second neutral position or thirty-six pairs). The significance of the treatment effect (i.e. neck position) was reported using

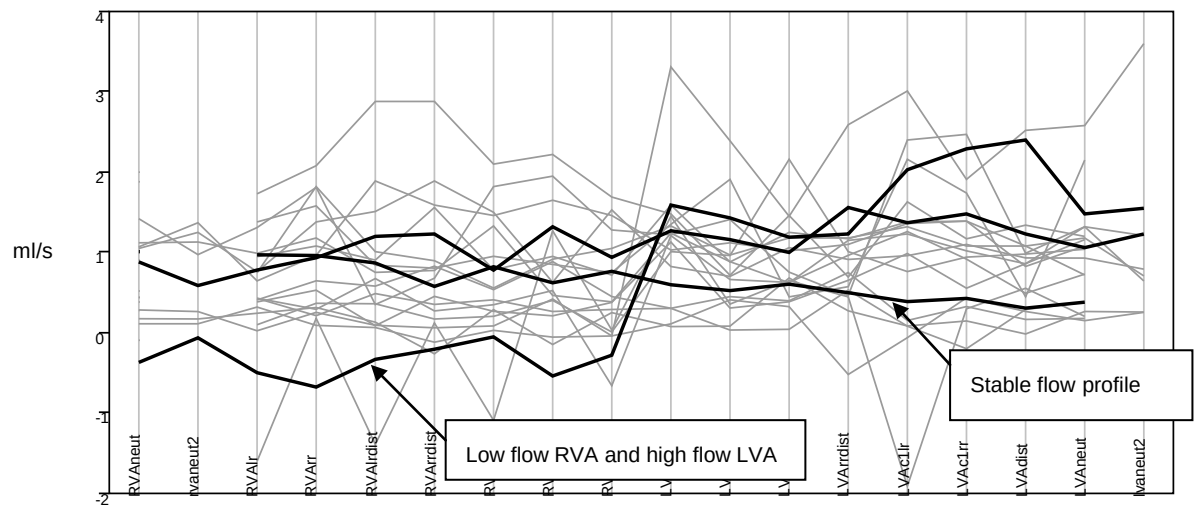
p values. The significance level was set at $\alpha=0.05$, but following a significant effect, post hoc testing of all pairwise differences was carried out. The results showed no significant change in flow volume relative to the neutral position for either of the vertebral arteries (RVA $p=0.28$, LVA $p=0.47$) but statistically significant difference between positions for the right internal carotid artery ($p<0.001$) and the left internal carotid artery ($p=0.01$) (shown bottom of Table 6.2).

Further analysis of the significant results for the left internal carotid relative to the neutral position using the Dunnett's test, in order to adjust for multiple tests, and comparing neutral with all the other positions, showed no significant difference despite the significant overall test result. Similarly, analysis of the right internal carotid artery values using Dunnett's test showed no significant change.

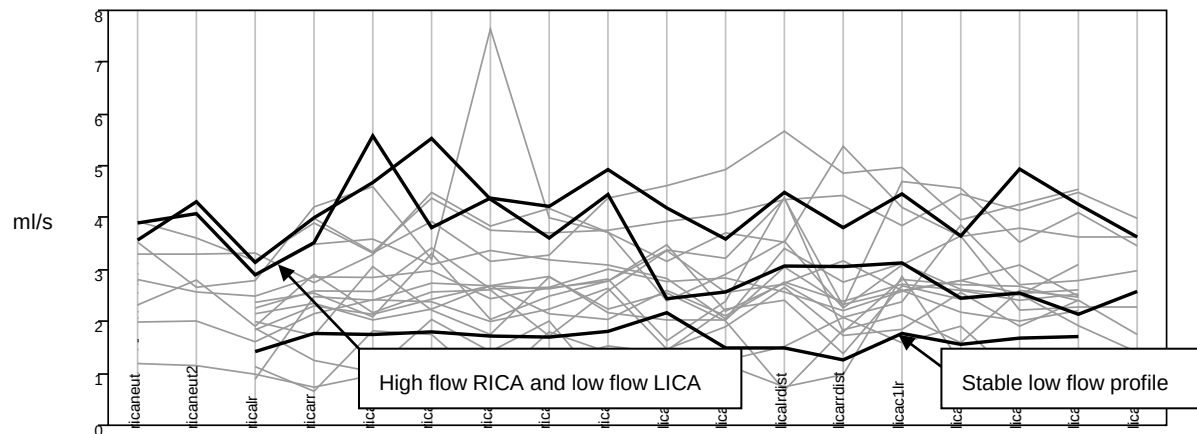
Given significant effects were found for both carotid arteries but no differences were identified between the neutral position and the remainder it was decided to explore further by conducting tests of all pairwise comparisons. The Bonferroni adjustment was used, so as to control for familywise error rate for the large number of paired comparisons. From the nine positions there were 36 possible combinations, so alpha was set at $\alpha = 0.05/36 = 0.0014$. This approach showed no difference for the left internal carotid artery but four combinations were significantly different for the right internal carotid: left rotation and right rotation/ distraction, left rotation and C1 left rotation, left rotation and distraction, left rotation and left rotation and distraction. All combinations involved left rotation. Mean average flow volume for right internal carotid artery in left rotation was unusually low and statistically different from the other positions (Appendix C p.229). Removing left rotation from the analysis

resulted in a non-significant result for the right internal carotid artery. As the Dunnett's test was negative for all positions compared with neutral and significant changes were not similarly demonstrated for the left internal carotid artery in right rotation, it is likely that this finding is due to a statistical anomaly, as it does not make sense clinically.

Although mean values of average flow volume were not significant for any position there were certain individuals with marked flow changes in some positions. Figure 6.7 shows parallel plots of flow volume in all positions to demonstrate individuals with large changes.



a)



b)

Figure 6.6 Individual parallel plots of flow volume (ml/s) in right (R) and left (L) a) vertebral arteries (VA) and b) internal carotid arteries (ICA) for all participants in each neck position, with specific plots highlighted to show large variation between arteries in some individuals. One individual with a stable flow profile is shown for comparison.

Blood supply to the brain

The total blood inflow (ml/s) to the brain for each position is shown in Table 6.3.

The total inflow to the brain did not vary substantially from neutral in any test position. Flow generally decreased slightly for both the end-range rotation and distraction positions but increased in the other positions. The total flow volume for all positions was analysed with a linear mixed effects model. No difference was found between positions ($p = 0.06$). In addition, flow changes were all less than 10%, which is considered to be within the normal variation for cerebral inflow (Kreiger, Streicher et al. 2012).

Table 6.3 Total blood inflow to the brain measured by sum of average flow volume (ml/s [95% CIs]) in internal carotid and vertebral arteries. Difference between neck position and neutral (ml/s, p value and % difference).

Neck position	Total blood inflow	Difference between neck position and neutral		
		Neck position minus neutral	P value	Percentage difference
Neutral	6.98 (5.83, 8.13)	N/A	N/A	N/A
Left rotation	6.52 (5.43, 7.62)	-0.5	0.18	-6.6
Right rotation	6.84 (5.65, 8.03)	-0.1	0.68	-2.0
Left rot/distraction	7.31 (5.96, 8.66)	0.3	0.33	4.7
Right rot/distraction	7.17 (5.78, 8.56)	0.3	0.57	4.3
C1-2 Left rotation	7.53 (5.94, 9.12)	0.6	0.10	7.9
C1-2 Right rotation	7.41 (6.29, 8.52)	0.4	0.21	6.2
Distraction	6.93 (5.61, 8.26)	-0.1	0.89	-0.7
Post-test neutral	7.58 (5.64, 9.52)	0.6	0.38	8.6

Variability of measurement

The correlation of the absolute differences between pairs of neutral readings and mean level for each pair of neutral measurements, Spearman $r = 0.38$, $p = 0.02$, suggested there might be an increase in variability with the level of the measurement

(i.e. amount of flow). The relationship was not quantified but based on this it seemed desirable to provide separate estimates for measurement variability for the two arteries as the level of flow differs substantially between them. For a mean average flow volume of 0.9 ml/s in the vertebral arteries, using a fixed effect analysis, the standard deviation of measurement was 0.25 (df = 18) . For a mean average flow volume of 2.97 ml/s in the internal carotid arteries, the standard deviation of measurement was 0.32 (df = 18).

Variability of measurement and position

It was found that additional variability was evident when comparing all positions.

The previous analysis, although identifying a significant main effect for position for the internal carotid arteries, did not provide any scientifically reasonable pattern of effect. Those effects of neck position on blood flow were therefore incorporated as part of a random source of variability due to the differences between positions.

Random effects models for each artery were used to estimate the variance component due to neck position variation (differences between positions for both sides) and measurement variation (neutral vs neutral 2) for both sides) to estimate a combined variability. For the vertebral arteries the standard deviation of measurement + neck position was 0.40 and for the internal carotid arteries was 0.54. These represent substantial increases over the pure measurement variability suggesting there are additional small but random effects associated with blood flow between different neck positions. That none of these effects appear to be systematic but rather random helps in understanding the impact of the different neck positions. The random effects model suggests there are differences in the effect on blood flow between people for a given neck position, but none of the variations are consistently different across all

people for a given position. Despite some individuals showing large changes in blood flow in one vertebral artery, none experienced any signs or symptoms of cerebral ischaemia.

Post hoc power analysis

We were unable to perform a power calculation prior to the study due to the lack of published studies using MRI, but with the benefit of the data collected we performed a post-hoc power analysis and estimated power for a range of differences between neutral and the experimental neck position. The power calculations used the standard deviations from the previous section for measurement + position and were based on a comparison of two experimental neck positions with a single independent samples t-test. For the vertebral artery, for a 50% change in average flow volume between neutral and any neck position power was 0.97, for a 36.4% change from the neutral position, power was 0.80. For the internal carotid artery, for a 50% change in flow volume power was 1, and even for as low a value as 16.4% change, power was still 0.80.

DISCUSSION

This comparative magnetic resonance imaging study examined blood flow in the craniocervical arteries in different neck positions and compared this to the neutral head position. The study found that blood flow was not negatively impacted by any of the neck positions used and that no neck position had greater effect on blood flow than any other. Total cerebral inflow remained fairly constant in all positions, similarly suggesting that cerebral perfusion was not negatively impacted by any of the neck positions. To date, there have been no previous studies investigating blood

flow in the craniocervical vessels in different neck positions using magnetic resonance imaging. The advantage of magnetic resonance imaging is that vessels can be easily visualised and flow can be measured simultaneously in all four vessels, with the additional ability to estimate total cerebral inflow. Clinically, the results of this study suggest that common neck positions used in manual therapy practice do not, in and of themselves, appear to pose a risk to blood flow to the brain and that concerns about the safety of the neck positions may be unfounded, at least on the grounds of their effects on blood flow, because of the homeostatic function of the Circle of Willis.

Blood flow in the craniocervical arteries varied between positions, but was not significantly changed by any neck positions used in common manual therapy procedures, compared to the neutral position. In addition, no position had any significantly greater effect on blood flow than any other, including those using potentially more stressful positions of end-range rotation and distraction. Previous studies examining blood flow changes during neck rotation have generally examined blood flow in specific arteries only, notably the vertebral arteries (Mitchell 2003; Zaina, Grant et al. 2003; Mitchell and Kramschuster 2008), which does not allow consideration of the cerebral circulation as a whole. Concerns have been raised that flow reduction in rotation may represent a risk factor for neurovascular complication subsequent to cervical manual therapy (Li, Zhang et al. 1999; Mitchell, Keene et al. 2004; Mitchell and Kramschuster 2008). Moreover, it has been suggested that clinicians should measure flow in the vertebral arteries as part of pre-manipulative screening of the cervical spine (Mitchell, Keene et al. 2004; Kerry and Taylor 2006). The current study contrasts with some previous studies where reduction in flow

velocity was demonstrated in the vertebral arteries associate with contralateral rotation (Mitchell 2003; Zaina, Grant et al. 2003; Mitchell and Kramschuster 2008). However, these were all ultrasound studies which did not measure actual flow volume. Interestingly, although not statistically significant, this study suggested that when flow is decreased in one vessel by a neck position, it appears to be compensated by increased flow in another. For example, in left rotation there was marked reduction in flow in the right internal carotid and vertebral arteries but a marked increase in flow in the left vertebral artery. Imaging measurement of flow in the vertebral arteries for pre-manipulative screening purposes would not therefore seem to be particularly useful. However, the positional tests themselves may still be useful to determine the adequacy of overall cerebral perfusion.

Studies have also reported greater reduction in flow with increasing range of rotation (Refshaug 1994; Zaina, Grant et al. 2003), and suggested that end-range contralateral rotation positions might have a greater effect on blood flow than more localised segmental rotation. The results of this study suggest that common manual therapy procedures including end-range neck rotation and rotation/distraction do not appear to be any more hazardous in terms of blood flow than more localised positions. It is important to consider however, that while a healthy artery should have capacity to easily withstand stress of this nature, the effects of mechanical stress on arteries which are in a weakened state either from underlying arteriopathy or a temporary friable state due to infection or the potential presence of pro-inflammatory factors in the circulation are as yet unknown in the human model. Future research into the effects of neck position on blood flow is therefore probably not warranted. However, other factors such as the state of the arterial wall and the effect of the

manipulative thrust may be more important determinants of risk from manual therapy applied to the neck and future studies could investigate these factors.

The present study showed that total blood inflow to the brain was not significantly changed from the neutral position by any of the test positions and none of the positions showed a compromise to cerebral blood supply. In the manipulation therapeutic positions flow was actually increased somewhat. This was further supported by the fact that no signs or symptoms of cerebral ischaemia were evident, despite marked reduction of flow in the vertebral arteries of some individuals.

Previous ultrasound studies have also demonstrated marked reduction or even cessation of vertebral artery flow during rotation in some individuals yet no signs of vertebrobasilar insufficiency being elicited (Rivett, Sharples et al. 1999). This is not surprising given the homeostatic function of the Circle of Willis in maintaining a constant blood supply to the brain. One position, C1-2 rotation to the left, showed a relatively large change in flow volume from the neutral but this was not statistically significant and was actually an increase in flow (7.9%), so did not appear to represent a risk to brain perfusion. As shown in a recent study, small fluctuations (<10) in flow volume to the brain normally occur according to an individual's arousal state and increase if a participant is anxious or doing a mental task, and this is not considered to be detrimental to brain function (Kreiger, Streicher et al. 2012).

Clinically the results of this study suggest that even if blood flow in one of vessel is markedly altered by a neck position or an individual has low or absent flow in one vessel it may still be adequately compensated for via the other vessels, so concerns about the safety of particular neck position in terms of cerebral ischaemia may

generally be unwarranted. However, if the Circle of Willis is not intact, for example missing a posterior communicating artery, then reduction in total blood flow to the brain may be possible, particularly if there is no other source of collateral circulation. Generally it is considered that in people with pre-existing vascular anomalies, the collateral circulation is usually well developed (Chen, Chao et al. 2010). This was demonstrated even in the neutral position in at least two individuals, who had markedly low flow in their right vertebral arteries but comparatively greater flow in the left vertebral and both internal carotid arteries. However, in the absence of radiological imaging, clinicians can generally rely only on production of signs or symptoms of cerebral ischaemia to identify individuals at potential risk of an adverse neurovascular event.

Strengths and limitations of the study

The main strengths of the study are the use of magnetic resonance imaging which provides high quality images of the craniocervical arteries and the ability to track them in different positions, which has not been undertaken previously. The advantage of using magnetic resonance imaging is that flow can be measured simultaneously in all four vessels which allows comparison of the overall effects of the different positions on blood flow, as well as the estimation of total cerebral inflow. The study used neck positions designed to replicate those used in typical manual therapy practice so the results can be related to the clinical situation. In addition, the neck positions selected allowed comparison between potentially more stressful end-range rotation/distraction positions with more localised segmental rotation positions in order to see if any were more hazardous than another in terms of the effects on blood flow.

There were some limitations of the study included that the scanner set-up, with the participant's head enclosed within a head and neck coil. However, while this made it a little more challenging to perform the techniques it was found possible to replicate the technique positions as described. In addition, in order to minimise the time spent in each position only a short segment of the arteries were examined at the level of C1, it is possible that during the rotation positions the arteries moved slightly cephalad causing a less straight section of artery to be imaged. This may have made it more difficult in some cases to accurately identify the centre of the arterial lumen in cross section to undertake flow analysis. Flow analysis may therefore have been performed nearer the arterial wall in some instances where flow might be more variable. Future studies could image a longer section of the artery to minimise this problem when associated acquisition times are reduced by improvements in technology.

Future research

One of the key components of neck manipulation is the high velocity thrust. It was not possible during this study to look at the effects of the manipulative thrust on blood flow as the participant's head would have had to be removed from the head coil for the procedure and then returned to it, making it difficult to compare flow measures as the baseline neutral position would be slightly different. Future studies could examine the effects of the manipulative thrust on blood flow in the craniocervical arteries. The study examined relatively young, healthy participants in whom it was assumed arteries were healthy without any pathology. The effect of neck position on blood flow in arteries with some form of arteriopathy may be

different and could be investigated in the future. The post-hoc calculation may be useful to determine appropriate sample sizes for future flow studies.

CONCLUSION

While concerns have been raised about the safety of manual therapy applied to the neck, in particular the upper cervical spine segments, none of the positions tested in this study demonstrated any significant change in blood flow volume from the neutral position. Moreover, no position including end range rotation, upper cervical rotation or strong distraction had any greater effect on blood flow than any other. Total blood supply to the brain was not adversely affected by any positions and in most positions relating to common manual therapy procedures such as rotation/distraction and C1-2 rotation, supply was actually increased somewhat. In addition, even if flow was reduced in one vessel it was generally compensated by increase in another, at least in healthy individuals. This suggests that the neck positions themselves are not inherently hazardous in terms of compromise to blood flow in the craniocervical arteries and it is more likely therefore that other factors such as the state of the arteries and the effect of the manipulative thrust may be more important. Future imaging studies focussing on blood flow in normal or individual craniocervical arteries may not be particularly useful.

CHAPTER 7

SUMMARY AND CONCLUSIONS

SUMMARY OF STUDY FINDINGS

LIMITATIONS OF THE STUDIES

GENERALISABILITY OF THE FINDINGS

CONCLUSIONS

CLINICAL IMPLICATIONS

FURTHER RESEARCH QUESTIONS

SUMMARY OF THESIS

SUMMARY OF STUDY FINDINGS

The aim of this thesis was to examine the risk factors for cervical spine manipulation in order to make recommendations for minimising risk in clinical practice. The thesis followed two approaches designed on the one hand, to explore the patient history and clinical presentation to identify features which might enhance recognition of those at risk and on the other hand, to evaluate the safety of the manual therapy procedures themselves. The investigation comprised four studies, three of which examined patients with craniocervical arterial dissection which is the most commonly described serious neurovascular event following cervical manipulation. The final study examined the effect of positions involved in common manual therapy procedures, including two manipulation techniques, on blood flow in the craniocervical arteries and blood supply to the brain

Study 1 (Chapter 3) examined the risk factors and clinical features of craniocervical arterial dissection in a retrospective medical records review. This study was exploratory in nature in order to provide an overview of the nature of the problem of craniocervical dissection, to gain an indication of the incidence of arterial dissection in the local region, to inform a planned prospective study and to identify the type of information available in the medical records about presenting clinical features, preceding events and associated risk factors. The study found that in radiologically confirmed cases vascular anomaly and recent minor mechanical trauma of the head including neck manual therapy were associated with dissection. Patients did not usually have other co-morbidities and had relatively few general cardiovascular risk factors. This was in contrast to the control ischaemic stroke patients who generally had co-morbidities and markedly more general cardiovascular risk factors.

Study 2 (Chapter 4) examined the radiological features and infarct topography of the group of radiologically confirmed craniocervical arterial dissection patients from Study 1, in order to identify what radiological features typical of dissection and associated infarction were present and to identify whether particular features were more common in the presence of certain risk factors, such as trauma. The study found that dissections were mainly extracranial and in the upper cervical region, and that a history of recent mechanical trauma to the head and neck, including neck manual therapy, and evidence of vascular anomaly were linked with a higher incidence of brain infarction.

Study 3 examined risk factors and clinical features in a prospective cohort of craniocervical arterial dissection patients and the preliminary findings are presented in Chapter 5. This study was informed by the results of Study 1 and therefore included only patients with radiologically confirmed dissection. The use of a structured interview facilitated thoroughness and consistency of information collection between participants, enhancing the validity of the data collected. This study identified that craniocervical arterial dissection patients generally presented with moderate to severe headache and/or neck pain, and commonly had a history of some recent minor trauma to their head or neck. Importantly, a high proportion of dissection participants (70%) experienced transient ischaemic features in the preceding weeks to their admission for dissection.

Study 4 (Chapter 6) examined the effect of different neck positions used in common manual therapy procedures on blood flow in the craniocervical arteries using

magnetic resonance imaging. The study identified that no position had greater effects on blood flow in any of the craniocervical arteries than any other. Specifically, combined end-range rotation and strong distraction positions of the neck as used in manipulations recommended by Cyriax (Cyriax and Cyriax 2000) had no greater effect on blood flow than more segmentally localised rotation positions (without distraction) recommended by Maitland and others (Hing, Reid et al. 2003; Maitland 2005). In addition, if blood flow reduced in one artery in any position, it appeared compensated for by an increase in one or more of the other arteries, so that total blood inflow to the brain was not affected. Thus, total blood flow to the brain was not adversely affected by any of the neck positions tested.

LIMITATIONS OF THE STUDIES

Study 1 (Chapter 3) identified a number of limitations typical of retrospective studies, such as the limited amount of information recorded and the lack of consistency of recording between case records. This indicated the need for a prospective study in order to standardise data collection as far as possible and focus in greater detail on antecedent and presenting signs and symptoms, as well as preceding events which may have acted as ‘trigger’ events. A further limitation of this study was that not all patients had radiological confirmation of craniocervical dissection and diagnosis in these cases was based on indicative history and clinical judgement. Some of these patients may therefore not have had a dissection, which could have affected the results of the study. However, this limitation was somewhat addressed in the chapter with additional sub-group analysis of the radiologically confirmed cases only. The findings of the risk factor analysis of only the confirmed

cases were also presented in this chapter and the published paper, and these findings were not substantially different from the dissection group as a whole.

The radiological review in Study 2 (Chapter 4) was limited by modest numbers due to the lack of radiological confirmation of dissection in some participants clinically diagnosed. This is largely related to the limitation associated with retrospective medical record reviews whereby access to imaging is not always available.

Radiological imaging records were not always archived, particularly prior to the use of web-based picture archiving systems, and so many of the earlier case files in Studies 1 and 2 had only a radiology report. This confined the review of the radiological features of the case to the details recorded in the report only. It is possible that actual inspection of the images may have revealed features previously unreported. While advances in imaging technology and the more routine use of modalities such as magnetic resonance imaging have improved the identification of the radiological features of dissection in recent years, many earlier patients had only ultrasound or CT imaging or imaging performed too late, when the dissection may have healed. This is in contrast to the multimodal imaging typical of contemporary practice which enables pathological features to be more readily identified at different stages.

Study 3 (Chapter 5) was also limited by modest numbers due to the low on-going incidence of craniocervical arterial dissection in the local population. However, the study sample of twenty dissection participants and twenty control participants allowed a preliminary analysis of the direction of the data. The findings of the preliminary analysis, if confirmed in the full sample d highlight some important

clinical considerations which will help inform manual therapy practitioners in their screening of patients presenting with head and neck pain.

Study 4 (Chapter 6) was limited by the difficulty in some participants in obtaining cross-sectional flow in the vertebral arteries in the rotation positions. This was due to the small size and tortuous course of the arteries in the upper cervical spine.

Movement of the neck and investigator hand positioning were also slightly affected by the presence of the head coil with some participants. The ability of the investigators to maintain some of the neck positions for extended periods of time without any movement restricted the data acquisition to a relatively small section of the arteries around the level of C1, although this is the primary region of interest. It would have been useful to image longer sections of the arteries in order to confirm blood flow measurements taken in the shorter, more tortuous distal sections.

Interpretation of the flow data was somewhat limited with respect to comparison with reference values, as blood flow analysis in the craniocervical arteries had not been previously performed in neck positions (other than neutral) using magnetic resonance imaging.

GENERALISABILITY OF THE FINDINGS

The findings of these studies can be generalised to the wider population when considering the screening of patients prior to manual therapy intervention in the cervical spine. Firstly, the mean age of participants in all four studies is similar to those in whom adverse events following cervical spine manipulation have been reported, namely young to middle aged adults under 55 years. There were also similar proportions of male and female participants in all studies, consistent with reported

findings of the lack of gender bias amongst documented cases of craniocervical arterial dissection (Schievinck 2001; Guillon, Berthet et al. 2003; Caso, Paciaroni et al. 2005; Debette and Leys 2009). Secondly, participants with craniocervical arterial dissection were recruited from a tertiary referral centre which services a wide geographical area with a mixture of a major metropolitan centre, several large regional centres, and smaller rural centres and remote communities. Selection of patients was not therefore confined to one area alone.

In Study 3 (Chapter 5), the investigation of risk factors for craniocervical arterial dissection was undertaken by interview of both dissection participants and control participants. This is akin to clinical practice whereby practitioners interview a patient prior to commencing any manual treatment. This enables findings from this study to be translated directly to the clinical encounter. Notably, the investigators did not have access to patient records prior to inviting them to participate in the study. This helped to avoid selection bias of those participants with particular risk factors, such as exposure to neck manipulation.

Studies 1, 2 and 3 (Chapters 3-5) had a higher proportion of vertebral artery to internal carotid artery dissection than is usually reported in the literature, so may not be completely representative of the typical population of young to middle aged individuals under 55 years with craniocervical arterial dissection. In our studies, between 45-57% of participants had vertebral artery dissection, whereas the reported ratio of vertebral to internal carotid artery dissections is approximately 1:2 (Schievinck 2001; Debette, Grond-Ginsbach et al. 2011). However, the study populations may be representative of the population utilising manual therapy, since

vertebral artery dissection has been more commonly reported as an adverse event following neck manipulation than internal carotid artery dissection (Haldeman, Kohlbeck et al. 1999).

Study 4 (Chapter 6) utilised experimental positions similar to those used in common manual therapy procedures and participants of a similar age to those who have been reported to seek manual therapy treatment for headache or neck pain (Hurwitz, Aker et al. 1996; Haldeman, Kohlbeck et al. 1999), so the findings may be generalised to this population of patients.

CONCLUSIONS

Minor mechanical trauma or stress to the neck, including manual therapy appears to be associated with craniocervical arterial dissection. Craniocervical arterial vascular anomaly may also be associated. Recent infection may be a consideration, particularly in internal carotid artery dissection. General cardiovascular factors, with the possible exception of migraine, do not appear to be associated with an increased risk of arterial dissection.

The initial presenting features of craniocervical arterial dissection were most commonly headache and neck pain, which may make differentiation from a musculoskeletal disorder difficult. The most commonly presenting ischaemic features of vertebral artery dissection were balance disturbance, dysarthria and limb weakness. Presenting features of internal carotid arterial dissection commonly included dysarthria, ptosis and limb weakness.

Patients frequently experience some transient signs or symptoms of cerebral ischaemia in the month preceding their admission for dissection. Neck positions used in common manual therapy procedures on average do not reduce flow in either the vertebral or internal carotid arteries, although some individuals may demonstrate marked changes in blood flow in a vessel. Reduction in blood flow in one artery is generally compensated for by an increase in another, so that overall blood flow to the brain is maintained. Total blood inflow to the brain appears not to be adversely affected by neck positions used in common manual therapy procedures, including manipulations advocated by Cyriax and Maitland.

CLINICAL IMPLICATIONS

The findings of these studies suggest that clinicians should screen patients presenting for treatment of headache or neck pain for a recent history of any trauma to the neck, and perhaps infection and migraine, and enquire and observe carefully for any features suggestive of transient brain ischaemia, such as speech or balance disturbance or limb weakness, particularly in cases where there has been recent exposure to mechanical trauma or stress to the head or neck. General cardiovascular screening of patients presenting for manual treatment of the cervical spine does not appear to be useful in indicating risk of arterial dissection (with the possible exception of diagnosed migraine) and therefore does not seem to be warranted. Practitioners should consider any putative risk factors carefully within a comprehensive clinical reasoning framework and factor these into their patient management, unless there are clear indicators of cerebral ischaemia in which case the patient should be referred urgently to the nearest emergency department with the relevant medical details of concern outlined in a written or verbal communication.

Neck positions used in common manual therapy procedures, including neck manipulation, generally do not appear to adversely affect blood flow in the craniocervical arteries in most individuals; however, practitioners should monitor patients closely for any signs or symptoms of ischaemic compromise during the application of manual procedures to the cervical spine as individual responses may vary. If clear ischaemic signs or symptoms are identified during either assessment or treatment, the practitioner should refer the patient promptly for medical evaluation. Measurement of blood flow in individual arteries in neck rotation does not appear to be a useful inclusion in pre-manipulative screening because reduction in flow in a single artery is compensated for by an increase in another vessel and therefore unlikely to be indicative of risk of cerebral ischaemia.

FURTHER RESEARCH QUESTIONS

The findings of both the retrospective and prospective studies show clearly that recent exposure to minor mechanical trauma to the head and neck is commonly temporally associated with craniocervical arterial dissection. However, while the trauma reported is often apparently innocuous and not unfamiliar to the participant, the question remains as to how to identify the underlying pre-existing tissue state which rendered the participant vulnerable to such a trigger. Further research into genetic and pro-inflammatory triggers for arterial dissection may be useful in this regard.

Study 4 (Chapter 6) examined the effects of neck position on blood flow in the craniocervical arteries of normal healthy participants, but few studies have been able

to examine the effect of mechanical trauma or neck positions on abnormal arteries. Future studies could examine the effects of mechanical trauma or neck position on pathological arteries. In addition, further research could investigate the effects of movement force and speed on the arteries, such as might be imparted by manipulative procedures utilising a high velocity thrust.

Finally, future work could also focus on the development of effective screening procedures or guidelines to enable manual therapy practitioners to detect and recognise the significance of risk factors, such as recent exposure to mechanical trauma to the neck, and also to more readily identify subtle transient ischaemic neurological features. It might be possible to develop a clinical prediction rule to improve recognition of patients at risk but first it is important to identify clear criteria to test. However, validation studies may be limited by the low incidence of arterial dissection generally and the even lower incidence of iatrogenic dissection. Such screening guidelines could also enable practitioners to more easily differentiate benign conditions such as mechanical neck pain and cervicogenic dizziness from the serious pathology of arterial dissection.

SUMMARY OF THESIS

Cervical manipulation is occasionally reported to be associated with serious adverse neurovascular events, the most commonly described of which is craniocervical arterial dissection. This thesis has reported four studies which investigated this issue from two different perspectives; on the one hand to improve identification of the patient at risk of an adverse neurovascular event, and on the other to explore common

manual therapeutic procedures to identify any which might be more hazardous than others.

The first three studies explored risk factors and clinical features of craniocervical arterial dissection. The main finding was that examination of the potential risk factors for craniocervical arterial dissection suggests that recent exposure to minor mechanical neck trauma appears to increase risk. Recent infection and vascular anomaly may also be associated with craniocervical arterial dissection, while general cardiovascular risk factors do not appear to be associated. With the possible exception of migraine, these may therefore be less useful predictors of risk prior to manual treatment of the neck. There may also be transient ischaemic clinical features which may act as 'warning signs' in the preceding few weeks prior to admission for dissection. Primary care practitioners should therefore closely question and observe patients for visual disturbance, limb weakness, dizziness and balance or speech deficits if they present with unusual headache or neck pain and with a recent history of minor neck trauma.

The final study investigated manual therapeutic techniques. This study found that neck positions used in common manual therapeutic procedures do not appear to be particularly hazardous in terms of blood flow, and end-range rotation and/or distraction techniques such as those recommended by Cyriax do not appear to have greater effects on blood flow in the craniocervical arteries than more localised segmental rotation positions espoused by Maitland and others. However, some individuals do have larger changes in individual arterial flow volume, and while these generally appear to be compensated for by the other arteries to maintain brain

perfusion, practitioners should carefully monitor patients for any signs and symptoms of brain ischaemia prior to and during manual treatment of the cervical spine.

The findings of this thesis add to existing knowledge about the safety of manual therapy in the cervical spine and highlight some important considerations which will help inform manual therapy practitioners in their clinical reasoning and management of patients presenting with head and neck pain.

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APPENDIX A

ETHICS APPROVALS FOR ALL STUDIES PARTICIPANT INFORMATION SHEETS, CONSENT FORMS, APPROVALS

ETHICS APPROVAL STUDY 1 AND 2

HUMAN RESEARCH ETHICS COMMITTEE



To Chief Investigator or Project Supervisor:	Associate Professor Darren Rivett
Cc:	HNEHREC
Re Project Title:	<i>Risk factors and natural history of craniocervical arterial dissection</i>
Date:	13 July 2007
HNEHREC Ref:	07/06/20/5.04

Dear Associate Professor Rivett

Thank you for your recent *Registration of HNEHREC Approval* for an Initial application for the above project, approved by the Hunter New England Health Human Research Ethics Committee (HNEHREC) on 3 July 2007.

The University's Human Research Ethics Committee (HREC) will be asked to note the HNEHREC approval at its meeting on 15 August 2007. Meanwhile you may proceed.

Should the HREC identify issues that require further consideration, you will be advised.

Your prompt registration of this approval is appreciated.

Yours sincerely

Ms Ruth Gibbins
Human Research Ethics Officer (Acting)

Research Services
Research Office
T +61 2 492 18333
F +61 2 492 17164
Ruth.Gibbins@newcastle.edu.au

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HUNTER NEW ENGLAND NSW HEALTH

17 December 2009

Assoc Prof Darren Rivett
School of Health Sciences
University of Newcastle

Dear Professor Rivett,

Re: Risk factors and clinical presentation of craniocervical arterial dissection

HNEHREC reference number: 09/11/18/5.04
HREC reference number: HREC/09/HNE/357
SSA reference number: SSA/09/HNE/358

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following sites:

- John Hunter Hospital

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to the research governance officer;
2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to the research governance officer.

Yours faithfully

Dr Nicole Gerrard
Research Governance Officer
Hunter New England Health

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)
(New Lambton NSW 2305)
Telephone (02) 49214 950 Facsimile (02) 49214 818
Email: hnehrec@hnehealth.nsw.gov.au
http://www.hnehealth.nsw.gov.au/Human_Research_Ethics

10 December 2009

HUNTER NEW ENGLAND NSW HEALTH

Dr D Rivett
School of Health Sciences
University of Newcastle

Dear Dr Rivett,

**Re: Risk Factors and Clinical Presentation of Craniocervical Arterial Dissection
(09/11/18/5.04)**

**HNEHREC Reference No: 09/11/18/5.04
NSW HREC Reference No: HREC/09/HNE/357**

Thank you for submitting the above protocol for single ethical review. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **18 November 2009**. This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Area Health Service website: http://www.hnehealth.nsw.gov.au/Human_Research_Ethics.

I am pleased to advise that following acceptance under delegated authority of the requested clarifications and changes to the Participant Information Statement by Dr Nicole Gerrand Manager, Research Ethics & Governance, the Hunter New England Human Research Ethics Committee has granted ethical approval of the above project.

The following documentation has been reviewed and approved by the Hunter New England Human Research Ethics Committee:

- The Participant Information Statement (Version 2 dated November 2009);
- The Participant Consent Form; and
- The Study Advertisement

For the protocol: **Risk Factors and Clinical Presentation of Craniocervical Arterial Dissection**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of **5 years** from the date of this letter, after which a renewal application will be required if the protocol has not been completed.

The *National Statement on Ethical Conduct in Human Research (2007)*, which the Committee is obliged to adhere to, include the requirement that the committee monitors the research protocols it has approved. In order for the Committee to fulfil this function, it requires:

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)
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Email: hnehrec@hnehealth.nsw.gov.au
http://www.hnehealth.nsw.gov.au/Human_Research_Ethics

- a report of the progress of the above protocol be submitted at 12 monthly intervals. Your review date is **December 2010**. A proforma for the annual report will be sent two weeks prior to the due date.
- A final report be submitted at the completion of the above protocol, that is, after data analysis has been completed and a final report compiled. A proforma for the final report will be sent two weeks prior to the due date.
- All variations or amendments to this protocol, including amendments to the Information Sheet and Consent Form, must be forwarded to and approved by the Hunter New England Human Research Ethics Committee prior to their implementation.
- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:
 - any serious or unexpected adverse events
 - Adverse events, however minor, must be recorded as observed by the Investigator or as volunteered by a participant in this protocol. Full details will be documented, whether or not the Investigator or his deputies considers the event to be related to the trial substance or procedure. These do not need to be reported to the Hunter New England Human Research Ethics Committee
 - Serious adverse events that occur during the study or within six months of completion of the trial at your site should be reported to the Manager, Research Ethics & Governance, of the Hunter New England Human Research Ethics Committee as soon as possible and at the latest within 72 hours.
 - All other safety reporting should be in accordance with the NHMRC's Safety Monitoring Position Statement – May 2009 available at http://www.nhmrc.gov.au/health_ethics/hrecs/reference/files/090609_nhmrc_position_statement.pdf
 - Serious adverse events are defined as:
 - Causing death, life threatening or serious disability.
 - Cause or prolong hospitalisation.
 - Overdoses, cancers, congenital abnormalities whether judged to be caused by the investigational agent or new procedure or not.
 - unforeseen events that might affect continued ethical acceptability of the project.
- If for some reason the above protocol does not commence (for example it does not receive funding); is suspended or discontinued, please inform Dr Nicole Gerrand, as soon as possible.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)
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http://www.hnehealth.nsw.gov.au/Human_Research_Ethics

Should you have any concerns or questions about your research, please contact Dr Gerrand as per her details at the bottom of the page. The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Please quote **09/11/18/5.04** in all correspondence.

The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully


For: **Dr M Parsons**
Chair
Hunter New England Human Research Ethics Committee

Hunter New England Research Ethics & Governance Unit

(Locked Bag No 1)
(New Lambton NSW 2305)
Telephone (02) 49214 950 Facsimile (02) 49214 818
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http://www.hnehealth.nsw.gov.au/Human_Research_Ethics

Research Information Statement

(To be retained by the participant)

Project Title: Risk Factors and Clinical Features of Cranio-cervical Arterial Dissection

Chief Investigator: Professor Darren Rivett, School of Health Sciences, The University of Newcastle. Tel. (02) 49217220. Email: Darren.Rivett@newcastle.edu.au

Co-investigators: Associate Professor Christopher Levi, Acute Stroke Unit, John Hunter Hospital. Tel. (02) 49855593. Email: Christopher.Levi@hnehealth.nsw.gov.au

Ms Lucy Thomas, School of Health Sciences, The University of Newcastle. Tel. (02) 49218680. Email: Lucy.Thomas@newcastle.edu.au

Associate Professor Mark Parsons, Acute Stroke Unit, Calvary Mater Hospital. Tel (02) 49213490.

Dr Michael Pollack, Acute Stroke Unit, Belmont Hospital. Tel. (02) 49214840.

You are invited to participate in the research project identified above which is being conducted by Lucy Thomas from the School of Health Sciences at the University of Newcastle as part of her PhD studies under the supervision of Professor Darren Rivett and Associate Professor Christopher Levi from the University of Newcastle and with the assistance of the other investigators listed above. You are being invited because you have suffered a stroke.

Why is the research being done?

The research team is interested in the causes of stroke in young people under 55 years old. We are particularly interested in a type of stroke, cervical artery dissection, which affects the arteries in the neck which supply blood to the brain. This type of stroke has occasionally been associated with some types of neck manipulation. The aims of the study are to determine whether young people who have suffered a stroke have similar symptoms or have participated in any activities prior to their stroke which may have made them more vulnerable. If these can be identified it may help to make common activities such as neck manipulation safer.

What does the research involve?

If you agree to participate in the study the investigators will review your medical records in association with your neurologist. Your personal information will be accessed, used and stored in accordance with Commonwealth Privacy Laws and the NSW Health Records and Information Privacy Act 2002. You will undergo treatment in the normal way for your condition but additional analysis of your blood may be undertaken. With your permission your blood sample will also be stored for more detailed analysis at a later stage. This analysis will involve genetic studies focusing

FACULTY OF HEALTH



on risk factors for stroke and artery dissection. You may also be asked to participate in a short interview and clinical examination by one of the investigators Lucy Thomas, who is a physiotherapist. This examination will involve gentle tests of joint and skin mobility. It will also involve a test of your blood pressure done using a small probe pushing against the skin.

What choice do you have?

Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the study. Whether or not you decide to participate in the study will not affect your care in any way. You may withdraw from the study at any stage without having to give a reason and this would not affect your treatment or follow up in any way.

How will your privacy be protected?

All the information collected during the study will be absolutely confidential and your identity will be removed immediately the data is recorded. The information will only be accessible to your neurologist and the research team and will be stored in a locked cabinet and destroyed after 5 years. The results of the study may be published in scientific journals and conference proceedings in the future and also recorded in the PhD thesis of Lucy Thomas, but you will not be able to be identified.

Thank you for your interest in this study.

Complaints about this study

The study has been approved by the Hunter New England Health Human Research Ethics Committee Approval no. 09/11/18/5.04. If you have any concerns please do not hesitate to discuss them with any of the investigators or with Dr Nicole Gerrand Manager Research Ethics and Governance, Hunter New England Health Tel. 49214950 or 49214943, Locked Bag 1 New Lambton 2305. Email: Nicole.Gerrand@hnehealth.nsw.gov.au

Prof Darren Rivett
Project Supervisor

A/Prof Christopher Levi
Head of Acute Services JHH

Ms Lucy Thomas
PhD Candidate

A/Prof Mark Parsons
Consultant Neurologist

Dr Michael Pollack
Consultant in Rehabilitation Medicine

Version 2: November 2009

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Participant Consent form
(To be retained by Chief Investigator)

Project Title: Risk Factors and Clinical Features of Cranio-cervical Arterial Dissection

Chief Investigator: Professor Darren Rivett, School of Health Sciences, The University of Newcastle. Tel.(02) 49217220. Email: Darren.Rivett@newcastle.edu.au

Co-investigators: Associate Professor Christopher Levi, Acute Stroke Unit, John Hunter Hospital. Tel. (02) 49855593. Email: Christopher.Levi@hnehealth.nsw.gov.au

Ms Lucy Thomas, School of Health Sciences, The University of Newcastle. Tel.(02)49218680. Email: Lucy.Thomas@newcastle.edu.au

Associate Professor Mark Parsons, Acute Stroke Unit, Calvary Mater Hospital. Tel (02) 49213490. Mark.Parsons@hnehealth.nsw.gov.au

Dr Michael Pollack, Acute Stroke Unit, Belmont Hospital. Tel. (02) 49214840.

Jacqueline.Mann@hnehealth.nsw.gov.au

I agree to participate in the research project and give my consent freely. I understand the project will be conducted as described in the Research Information Statement and a copy has been given to me. The procedures, demands and risk of the project have been explained to me and I have been given ample opportunity to ask any questions related to my involvement.

I understand I can withdraw from the study at any time without incurring any ill will. I agree that data from this study may be published but my identity will not be disclosed.

I understand that if I have any questions about the study I can contact any of the investigators who will be happy to answer them.

I agree to my blood sample being stored for future research

Yes/No

Signature of Participant

Print name

Date

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version1 Oct 2009

HUMAN RESEARCH ETHICS COMMITTEE



Notification of Expedited Approval

To Chief Investigator or Project Supervisor:	Professor Darren Rivett
Cc Co-investigators / Research Students:	Conjoint Professor Christopher Levi Doctor Grant Bateman Associate Professor Peter Stanwell Mrs Lucy Thomas
Re Protocol:	The effect of selected manual therapy interventions for mechanical neck pain on vertebral and internal carotid arterial blood flow and cerebral perfusion
Date:	12-Jan-2011
Reference No:	H-2010-1305
Date of Initial Approval:	11-Jan-2011

Thank you for your **Response to Conditional Approval** submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission was considered under **Expedited** review by the Chair/Deputy Chair.

I am pleased to advise that the decision on your submission is **Approved** effective **11-Jan-2011**.

In approving this protocol, the Human Research Ethics Committee (HREC) is of the opinion that the project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research, 2007, and the requirements within this University relating to human research.

Approval will remain valid subject to the submission, and satisfactory assessment, of annual progress reports. *If the approval of an External HREC has been "noted" the approval period is as determined by that HREC.*

The full Committee will be asked to ratify this decision at its next scheduled meeting. A formal *Certificate of Approval* will be available upon request. Your approval number is **H-2010-1305**.

If the research requires the use of an Information Statement, ensure this number is inserted at the relevant point in the Complaints paragraph prior to distribution to potential participants You may then proceed with the research.

Conditions of Approval

This approval has been granted subject to you complying with the requirements for *Monitoring of Progress*, *Reporting of Adverse Events*, and *Variations to the Approved Protocol* as detailed below.

PLEASE NOTE:

In the case where the HREC has "noted" the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, or a Renewal of approval, you will apply to the External HREC for approval in the first instance and then Register that approval with the University's HREC.

- **Monitoring of Progress**

Other than above, the University is obliged to monitor the progress of research projects involving human

Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

Best wishes for a successful project.

Professor Alison Ferguson
Chair, Human Research Ethics Committee

For communications and enquiries:
Human Research Ethics Administration

Research Services
Research Office
The University of Newcastle
Callaghan NSW 2308
T +61 2 492 18999
F +61 2 492 17164
Human-Ethics@newcastle.edu.au

Linked University of Newcastle administered funding:

Funding body	Funding project title	First named investigator	Grant Ref
University of Newcastle/New Staff Grant (**)	Factors affecting the safety of cervical manipulation	Thomas Lucy,	G0190274

Professor Darren Rivett

Head, School of Health Sciences
Faculty of Health
University Drive, Callaghan
NSW 2308 Australia
Phone: +61 2 4921 7220
Fax: +61 2 4921 7053
Email: Darren.Rivett@newcastle.edu.au

Information Statement for the Research Project:

The effect of selected manual treatment interventions for mechanical neck pain on vertebral and internal carotid artery blood flow and cerebral perfusion

Version 2: 8/12/10

You are invited to participate in the research project identified above which is being conducted by Lucy Thomas from the School of Health Sciences at the University of Newcastle. This research is a pilot study and comprises one component of her Doctor of Philosophy degree under the supervision of Professor Darren Rivett, Head of the School of Health Sciences at The University of Newcastle and Professor Chris Levi from The Department of Neurology at the John Hunter Hospital.

Why is the research being done?

The purpose of the research is to examine the neck positions of standard clinical treatments that are used to treat neck pain and headache to see if they have any effect on blood flow in the arteries which supply blood to the brain. Whilst these treatments are commonly used in clinical practice it is not known whether the neck positions have any effect on the circulation of blood to the brain.

Who can participate in the research?

We are seeking people aged between 18 and 65 years with **NO** history of serious neck or head injury to participate in this research.

This study is not suitable for you if you;

- have been diagnosed with an inflammatory disease such as rheumatoid arthritis by your doctor
- have been previously diagnosed with any instability in your cervical spine.
- have a cardiac pacemaker or any other internal electronic device
- have any metal implants in your body or have worked with metal grinding equipment
- may be pregnant

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version 2 8/12/10

- experience claustrophobia, as you would be required to be in the confined space of a MRI scanner.

What choice do you have?

Your participation in this research is entirely voluntary. Only those people who agree to participate will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you.

If you do decide to participate, you may withdraw from the project at any time without giving a reason and have the option of removing your data from the study if you wish.

What would you be asked to do?

If you agree to participate, you will be asked to attend the Radiology Department at John Hunter Hospital for one appointment. During this appointment you will be asked to undertake a magnetic resonance imaging (MRI) scan of your neck while lying in a resting position. The researcher will then place your head and neck in a different position to examine any effect on blood flow in your neck arteries and another MRI scan will be taken. Each position will be maintained for approximately 3 minutes to enable the scan to be performed. Six (6) positions will be evaluated. You will have the opportunity to rest between test positions. You may stop the testing at any point if you are uncomfortable or simply wish to do so.

How much time will it take?

You will only need to attend the hospital once. The total examination should take about one hour.

What are the risks and benefits of participating?

There is no direct health or financial benefit to you from agreeing to participate in this study. Your participation may allow us to better understand the effects of manual treatment of the neck on blood flow to the brain and assist in directing further research and education into this area. All scans will be reviewed by the radiologist on the research team. If in the unlikely event some abnormality is detected, the radiologist will discuss this with you and provide you with a report to take to your general practitioner.

Provided you do not have a cardiac pacemaker or other metal implant and are not pregnant, there are no known adverse effects from undergoing an MRI scan. There is a slight risk of experiencing some discomfort from having your head and neck sustained in a test position for the duration of scanning. This is being managed by allowing you as much time to rest in between test positions as you need. You can also stop the testing at any time if you are uncomfortable. Some people may also experience claustrophobia due to the confined space of the MRI scanner. Once

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again, you are free to indicate to the researcher that you wish to stop or rest at any time. The MRI scanner also generates a considerable amount of noise whilst operating. Hearing protection is available for your use to minimise discomfort associated with this noise.

How will your privacy be protected?

All information recorded for the purposes of this study will be coded and identified only by study number. No personal identifying information will be kept with the MRI scans. Data will be securely retained for 7 years in a research storage area within an office of the School of Health Sciences at The University of Newcastle.

How will the information collected be used?

The findings from this study will form part of the PhD thesis of Lucy Thomas, and will be submitted for publication in scientific journals. Results of the study will be presented at future University Seminars and at appropriate national or international conferences. No identification of participating individuals will be possible from the presentation of results in any form. You will be able to access a summary of the results of the study via email from Lucy Thomas once the results of the study are analysed.

What do you need to do to participate?

Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or you have questions, contact a member of the research team.

If you would like to participate, please complete the attached consent form and return it to Lucy Thomas, School of Health Sciences. She will then contact you to arrange a time convenient to you to perform the clinical tests at the John Hunter Hospital.

Further information

If you would like further information please contact Lucy Thomas on 49218680 Lucy.Thomas@newcastle.edu.au or Professor Darren Rivett Darren.Rivett@newcastle.edu.au.

Thank you for considering this invitation.

Professor Darren Rivett
Head, School of Health Sciences

Lucy Thomas
Lecturer in Physiotherapy



THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

Project supervisor

PhD candidate

Complaints about this research

This project has been approved by The University of Newcastle Human Research Ethics Committee, Reference no.xxxxxx

Should you have concerns about your rights as a participant in this research, or you have a complaint about the manner in which the research is conducted, it may be given to the researcher, or, if an independent person is preferred, to Ms Ruth Gibbins, Senior Human Research Ethics Officer, Research Office, The University of Newcastle, University Drive, Callaghan NSW 2308. Ph. 02 4921 6333 Fax. 02 4921 7164 Email: Ruth.Gibbins@newcastle.edu.au

Research Team:

Lucy Thomas, Lecturer in Physiotherapy and PhD candidate
School of Health Sciences
The University of Newcastle

Professor Darren Rivett
Head, School of Health Sciences
The University of Newcastle

Professor Chris Levi
Department of Neurology
John Hunter Hospital

Dr Grant Bateman
Radiologist, Hunter New England Health Service
Conjoint Associate Professor, The University of Newcastle

Associate Professor Peter Stanwell
School of Health Sciences
The University of Newcastle

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MRI SAFETY SCREENING QUESTIONNAIRE

Patient Name: _____
 DOB: _____
 Weight _____ kg/stone Height _____ cm/feet inches

Office Use Only
 RIS
 Sticker

WARNING: Due to the MRI system having a very strong magnetic field that is always on, it may be inappropriate/ hazardous for some individuals to have a scan. Therefore **all** questions must be answered accurately to determine your eligibility. Incorrect information could result in serious injury. If you do not fully understand any of the questions please ask for help.

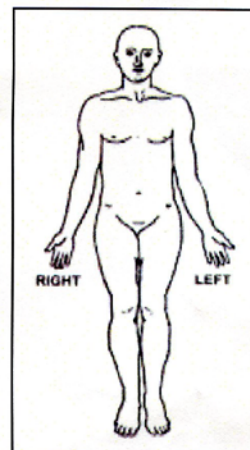
Have you ever had an operation of any kind, at any time in your life? ☐ Yes ☐ No
 List **all** operations, approximate dates, and mark the operation areas on the figure opposite.

Have you had an MRI examination before? ☐ Yes ☐ No If yes, when and where? _____

Do you have any of the following? (Please circle Yes or No)

Yes No Cardiac pacemaker/ Defibrillator/ Pacing wires
 Yes No Artificial heart valve
 Yes No Aneurysm clip
 Yes No Ear implant (e.g. Stapes, Cochlear)/ Bionic ear
 Yes No Vascular implant/ Stent/ Coil/ Filter/ Aortic graft
 Yes No Neurostimulator or Drug infusion pump
 Yes No Electronic or Magnetically activated implant or device
 Yes No Any other type of prosthesis/ implant (eye, penile etc.)

If you answered yes to any of these questions, please call 49213396, to allow implants to be checked to assess your suitability for MRI.



Yes No Joint replacement or artificial limb
 Yes No Metal rods, plates or screws in/on bones
 Yes No Metal/ Shrapnel/ Bullet injuries
 Yes No Hearing aid

Yes No False teeth/ Removable bridgework
 Yes No Body piercing
 Yes No Tattoos
 Yes No Nicotine or medication patches

Yes No Have you ever been a metal worker (e.g. welding, grinding, lathe)?
 Yes No Have you ever had metal in your eye following an injury or operation? If yes, has it been removed? ☐ Yes ☐ No
 Yes No Is there any possibility of metal in your body through injury or surgery, other than that stated on this sheet?

Yes No Do you have a history of kidney (renal) disease?
 Yes No Are you on dialysis?
 Yes No Have you ever had an allergic reaction to contrast media?

Yes No Do you have liver failure?
 Yes No Previous or awaiting a liver transplant?
 Yes No Are you diabetic?

Yes No Do you suffer from claustrophobia?
 Yes No Is there any possibility you could be pregnant?

Yes No Are you breastfeeding?

Yes No Have you filled out and understood all questions on this form?

I hereby confirm that I have read, understood and correctly answered the above questions and agree to have an MRI and procedures necessary to complete the examination

Signature of person completing form: _____ Date ____ / ____ / ____

Form completed by: ☐ Patient ☐ Relative ☐ Doctor ☐ Other (please specify) _____

Print name and contact number/ page number

WARNING: Before entering the scan room **all** metallic objects must be removed including watches, jewellery, hearing aids, wallet, credit cards, coins, keys, pens/pencils, scissors, mobile phones, hair pins, clips, piercings, clothing with metal e.g. bra, jeans, zips, studs. Lockers available.

Office Use Only:

Form information reviewed by, and first time out identification: _____

Signature

Designation

2nd Time Out identification by: _____

Participant Consent form
(To be retained by Chief Investigator)

Project Title: The effect of selected manual therapy interventions for mechanical neck pain on vertebral and internal carotid arterial blood flow and cerebral perfusion

Chief Investigator: Professor Darren Rivett, School of Health Sciences, The University of Newcastle. Tel.(02) 49217220. Email: Darren.Rivett@newcastle.edu.au

Co-investigators: Professor Christopher Levi, Acute Stroke Unit, John Hunter Hospital. Tel.(02) 49855593. Email: Christopher.Levi@hnehealth.nsw.gov.au

Ms Lucy Thomas, School of Health Sciences, The University of Newcastle. Tel.(02)49218680. Email: Lucy.Thomas@newcastle.edu.au

Dr Grant Bateman, Clinical Director, Department of Radiology, John Hunter Hospital. Tel.(02) 49213459. Email: Grant.Bateman@hnehealth.nsw.gov.au

Associate Professor Peter Stanwell, School of Health Sciences, The University of Newcastle. Tel.(02)49216586. Email: Peter.Stanwell@newcastle.edu.au

I agree to participate in the research project and give my consent freely. I understand the project will be conducted as described in the Research Information Statement and a copy has been given to me. The procedures, demands and risk of the project have been explained to me and I have been given ample opportunity to ask any questions related to my involvement.

I understand I can withdraw from the study at any time without any disadvantage.

I agree that data from this study may be published but my identity will not be disclosed.

I understand that if I have any questions about the study I can contact any of the investigators who will be happy to answer them.

Signature of Participant

Print name

Date

APPENDIX B
DATA COLLECTION PROFORMA FOR STUDIES

DATA EXTRACTION PROFORMA STUDY 1 AND 3

Craniocervical arterial dissection study

ID label or

MRN.....

Date of birth..... Sex M F Age.....

Date of Admission.....

Diagnosis

A. History (describe how the stroke occurred and when you first became aware of symptoms)

.....

Preceding events (any activities you may have been doing prior to stroke onset)

.....

B. Risk factors- mechanical trauma

Research suggests that some strokes may be associated with a minor injury or strain of the neck. Everyday activities such as manual treatment of the neck, jerky head movements, heavy lifting or physical work, sports activities, sexual intercourse or having hair washed at the hairdressers have been implicated.

In the past 4 weeks have you had any strain or blow to your head or neck from any of the following?

	Yes	No	If yes describe the injuring movement to your neck and the amount of force?
Manual treatment of your neck			
mild direct neck trauma			
mild indirect neck trauma			
Sexual intercourse			
Jerky head movements			
Sports activity- straining neck or hitting head			
Heavy lifting			
Any adverse response to manual neck treatment in past?			

(looking for direction neck may have moved in, the force involved- particularly rotational strain or traction on neck, high force, rapid movement)

Prompting questions:

- In the last 4 weeks have you had any manual therapy such as physiotherapy, chiropractic or osteopathic treatment to your neck?
If so, can you describe the direction your neck was moved in and the amount of force used?
.....
- Do you have regular manual treatment of your neck? How often?.....
Last treatment?.....
- Have you ever had any adverse effects from manual therapy to your neck?
Describe.....
- In the last 4 weeks have you engaged in any physical activity such as a sport or heavy lifting which may have directly or indirectly put a strain on your neck or shoulders?
Can you describe the position your head was in and the amount of force or effort?
.....

Risk factors- Cardiovascular				
	Yes	No	Additional details (or circle)	
Has anyone in your family had a stroke under 55 years?				
Do you smoke? (Circle)			Currently	in past
Do you have high blood pressure? (Circle)			Reported	on anti-hypertensive medication
Do you have high cholesterol? (Circle)			Reported	diagnosed by Dr
Are you on the contraceptive pill? (Circle)			Currently	recent past
Are you diabetic? (Circle)			IDDM	NIDDM
Do you suffer with migraines? (Circle)			Diagnosed by Dr	on medication reported
			frequency	

Risk factors- General health

Height..... Weight.....

How is your general health, do you have any other medical conditions?

In the last 4 weeks have you had viral illness or infection? Y/N

Describe.....

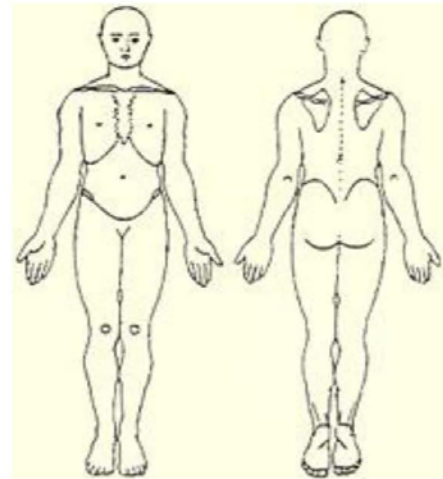
In the last 4 weeks have you taken any recreational drugs? Y/N

General health	Yes	No	Describe
Recent viral illness			
Recent infection			
Substance abuse			

Connective tissue disease	Yes	No	Describe
Type II Ehler's Danlos			
Marfan's syndrome			
Fibromuscular dysplasia			

Date	FBC	CRP	Immunology	Coagulation times On adm	

Presenting signs and symptoms (record on chart)
Signs: eg. weakness- upper/lower limb, facial palsy, horner's, ptosis, dyarthria, aphasia, dysphasia, swallowing deficit, unsteadiness, ataxia, vomiting, other...
Symptoms: eg. headache, neck pain, dizziness, nausea, paraesthesia - facial, upper/lower limb, visual deficit (describe), confusion, other...



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MRI (date).....
report.....

MRA (date).....
report.....

U/S (date).....
report.....

CT (date).....
report.....

```

CTA
(date).....
Report.....

Treatment Heparin Warfarin..... Clopidogrel..... Aspirin.....
.....
.....

Outcome at discharge MRS score.....
.....
.....
.....

APPENDIX C
STATISTICAL ANALYSIS

LOGISTIC REGRESSION ANALYSIS STUDY 3

NORMALITY PLOTS STUDY 4

Study 3: Exact logistic regression analysis of risk factors

Exact logistic regression

Number of obs =	40
Model score =	.7647059
Pr >= score =	0.6614

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
recentinf	2.205542	4	0.6614	.2730372	27.48134

Exact logistic regression

Number of obs =	40
Model score =	.7647059
Pr >= score =	0.6614

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
vascanom	2.205542	4	0.6614	.2730372	27.48134

Exact logistic regression

Number of obs =	40
Model score =	21
Pr >= score =	0.0000

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
trauma	53.44362*	14	0.0000	7.499211	+Inf

(*) median unbiased estimates (MUE)

Exact logistic regression

Number of obs =	40
Model score =	.3513514
Pr >= score =	1.0000

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
contissue	2.073171	2	1.0000	.0997619	130.9947

Exact logistic regression

Number of obs =	40
Model score =	0
Pr >= score =	1.0000

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
HTN	1	6	1.0000	.2085823	4.794271

Exact logistic regression

Number of obs =	40
Model score =	1.714286
Pr >= score =	0.3203

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
smoking	.4168766	5	0.3203	.0838352	1.861005

Exact logistic regression

Number of obs =	40
Model score =	11.32258
Pr >= score =	0.0012

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
cholesterol	.0498053*	0	0.0012	0	.3570897

(*) median unbiased estimates (MUE)

Exact logistic regression

Number of obs =	40
Model score =	2.08
Pr >= score =	0.2733

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
pill	.3370721	3	0.2733	.0469859	1.840435

Exact logistic regression

Number of obs =	40
Model score =	4.68
Pr >= score =	0.0648

Diagnosis	Odds Ratio	Suff.	2*Pr(Suff.)	[95% Conf. Interval]	
migraine	5.735188	8	0.0648	.9222181	64.61989

STUDY 4

TESTS FOR NORMALITY

Vertebral artery

Shapiro-Wilk W test for normal data					
Variable	Obs	W	V	z	Prob>z
RVaneut	20	0.96432	0.845	-0.340	0.63320
RVAlr	20	0.91317	2.055	1.452	0.07326
RVArr	20	0.96354	0.863	-0.297	0.61674
RVAIrdist	20	0.94719	1.250	0.450	0.32642
RVArrdist	20	0.91755	1.952	1.348	0.08889
RVAcilr	20	0.96410	0.850	-0.328	0.62854
RVAcilrr	20	0.97526	0.586	-1.078	0.85958
RVAdist	20	0.97341	0.629	-0.933	0.82454
LVAneut	20	0.91778	1.946	1.342	0.08981
LVAIrr	20	0.85897	3.338	2.429	0.00756
LVArr	20	0.93946	1.433	0.725	0.23420
LVAIrdist	20	0.95052	1.171	0.319	0.37583
LVArrdist	20	0.91340	2.050	1.447	0.07481
LVAcilr	20	0.94506	1.300	0.529	0.29823
LVAcilrr	20	0.97431	0.608	-1.003	0.84196
LVAdist	19	0.87705	2.807	2.073	0.01908

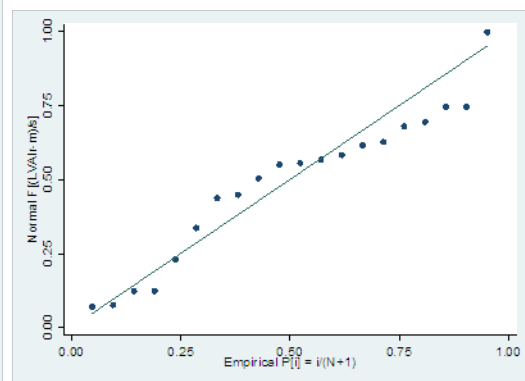
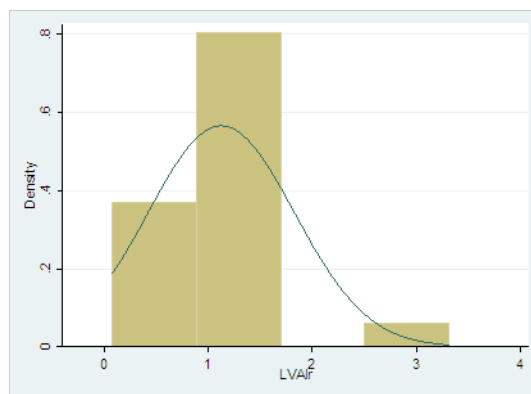
Internal carotid artery

Shapiro-Wilk W test for normal data					
Variable	Obs	W	V	z	Prob>z
ricaneut	20	0.97321	0.634	-0.918	0.82065
ricalr	20	0.94761	1.240	0.434	0.33228
ricarr	20	0.95612	1.039	0.077	0.46947
ricalrdist	20	0.94767	1.239	0.431	0.33313
ricarrdist	20	0.97110	0.684	-0.765	0.77784
ricacilr	20	0.88106	2.815	2.086	0.01849
ricacilrr	20	0.96365	0.860	-0.303	0.61906
ricadist	20	0.98325	0.396	-1.865	0.96890
licaneut	20	0.93283	1.590	0.935	0.17502
licalr	20	0.94965	1.192	0.354	0.36180
licarr	20	0.94387	1.329	0.573	0.28346
licalrdist	20	0.96493	0.830	-0.375	0.64630
licarrdist	20	0.90258	2.306	1.684	0.04611
licacilr	20	0.92644	1.741	1.118	0.13184
licacilrr	20	0.95597	1.042	0.083	0.46688
licadist	20	0.96153	0.911	-0.189	0.57481

Plots for selected positions showing non-normal distribution

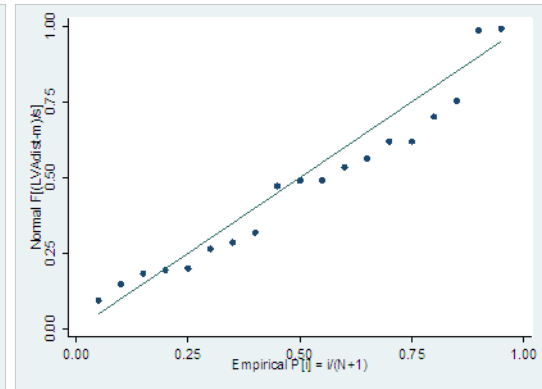
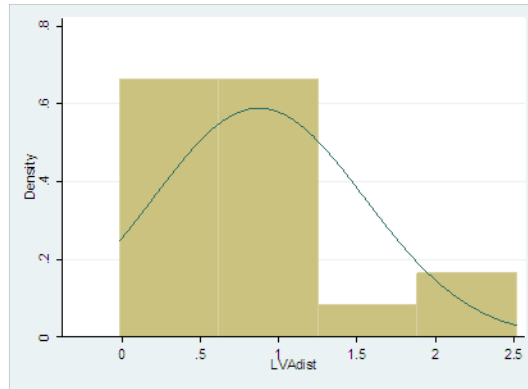
```
. sum LVAIrr, detail
```

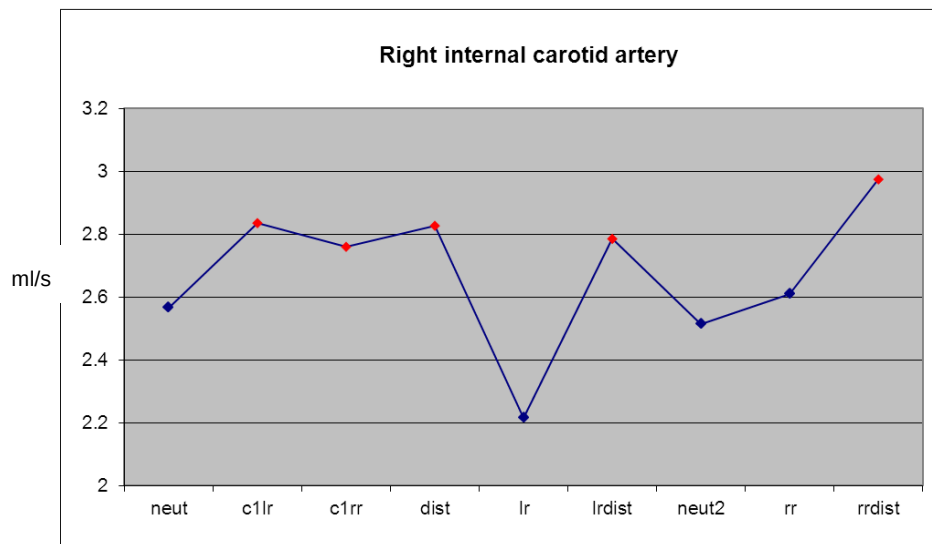
LVAIrr					
Percentiles	Smallest				
1%	.077	.077			
5%	.094	.111			
10%	.2075	.304	Obs	20	
25%	.7115	.305	Sum of Wgt.	20	
50%	1.215		Mean	1.1215	
75%	1.4	Largest	Std. Dev.	.7050261	
90%	1.59	1.48	Variance	.4970618	
95%	2.45	1.59	Skewness	1.134541	
99%	3.31	3.31	Kurtosis	5.892122	



```
. sum LVAdist, detail
```

LVAdist				
	Percentiles	Smallest		
1%	-.015	-.015		
5%	-.015	.166		
10%	.166	.265	Obs	19
25%	.307	.29	Sum of Wgt.	19
50%	.859		Mean	.8744211
75%	1.08	Largest	Std. Dev.	.6765775
90%	2.4	1.23		
95%	2.52	1.34	Variance	.4577571
99%	2.52	2.4	Skewness	1.167823
		2.52	Kurtosis	3.950887





Mean average flow volume (ml/s) for right internal carotid artery in the nine neck positions showing unusually low value for left rotation which was responsible for initial statistically significant test comparing difference in flow between neck positions using linear mixed model with Bonferroni adjustment (Chapter 6 p.170)

APPENDIX D
PUBLISHED PAPERS

STUDY 1



Original article

Risk factors and clinical features of craniocervical arterial dissection

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ARTICLE INFO

Article history:

Received 18 May 2010

Received in revised form

6 December 2010

Accepted 15 December 2010

Keywords:

Vertebral artery dissection

Carotid artery

Internal dissection

Cervical manipulation

ABSTRACT

Craniocervical arterial dissection is one of the most common causes of ischaemic stroke in young people and is occasionally associated with neck manipulation. Identification of individuals at risk will guide risk management. Early recognition of dissection in progress will expedite medical intervention. Study aims were to identify risk factors and presenting features of craniocervical arterial dissection. Medical records of patients from the Hunter region of New South Wales, Australia aged ≤ 55 years with radiographically confirmed or suspected vertebral or internal carotid artery dissection, were retrospectively compared with matched controls with stroke from some other cause. Records were inspected for details of clinical features, presenting signs and symptoms and preceding events. Records of 47 dissection patients (27 males, mean age 37.6 years) and 43 controls (22 males, mean age 42.6 years) were inspected. Thirty (64%) dissection patients but only three (7%) controls reported an episode of mild mechanical trauma, including manual therapy, to the cervical spine within the preceding three weeks. Mild mechanical trauma to the head and neck was significantly associated with craniocervical arterial dissection (OR 23.53). Cardiovascular risk factors for stroke were less evident in the dissection group (<1 factor per case) compared to the controls (>3).

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1. Introduction

Craniocervical arterial dissection (CAD) is one of the most common causes of ischaemic stroke in the young to middle aged population (Touze et al., 2003; Dittrich et al., 2007), accounting for 10–25% of all ischaemic stroke in this age group. It is considered to often occur spontaneously, without obvious cause, with an annual incidence of 2.5–3/10,000 (Schievinck, 2001; Dziewas et al., 2003).

There is limited evidence to suggest that young persons suffering a 'spontaneous' CAD may actually have a pre-existing but subclinical arteriopathy, vascular anomaly or genetic predisposition (Dittrich et al., 2007). Such intrinsic susceptibility may be caused by a number of different factors, such as subclinical connective tissue disorders (Brandt et al., 1998; Schievinck, 2001) or a more generalised arteriopathy (Volker et al., 2005). In patients with such an existing intrinsic susceptibility, exposure to an extrinsic trigger such as minor mechanical trauma to the neck or a recent infection or viral illness, may initiate dissection. Cervical spine manipulation has occasionally been associated with serious adverse events (Assendelft et al., 1996; Hurwitz et al., 1996), in particular dissection of the vertebral or

internal carotid arteries (Paciaroni and Bogousslavsky, 2009). Recent infection has been proposed as a possible trigger for dissection, perhaps associated with the recognised seasonal variation of spontaneous CAD, with a peak in autumn and winter (Schievinck, 2001; Paciaroni et al., 2006); dissection potentially occurring due to the presence of pro-inflammatory mediators and an immunological host response causing temporary friability of the arterial wall (Guillon et al., 2003; Lindsberg and Grau, 2003).

Traditional risk factors for cardiovascular disease are not generally thought to be contributive in dissection as cases are generally under 55 years and therefore less likely to have developed associated conditions, such as atherosclerosis (Schievinck, 2001). Nonetheless, Kerry and colleagues have recommended that manual therapists should consider assessment of vascular risk factors (incorporating a system based approach) for all patients for whom manual treatment for the neck is proposed (Kerry et al., 2008).

If individuals with intrinsic susceptibility who may be at greater risk of dissection can be more readily identified, appropriate risk management for neck manipulation may be applied. However, it is likely pre-manipulative protocols used by manual therapy practitioners, which often include provocative positional tests, do not identify all patients at risk and are not ideal for screening purposes (Refsauge, 1994; Kerry et al., 2008; Thomas et al., 2009). Clinical screening is further complicated by the fact that signs and

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symptoms of CAD may include headache and neck pain, mimicking a musculoskeletal presentation. Indeed, some patients might actually seek treatment from a manual therapy practitioner for the painful symptoms of a dissection already in progress (Haneline and Lewkovich, 2005; Cassidy et al., 2008) and differential diagnosis may be difficult. If the early signs and symptoms of CAD can be more easily recognised, including the more subtle neurological findings, inappropriate interventions such as manipulation may be avoided and medical treatment expedited, potentially reducing the impact of the stroke.

Previous research has identified patients with CAD from hospital or stroke data banks, individual clinic records and medico-legal reports. Often these studies were uncontrolled and age limitations not always applied (Haldeman et al., 2002; Haneline and Lewkovich, 2005; Arnold et al., 2009). Findings are commonly inconsistent between studies and consensus has yet to be reached on definitive risk factors for dissection.

The aim of the current study was to retrospectively investigate young patients, under 55 years, with radiologically confirmed or clinically suspected vertebral or internal carotid artery dissection presenting to hospital in the Hunter and Manning regions of New South Wales, Australia. Specifically, the aims were to identify risk factors for dissection from the patient history, examine and describe the presenting clinical features, and gain an understanding of the natural history and outcome for patients following CAD.

2. Methods

Cases of vertebral or internal carotid artery dissection were identified via the medical record coding system of the John Hunter Hospital between 1998 and 2009. This hospital is a large tertiary referral hospital of 550 beds servicing the Hunter and Manning regions with a population of approximately 617,000 (Australian Bureau of Statistics, 2009). The medical records database was searched using the international diagnostic coding system ICD-10 (World Health Organisation, 2007) for patients with radiologically confirmed or suspected vertebral or internal carotid arterial dissection.

The database was searched in the following diagnostic categories:

- 1670 dissection of cerebral arteries non ruptured;
- 1630–1639 cerebral infarction unspecified;
- 1640 stroke not specified as haemorrhage or infection;
- 1660–1669 occlusion and stenosis of unspecified cerebral artery;
- 1650–1659 occlusion and stenosis of carotid artery.

Although some of these codes do not directly identify vertebral or internal carotid dissection, in case of possible miscoding it was expected that dissection cases would at least be coded under one of these categories. An additional search was also made of the hospital electronic discharge referral system using keywords of vertebral or internal carotid artery dissection. Throughout the course of the study regular communication with research and clinical staff of the neurology unit was made to identify any new dissection cases.

Inclusion criteria were all patients under 55 years with radiologically confirmed or suspected vertebral or internal carotid artery dissection. Control subjects were age and sex matched patients with a clinico-radiological diagnosis of stroke from some cause other than arterial dissection. Patients diagnosed with sub-arachnoid haemorrhage were excluded as this is a rare condition with a distinctively different presentation.

Once the medical record numbers of patients were identified, medical notes were retrieved and data extracted using a standardised data extraction proforma administered by the lead author. Information was sought in the medical notes of both dissection and control subjects about the presenting signs and symptoms of the stroke, the history of preceding events, in particular minor mechanical trauma and specifically manual treatment of the neck, pre-existing medical status including reports of any recent infection or febrile illness, and pre-existing cardiovascular risk factors. Details of any radiological and haematological investigations were also recorded.

Brain and vascular imaging was accessible through the John Hunter Hospital Picture Archiving Communication System (PACS) and was reviewed using a standardised proforma. The brain imaging was evaluated on-line by two experienced stroke neurologists (CL and MP) blinded to the case or control status. The imaging diagnosis of confirmed CAD was made by consensus.

The outcome of the stroke was recorded as a modified Rankin score (MRS) (van Swieten et al., 1988). The MRS is widely used for assessing global outcomes following stroke. It has been demonstrated to have acceptable inter-rater reliability ($\kappa = 0.71$ – 0.95) (van Swieten et al., 1988; Wolfe et al., 1991; Wilson et al., 2005). The project was approved by the Hunter New England Area Human Ethics Committee.

3. Data analysis

Descriptive statistics were used to summarise the demographic data, outcomes and risk factors. Simple logistic regression was performed for the major risk factors identified. All factors with a *p* value of 0.2 or less were included in a multiple logistic regression model; outcomes were expressed as odds ratios with 95% confidence intervals. Statistical analysis was performed using the STATA statistical/data analysis software (version 11, Statacorp, Texas, USA).

4. Results

The medical records of 47 dissection subjects and 43 age and sex matched controls were reviewed. Of the dissection subjects, 27 (57%) had sustained a dissection of the vertebral artery or basilar artery (VBAD) and 20 (43%) subjects had sustained a dissection of the internal carotid artery (ICAD). Subject demographics and characteristics are reported in Table 1. Of the subjects, 36 (77%) had radiographic confirmation of their dissection arrived at by consensus between the two reviewing neurologists (CL and MP). The neurologists were in agreement on all cases. For the remaining 11 subjects, diagnosis of dissection was based on suggestive history and clinical examination at the time of admission as well as radiological suspicion of dissection.

Table 1
Subject characteristics.

Subject characteristics	Dissection subjects <i>N</i> = 47	Control subjects <i>N</i> = 43	<i>P</i> value
Vertebrobasilar artery territory	27 (57%)	5 (12%)	<0.0001
Radiological confirmation	20 (74%)	5 (100%)	<0.0001
Clinical diagnosis but no imaging confirmation	7 (26%)	0	–
Internal carotid artery territory	20 (43%)	38 (88%)	<0.0001
Radiological confirmation	16 (80%)	38 (100%)	<0.0001
Clinical diagnosis but no imaging confirmation	4 (20%)	0	–
Age yrs $\pm$ SD	37.6 $\pm$ 10	43.6 $\pm$ 7.3	0.42
Males	27	22	0.7

Table 2a

Risk factors identified in dissection and control subjects. VBA = vertebrobasilar artery ICA = internal carotid artery.

Risk factor	Dissection subjects N = 47	Control subjects N = 43	Odds ratio (95%CI)	Adjusted odds ratio ^a (95%CI)	P value
Recent head or neck trauma	30 (64%) (17 VBA, 13 ICA)	3 (7%)	23.53 (6.31, 87.70)	23.51 (5.71, 96.89)	<0.000
Neck manual therapy	11 (23%) (8 VBA, 3 ICA)	1 (2%)	12.8 (1.58, 104.28)	12.67 (1.43, 112.0)	0.009
Recent infection	12 (26%) (6 VBA, 6 ICA)	4 (9%)	3.34 (0.99, 11.32)	3.77 (1.07, 13.24)	0.040
Craniocervical vascular anomaly ^b	17 (36%) (17 VBA)	7 (16%)	2.62 (0.90, 7.60)	3.0 (0.99, 9.02)	0.068

^a Multiple regression analysis with odds ratios adjusted for age and gender.^b Anomalies involving the posterior circulation such as ectatic or hypoplastic VA or VA ending in posterior inferior cerebellar artery (PICA).

4.1. Risk factors

Thirty (64%) of the dissection subjects (17 VBAD, 13 ICAD) had a history of minor mechanical trauma to the neck (i.e. no evidence of fracture or dislocation) within the preceding three weeks, of which 11 (23%) subjects (8 VBAD, 3 ICAD) had a report of recent manual therapy to their neck (Tables 2a,b). An additional three (6%) subjects had a history of head trauma within the past several years. In contrast, only three (7%) control subjects had a history of recent mechanical trauma to the head or neck, and only one of these cases involved manual therapy to the cervical spine. This equates to an odds ratio (95% CIs) of 23.53 (6.31, 87.7) for mechanical neck trauma ($p < 0.001$) and 12.8 (1.58, 104.28) for neck manual therapy ($p = 0.009$), both of which remain significant in the adjusted model (adjusted for age and gender). The types of trauma are shown in Table 3.

Seventeen (36%) of the dissection subjects had radiological evidence of vessel abnormalities involving the posterior circulation, such as an ectatic or hypoplastic vertebral artery or one ending in the posterior inferior cerebellar artery. On the other hand, only seven (16%) control subjects had a report of vessel abnormalities within the cerebral circulation. The adjusted odds ratio of 3.0 (95% CI 0.99, 9.02) narrowly missed significance in the adjusted model.

Twelve (26%) of the dissection subjects had a history of recent infection or viral illness prior to their admission to hospital compared with just four (9%) of the control subjects, for an adjusted odds ratio of 3.77 (95% CI 1.07, 13.24). Dissections occurred most frequently during autumn and winter (30 subjects, 64%), whereas 53% (23 subjects) of strokes in the control group occurred during these seasons.

Blood investigations were inconsistently reported in the medical notes so no meaningful comparisons could be made between groups.

4.2. Cardiovascular risk factors

The occurrence of cardiovascular risk factors is reported in Table 4a,b. Risk factors displaying statistical significance were hypertension, odds ratio (OR) 0.23 (95% confidence intervals (CI) 0.09, 0.58), smoking OR 0.22 (CI 0.13, 0.73) and elevated cholesterol OR 0.27 (CI 0.11, 0.66). Notably, these were more likely to occur in controls.

In general, the controls had considerably more cardiovascular risk factors than the dissection subjects; an average of 3.23 (SD 1.6)

or more risk factors and other co-morbidities, in contrast to the dissection subjects who were generally without other co-morbidities until their dissection and had an average of 1.4 (SD 1.3) cardiovascular risk factors.

Sub-group analysis of risk factors was performed for the radiologically confirmed cases (i.e. excluding the 11 unconfirmed) and findings were similar except that recent infection was no longer significant ($p = 0.29$) and vascular anomaly became significant ($p = 0.13$) (Tables 2b and 4b).

4.3. Clinical presentation

The most commonly presenting feature in the dissection group was headache; reported by thirty eight (81%) subjects compared with 22 (51%) controls. The frequency and distribution of reported signs and symptoms are shown in Tables 5 and 6.

In subjects with VBAD, the most common signs and symptoms were headache, neck pain, dizziness and unsteadiness. Headache was present in 23 (85%) subjects, commonly in the occipital region (65% VBAD subjects), but notably was not present in all subjects and was not always severe. Dizziness was experienced by 14 (52%) subjects. Unsteadiness or ataxia was present in 18 (67%) subjects.

In subjects with ICAD, the most common signs and symptoms were headache, ptosis, facial palsy, and upper and lower limb weakness. Headache occurred in 15 (75%) subjects and was commonly reported in the retro-orbital (47%) or temporal (47%) regions. Ptosis and facial palsy each occurred in twelve (60%) subjects, upper limb weakness in 13 (65%) cases and lower limb weakness in ten (50%).

In the control group, which comprised largely anterior circulation stroke, headache was a presenting feature in only 22 (51%) of subjects and was not localised to any particular region. Dysphasia (30 subjects, 70%), upper (32 subjects, 74%), and lower limb weakness (26 subjects, 60%), upper limb paraesthesia (20 subjects, 47%) and facial palsy (20 subjects, 47%) were much more commonly reported in controls.

4.4. Outcome

The majority (72%) of patients in both the dissection and control groups had a favourable outcome i.e. MRS ≤ 2 (Table 7). An MRS of 2 means a patient is able to walk and manage their own affairs (van Swieten et al., 1988).

Table 2b

Risk factors identified in dissection and control subjects: sub-group analysis of radiologically confirmed cases. VBA = vertebrobasilar artery ICA = internal carotid artery.

Risk factor	Confirmed dissection subjects N = 36	Control subjects N = 43	Odds ratio (95%CI)	Adjusted odds ratio ^a (95%CI)	P value
Recent head or neck trauma	23 (64%) (13 VBA, 10 ICA)	3 (7%)	26.67 (6.83, 104.17)	25.29 (6.04, 105.82)	<0.000
Neck manual therapy	8 (22%) (7 VBA, 1 ICA)	1 (2%)	12.0 (1.42, 101.30)	12.67 (1.43, 112.0)	0.022
Recent infection	8 (22%) (4 VBA, 4 ICA)	4 (9%)	1.94 (0.62, 6.08)	1.90 (0.58, 6.22)	0.287
Craniocervical vascular anomaly ^b	14 (39%) (9 VBA, 5 ICA)	7 (16%)	3.27 (1.14, 9.36)	4.46 (1.37, 14.60)	0.013

^a Multiple regression analysis with odds ratios adjusted for age and gender.^b Anomalies involving the posterior circulation such as ectatic or hypoplastic VA or VA ending in posterior inferior cerebellar artery (PICA).

Table 3

Breakdown of types of minor mechanical trauma described in patient history. Note that trauma may have been categorised under more than one type.

Minor mechanical trauma	Dissection subjects <i>n</i> = 30	Control subjects <i>n</i> = 3
Manual therapy	11 (6 chiro, 2 massage, 1 osteo, 2 physio)	1 (osteo)
Sport with direct trauma to head/neck	9 (1 martial arts, 4 fall from horse/bike/wakeboard, 1 rugby, 1 netball, 1 gymnastics, 1 head clash)	0
Heavy lifting	3 (1 boxes, 2 gym work)	0
Motor vehicle accident	2	1
Direct trauma to neck	2 (1 twisting, 1 attempted hanging)	0
Indirect trauma to neck	3 (1 show ride, 1 horse riding, wisdom teeth extraction)	1 (playing squash)

5. Discussion

The present investigation is the first retrospective study of CAD patients from a manual therapy perspective. It is one of few case controlled studies of dissections and importantly used a representative sample of young strokes rather than those potentially more severe cases who might undertake medico-legal action. The overarching aim was to identify key findings which may be of use to manual therapy practitioners in the management of patients presenting with neck pain or headache, and specifically to help therapists identify those patients in whom manual therapy may be inappropriate.

5.1. Risk factors

The main finding of our study in the identification of risk factors was that there was a statistically significant association of recent minor mechanical trauma, including manual therapy to the neck, and CAD, in comparison to a control group. This finding is consistent with that of other authors investigating CAD, though not all previous studies used a control group (Dziewas et al., 2003; Touze

et al., 2003; Dittrich et al., 2007). It is therefore important for manual therapy practitioners to be aware of the possibility of arterial dissection in a patient presenting with headache or neck pain and reporting a recent history of even minor head or neck trauma. In such cases, manual therapy practitioners should be particularly alert to the presence of other more subtle neurological signs and symptoms such as balance impairments, ptosis or visual disturbances. Moreover, the results of the study serve to caution practitioners to use minimal force when treating the cervical spine and to be alert to the potential dangers of a patient suddenly developing neck pain or headache following manual treatment to the neck (Smith et al., 2003).

All presenting young stroke patients are routinely questioned about previous manual therapy to the neck in our neurology unit, so it was possible to compare this factor between the groups. Therefore the potential limitation of this question not having been asked of the control patients was less likely in our study, although it is acknowledged that a negative response may not have always been recorded. However, when patients had reported prior manual treatment, no detail of the type or procedure was recorded. It was thus not possible to determine the relative risk of one type of manual therapy (e.g. manipulation), let alone specific technique, over another. Although therapists may feel safer in using gentler manual techniques, it should be borne in mind that the condition they are treating could in fact be a dissection mimicking a musculoskeletal presentation. Therapists must therefore be able to recognise a possible dissecting artery and expedite onward medical referral, rather than risk being implicated in the cause or potentially progressing the pathology (Cassidy et al., 2008).

Although recent infections occurred more frequently in the dissection group and dissections were more common in autumn and winter compared to the control group, this factor was of borderline statistical significance in this study ($p = 0.04$). This may have been due to low numbers of subjects or reporting bias of minor conditions. Similarly information on blood results, which may have helped identify any inflammatory factors, was limited. Although information about recent infections or viral illness was reported as part of the normal history taken on admission to

Table 4a

Cardiovascular risk factors identified in dissection and control subjects.

Risk factor	Dissection subjects <i>N</i> = 47	Control subjects <i>N</i> = 43	Odds ratio (95%CI)	Adjusted odds ratio ^a (95%CI)	<i>P</i> value
Hypertension	9 (19%)	23 (53%)	0.23 (0.09, 0.58)	0.29 (0.11, 0.79)	0.001
Current or past smoker	14 (30%)	28 (65%)	0.31 (0.13, 0.73)	0.31 (0.13, 0.78)	0.001
High cholesterol	11 (23%)	23 (53%)	0.27 (0.11, 0.66)	0.33 (0.12, 0.85)	0.001
Family history of stroke	4 (9%)	6 (14%)	0.40 (0.13, 1.29)	0.55 (0.16, 1.88)	0.126
Oral contraception	5 (11%)	4 (9%)	1.46 (0.38, 5.58)	1.32 (0.31, 5.69)	0.578
Migraine	11 (23%)	8 (19%)	1.62 (0.56, 4.64)	1.54 (0.51, 4.67)	0.373

^a Multiple regression analysis with odds ratios adjusted for age and gender.

Table 4b

Cardiovascular risk factors identified in dissection and control subjects: sub-group analysis of confirmed cases.

Risk factor	Confirmed dissection subjects <i>N</i> = 36	Control subjects <i>N</i> = 43	Odds ratio (95%CI)	Adjusted odds ratio ^a (95%CI)	<i>P</i> value
Hypertension	7 (19%)	23 (53%)	0.23 (0.83, 0.64)	0.28 (0.09, 0.85)	0.005
Current or past smoker	12 (33%)	28 (65%)	0.33 (0.13, 0.83)	0.33 (0.13, 0.89)	0.018
High cholesterol	8 (22%)	23 (53%)	0.25 (0.92, 0.67)	0.28 (0.10, 0.82)	0.006
Family history of stroke	4 (11%)	6 (14%)	1.86 (0.69, 4.98)	2.18 (0.76, 6.26)	0.213
Oral contraception	5 (14%)	4 (9%)	1.53 (0.38, 6.36)	1.69 (0.38, 7.63)	0.525
Migraine	10 (28%)	8 (19%)	1.98 (0.66, 5.88)	1.99 (0.64, 6.27)	0.220

^a Multiple regression analysis with odds ratios adjusted for age and gender.

Table 5

Reported symptoms in the dissection and control subjects (UL = upper limb, LL = lower limb) VBA = vertebralbasilar artery ICA = internal carotid artery.

Symptoms	VBAD N = 27	ICAD N = 20	Total dissection subjects N = 47	Control subjects N = 43
Headache	23 (85%)	15 (75%)	38 (81%)	22 (51%)
Neck pain	18 (67%)	9 (45%)	27 (57%)	6 (14%)
Dizziness	14 (52%)	1 (0.5%)	15 (32%)	3 (7%)
Visual disturbance	9 (33%)	7 (35%)	16 (34%)	12 (28%)
Paraesthesia (face)	8 (30%)	6 (30%)	14 (30%)	8 (19%)
Paraesthesia (UL)	9 (33%)	7 (35%)	16 (34%)	20 (47%)
Paraesthesia (LL)	4 (15%)	5 (25%)	9 (19%)	14 (33%)

hospital, data were not available on their temporal relationship to the subject's stroke. Despite this, it may be prudent for clinicians to question patients about recent infection or viral illness and be cautious of more vigorous techniques in such cases.

Recently Kerry et al. (2008) have recommended that manual therapists should consider vascular risk assessment (incorporating a system based approach) of patients prior to treatment of the neck. However cardiovascular risk factors commonly associated with stroke were not strongly represented in this dissection group in comparison to the non-dissection controls. Data on cardiovascular risk factors in a similar age general population in Australia is not available except for smoking (20%). Smoking is reported as being slightly higher in the dissection group (33%) but this is about half the rate of the non-dissection group (65%) (Australian Institute of Health and Welfare, 2005; Australian Bureau of Statistics, 2009). Indeed, this study there was a mean of 1.4 cardiovascular risk factors per dissection subject compared with 3.23 in the non-dissection group. This suggests that in younger patients, routine assessment of such factors in the patient examination (e.g. taking of blood pressure) may not be particularly useful for manual therapists in determining the risk of adverse neurovascular events following manual therapy to the cervical spine.

5.2. Signs and symptoms

Considering some current clinical recommendations and pre-manipulative guidelines for practitioners employing manual therapy for neck disorders (George et al., 1981; Rivett et al., 2006; Kerry et al., 2007), it is important to note that headache was not always present and not always severe in either VBAD or ICAD subjects, although it was more common in VBAD (85%) and ICAD (75%) subjects than controls (51%). Similarly, neck pain and dizziness were more likely to occur in VBAD than ICAD subjects or controls. It was particularly surprising to find that dizziness was present in only 52% of the VBAD cases, yet this symptom has often

Table 6

Reported clinical signs in the dissection and control subjects (UL = upper limb, LL = lower limb) VBA = vertebralbasilar artery ICA = internal carotid artery.

Signs	VBAD N = 27	ICAD N = 20	Total dissection subjects N = 47	Control subjects N = 43
Unsteadiness/ataxia	18 (67%)	8 (40%)	26 (55%)	15 (35%)
Weakness (UL)	9 (33%)	13 (65%)	22 (47%)	32 (74%)
Weakness (LL)	11 (41%)	10 (50%)	21 (45%)	26 (60%)
Dysphasia/dysarthria/aphasia	12 (44%)	9 (45%)	21 (45%)	30 (70%)
Facial palsy	6 (22%)	12 (60%)	18 (38%)	20 (47%)
Ptosis	5 (19%)	12 (60%)	17 (36%)	2 (5%)
Nausea/vomiting	7 (26%)	6 (30%)	13 (28%)	6 (14%)
Dysphagia	7 (26%)	1 (0.5%)	8 (17%)	2 (5%)
Drowsiness	1 (4%)	4 (20%)	5 (11%)	1 (2%)
Confusion	2 (7%)	3 (15%)	5 (11%)	6 (14%)
Loss of consciousness	4 (15%)	4 (20%)	8 (17%)	2 (5%)

been stressed as the primary clinical indicator of vertebralbasilar flow insufficiency (Grant, 1988; Maitland, 2005; Petty, 2006). The presence or absence of nystagmus was rarely recorded, although other visual disturbances were reported. Ataxia or balance problems were also a fairly common finding in the VBAD group (67%), so manual therapists should be alert to this finding in an assessment of a patient with neck pain or headache and perhaps consider formal testing of balance more routinely. Similarly findings for the ICAD cases suggest it may be appropriate to perform a focused cranial nerve examination (e.g. for facial palsy or ptosis) if specific symptoms are reported in the history or signs are evident on casual observation.

One of the main limitations of retrospective studies is that medical records are not always detailed and it is acknowledged that negative responses to questions in the history may not always be recorded. Details of blood results and radiological imaging were sometimes limited. Radiological imaging such as magnetic resonance angiography (MRA) and computerised tomographic angiography (CTA) are not always sensitive enough to detect the more subtle signs of dissection, in particular vertebral artery dissection (Levy et al., 1994; Vertinsky et al., 2008). Furthermore, if imaging is not performed within a few days of the onset of symptoms it may not provide evidence of a dissection, despite an initial clinical diagnosis of dissection. Radiographic findings may change in a matter of days or even hours (Schievinc, 2001). Indeed, in our study radiological confirmation of dissection was not possible in all subjects; 11 subjects did not have clear radiological evidence at the time the imaging was performed and in some cases this was a few weeks or even months after the onset of their symptoms. A further limitation of the current study is that the sample size is modest, reflecting the relative rarity of CAD and despite electronic records at a large tertiary teaching hospital being searched over a 12 year period. Finally, although the study was limited to subjects under 55 years, as this is the sub-group in whom CAD complications are most commonly reported, it is possible that other serious neurovascular complications may occur in older people.

Future studies should ideally be undertaken prospectively to ensure all relevant clinical information can be collected for both dissection and control cases, including timely imaging. Ideally future studies should also be multi-centre to ensure a greater number of subjects are captured so that more meaningful analysis of associations can be made between groups for different factors.

Considering the results, there is clearly a significant association between recent minor mechanical trauma, including manual therapy, to the cervical spine and CAD. Manual therapists should therefore be alert to such a history in patients presenting with head and neck pain and be prepared to perform a focused neurological examination, where indicated, for subtle neurological signs and symptoms. Practitioners should also be aware that these patients may present complaining of severe headache or neck pain, but not always, and that dizziness which has traditionally been associated with VBAD is only present in about half of the cases. It is anticipated that the results of this study will enable clinicians to better recognise a dissection in progress and the factors potentially associated with an increased risk of an adverse neurovascular event from manual therapy to the neck.

Table 7

Stroke outcome in terms of disability (expressed as a Modified Rankin Score [MRS]) for dissection and control subjects. MRS ≤ 2 means patient is able to walk and manage their own affairs.

MRS	Dissection subjects N = 47	Control subjects N = 43
Favourable ≤ 2	34	31
Unfavourable > 2	10	8
Ungraded	3	4

6. Conclusion

Recent minor mechanical trauma, including manual therapy to the cervical spine, is significantly associated with CAD. General cardiovascular risk factors do not appear to be strongly represented in CAD patients, suggesting they may not be useful indicators of the risk of adverse neurovascular complication associated with manual treatment of the neck. However, there may be other types of serious neurovascular complications which could indeed exhibit such factors. The utility of assessing for cardiovascular risk factors should therefore not be dismissed on these data alone. Manual therapists need to be aware of the more common symptoms of a dissection in progress, some of which may mimic a mechanical neck disorder, and be prepared to test for subtle neurological signs, such as imbalance or cranial nerve impairment.

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STUDY 2

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Thomas, L, Rivett, D, Levi, C (2012) Risk factors, radiological features and infarct topography of craniocervical arterial dissection. *International Journal of Stroke*. DOI:10.1111/j.1747-4949.2012.00912.x

STUDY 3

STUDY PROTOCOL

Open Access

Risk factors and clinical presentation of craniocervical arterial dissection: A prospective study

Lucy C Thomas*, Darren A Rivett, John R Attia and Christopher R Levi

Abstract

Background: Craniocervical arterial dissection is a major cause of ischaemic stroke in young adults. The pathogenesis is not fully understood but is thought to be related to a combination of an intrinsic weakness in the arterial wall and an external trigger. Intrinsic susceptibility is thought to be a generalised arteriopathy, vascular anomaly or genetic predisposition. Proposed extrinsic factors include recent viral infection and minor mechanical trauma to the neck, including neck manipulation, which has raised concerns amongst manual practitioners in particular as to the appropriate screening of patients and avoidance of more vigorous therapeutic techniques. The presenting features of dissection may mimic a musculoskeletal presentation, creating a diagnostic dilemma for primary care practitioners. Early recognition is critical so that appropriate management can be commenced. The aims of this study are to prospectively investigate young patients ≤ 55 years admitted to hospital with radiologically diagnosed craniocervical arterial dissection compared to matched controls with stroke but not dissection, to identify risk factors and early presenting clinical features, so these may be more readily identified by primary care practitioners.

Methods: Patients ≤ 55 years presenting to hospital with craniocervical arterial dissection and controls will have their medical records reviewed and be interviewed and questioned about possible risk factors, preceding events to admission such as recent neck trauma, and presenting clinical features including any preceding transient ischaemic features. Clinical assessment will include a connective tissue screening examination to identify subclinical connective tissue disorders. Radiology and blood screening will be reviewed for typical features and inflammatory markers. Functional outcome will be reviewed to determine the burden of the stroke.

Discussion: This study will provide descriptive and comparative data on intrinsic and extrinsic risk factors for craniocervical arterial dissection and outline the typical clinical presentation, including the nature of early presenting features which might assist practitioners to identify those patients for whom vigorous manual therapy of the neck is inappropriate and alert them to those for whom immediate urgent medical care should be sought.

Background

Craniocervical artery dissection (CAD), a tearing of the intimal, medial or adventitial layers of the wall of the internal carotid or vertebral arteries, is a major cause of ischaemic stroke in young to middle aged individuals in the fourth and fifth decades [1,2], perhaps accounting for up to 10-25 % of ischaemic stroke in this age group [3]. CAD has an annual incidence of 2.5-3:100,000 [3-5], however this may be an underestimate as cases with

mild clinical signs and symptoms may not always be recognised and dissections may resolve spontaneously [2].

The aetiology of CAD is not fully understood and many cases are described as occurring spontaneously when no obvious mechanism or trigger can be identified. However, it has been suggested that for dissection to occur there is a contribution from both intrinsic and extrinsic factors. It has been proposed that the mechanism involves both a pre-existing intrinsic susceptibility such as an underlying arteriopathy, and a precipitating event which may be fairly innocuous [2,3,6,7]. The underlying

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arteriopathy may be in the form of a vascular anomaly, a genetic pre-disposition [8] such as a subclinical connective tissue disease, or may be a transient situation perhaps caused by an infection or pro-inflammatory state giving rise to a temporary friability of the vessel wall [9,10]. In patients with such an existing susceptibility, exposure to a precipitating event such as minor mechanical trauma or activities imparting some stress to the neck [11,12] may trigger a dissection of the artery [13]. Such minor trauma is usually innocuous, such as might occur during the course of normal daily activities. Frank trauma, such as may happen during a motor vehicle accident has not usually been reported [14,15].

Cervical spine manual therapy has been hypothesised as one type of minor trauma or neck stress which may be a trigger for CAD. This has raised concerns amongst manual practitioners as to whether the nature of manipulative techniques is responsible for reported cases or whether some patients already have CAD in its early stages when it is difficult to diagnose. Notably, the clinical presentation of CAD usually includes neck pain and headache, which may in many cases mimic a musculoskeletal disorder or migraine [2,3,7]. It is therefore possible that CAD might not be recognised early in its presentation, particularly in the absence of clear ischaemic (or neurological) features. This may lead the patient to seek pain treatment from their primary care practitioner or manual therapist for the painful symptoms which are in reality resulting from a dissection in progress [16].

Previous reviews have often included a number of retrospective studies of CAD [2,3,17] some of which have shown conflicting findings in respect of the presence of particular risk factors [2]. Exposure to minor mechanical trauma of the neck has been shown to be associated with CAD by a number of authors [4,13,18,19], however detailed characterisation of the types of trauma and direction of force application has been limited. Retrospective studies are often limited and biased by the information available in hospital databases, highlighting the need for prospective studies which include interviews of patients close to the time of their dissection.

Previous prospective studies have tended to be from large hospital series and were therefore medically focussed, again relying on routine information in the hospital records and did not always use a face to face interview [13-15,20,21]. They may have therefore been subject to selection bias if investigators were able to choose whether or not to include participants based on information available in the records [15,22]. Some previous studies have also lacked age limitations so may have included older patients with atherosclerosis or other age related conditions. Moreover, they did not always include a control group for comparison. In particular, they

generally report limited information or historical details about preceding activities and events, as well as occurrence of any transient ischaemic features in the weeks preceding hospitalisation which might facilitate early recognition of CAD. These details are of particular interest to primary care practitioners to assist them to more readily identify those patients at risk of CAD or who may be presenting with early symptoms.

It has been argued that the timely recognition of potential risk factors and more subtle early presenting neurological signs or symptoms of CAD is critical [2,23] so that the patient is not exposed to inappropriate manual treatment of the neck. Early recognition is also critical in the case of a patient presenting with a dissection in progress, so that referral for appropriate medical management can be made promptly. There is also a need to characterise the presenting features of vertebral and internal carotid artery dissection, in particular ischaemic features, with more descriptive detail, so as to aid recognition of the significance of early signs and symptoms.

In manual therapy texts and guidelines on the topic of vertebrobasilar insufficiency (VBI) [24], an insufficiency of blood flow to the hindbrain, much emphasis has been placed on the presence of dizziness as an indicator of VBI. However it is possible that other clinical features may be earlier or more useful indicators of the presence of dissection and associated VBI. Identification of early clinical features related to dissection of craniocervical arteries may help in the prompt recognition of these conditions in patients presenting to physiotherapists and other practitioners.

A recent retrospective study of risk factors and clinical features of CAD by our research group examined the medical records of 47 patients ≤ 55 years who had suffered a vertebral or internal carotid dissection, and found that 64 % had a recent history of minor mechanical trauma to the neck [25]. Other preceding events and proposed risk factors such as recent infection and hypertension were less well documented. This retrospective study was however limited by inconsistent recording of data in the medical records. Hence we have designed a prospective study to further investigate the risk factors and presenting clinical features of CAD patients in the Hunter region of New South Wales, Australia.

The purpose of the proposed study is therefore to prospectively investigate the presenting clinical features and pre-existing health status of CAD patients ≤ 55 years in order to identify risk factors and describe the common early clinical features.

Aims and hypotheses

The specific aims of the study are to test the following hypotheses in a prospective cohort of patients with radiologically confirmed CAD:

1. That the following risk factors will be independently associated with vertebral or internal carotid arterial dissection:
 - recent minor mechanical trauma to the head or neck
 - cervical spine manual therapy, specifically high velocity thrust manipulation or end-range rotational mobilisation techniques or deep upper cervical soft tissue massage
 - recent infection, febrile illness or clinical markers of pro – inflammatory states
2. That patients presenting with craniocervical arterial dissection pain will have no antecedent ischaemic neurological features.

Methods

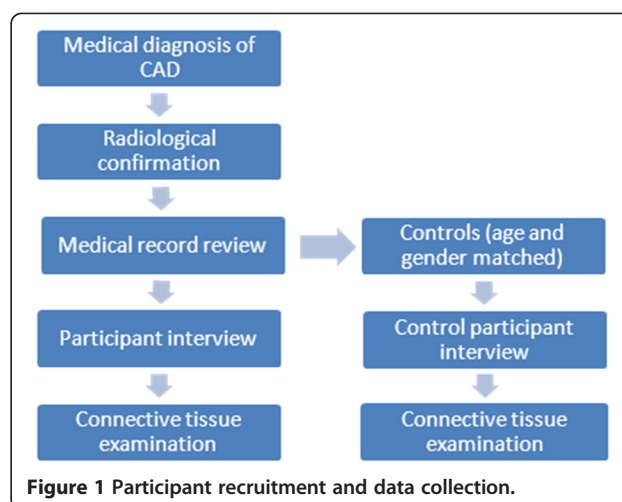
Design

The study is a prospective case control design examining patients with CAD and age and gender matched controls with ischaemic stroke but without CAD. The case-control design will be used to examine chronic risk factors, i.e. mild connective tissue disorder, vascular anomaly and cardiovascular factors, and clinical characteristics between participants. A case cross-over design will be used to examine acute risk factors or triggers i.e.; mechanical trauma and recent infection. Participants will be asked about exposure to the trigger event in the last 24 hours, the last week and within the last month. This will allow participants to act as their own controls as well as allowing comparison between dissection and control groups. The flow of participants through the study is shown in Figure 1.

Participants

All patients ≤ 55 years presenting to hospital in the Hunter region of New South Wales, Australia with a radiological diagnosis of stroke caused by extracranial vertebral or internal carotid arterial dissection and who give their informed consent will be included in the study. Control participants will be age and gender matched patients who present with stroke from some other cause than dissection and who also give their informed consent to participate. Patients with CAD of iatrogenic origin will be excluded. Patients presenting with subarachnoid haemorrhage (SAH) will be excluded because this is a rare condition with distinctively different presenting features from dissection. Patients with primary intracranial dissection will also be excluded as this is commonly associated with SAH.

The diagnosis of CAD will be confirmed by radiological review. Imaging will be performed using computed tomography (CT) or magnetic resonance imaging (MRI), as ordered by the admitting neurologist.



Radiological imaging will be reviewed online post hoc by two neurologists to describe the radiological features. Criteria applied will be visualisation of the following typical features of dissection [26]:

- i). dissection flap or double lumen
- ii). mural haematoma
- iii). crescent sign – a crescentic rim of hyperintense signal
- iv). long tapering stenosis characterised by string or 'pearl and string' sign
- v). increase in external diameter or vertebral or internal carotid artery due to wall thickening or narrowing of the lumen
- vi). pseudoaneurysm or dissecting aneurysm.

The degree of vessel stenosis, defined as a reduction in the lumen, will be graded as a percentage of vessel occlusion. Cerebral infarction will be defined as high signal on diffusion weighted imaging ($B = 1,000$) in the acute phase and as high signal on FLAIR T2 weighted imaging in the subacute phase. Infarct topography will be mapped. Imaging will also be inspected for any evidence of vascular variant or anomaly of the anterior or posterior cerebral circulation.

Participant characteristics

Descriptive data will be collected including demographic details, the type and location of the dissection, the presence of infarction and the burden of stroke. This information will be collected from the patient records and by structured interview when the participant is medically stable. The interview will be undertaken by one of the investigators who is a registered physiotherapist with post-graduate qualifications in manual therapy and 28 years of clinical experience. Burden of stroke will be

assessed at discharge from the discharge summary; details of residual signs and symptoms, Modified Rankin Score (mRS) [27] and National Institute of Health Stroke Score (NIHSS)[28]. The mRS is widely used for assessing global outcomes following stroke. The score is out of five where zero denotes full recovery, five denotes death and a score of two or less means a patient is able to walk and manage their own affairs [27]. The mRS has been demonstrated to have acceptable inter-rater reliability ($\kappa = 0.71-0.95$) [27,29,30]. The NIHSS is a well validated tool used in the evaluation of neurological deficit in stroke patients [31]. It has moderate to excellent inter-rater reliability (ICC 0.82), and high validity ($r = 0.68$) when compared to infarct volume on CT imaging [31,32].

Measurement of risk factors for CAD

Details of risk factors will be collected from the medical notes and a structured participant interview (see Additional file 1: Appendix 1). For the acute risk factors (minor mechanical trauma and recent infection) participants will be asked about exposure to these events within the last 24hours, the last week and the previous month.

Minor mechanical trauma

Minor mechanical trauma or stress to the neck will be investigated under the following categories based on the work of Dittrich et al. [13]:

- Heavy lifting
- Direct and indirect trauma to the head and neck
- Jerky or abrupt movements of the head
- Sporting activities
- Manual therapy.

If any trauma or stress to the neck is reported, specific descriptive details of the amount of force involved and direction of movement of the head and neck will be sought from the participant. If the participant has undergone recent manual therapy to the neck, descriptive details of the therapeutic procedure received will be sought from the participant.

Recent infection

Recent infection is defined as any infection or viral illness reported by the participant within the last month. Details of the type and severity of the condition, whether it was confirmed by a health professional and the need for medical intervention, such as antibiotic treatment, will be identified in the medical records or from the patient interview. Details of haematological results at the time of admission, specifically full blood count, erythrocyte sedimentation rate, C-reactive protein,

immunological studies and coagulation times will be collected from the medical records. These will be examined for the presence of existing pro-inflammatory factors.

Vascular anomaly

Vascular anomaly or anatomical variant is defined as radiological evidence of a hypoplastic or aplastic cerebral artery or an anomalous course or termination of a cerebral artery such as a vertebral artery ending in posterior inferior cerebellar artery. Evidence of vascular anomaly or anatomical variant will be identified from the review of radiological imaging of the participants.

Cardiovascular factors

The presence of cardiovascular factors are defined as a reported medical diagnosis of hypertension, hypercholesterolemia, history of smoking, diabetes, migraine, family history of young stroke and contraceptive pill use.

- Hypertension is defined as a systolic pressure >140 mmHg and diastolic pressure >90 mmHg according to Australian Heart Foundation guidelines [33].
- Hypercholesterolemia is defined as a total cholesterol level >200 mg/dL[34]
- Smoking (current/past, cigarettes/day)
- Diabetes- (medical diagnosis of type one or type two diabetes)
- Migraine (medical diagnosis of migraine, on medication for migraine, self-report of migraine)
- Family history of young stroke <55 years
- Current or recent contraceptive pill use

Connective tissue disorder

Evidence of mild connective tissue disorder is defined as joint hypermobility, skin hyperextensibility or skin fragility. These features will be measured using a 25 item scale described by Dittrich et al. [35]. A sum score of all positive items will be calculated, where 0 = no disorder and scores >10 = strong disorder. The cut off used for the presence of connective tissue disorder is eight, based on the work of Dittrich [35]. The examination includes tests for joint hypermobility and skin fragility and extensibility. Also included will be additional questions about a reported history of hypermobile joints and the ability to contort the body as a child.

Joint hypermobility measurement includes items comprising the Beighton scale [36]. This has been shown to have good inter-rater reliability (ICC 0.72, 0.79) [37,38]. Skin extensibility is measured manually by pinching the skin on the volar aspect of the forearm one third of the distance from the elbow to the wrist with the elbow at 90° or in full extension. Skin is pulled up and the distance measured and quantified as ≤ 1 cm, >1 cm, >2 cm,

>3 cm. >4 cm or >5 cm, with the pathological level determined as >2 cm [39].

Measurement of presenting clinical features of CAD

Detailed characterisation of the features that commonly present during the process of both vertebral and internal carotid artery dissections will be collected. In addition the presence of any early warning signs, notably transient ischaemic signs or symptoms in the preceding month will be collected. Features will be categorised under the following headings:

- Headache (presence, location, severity)
- Neck pain (presence, location, severity)
- Facial palsy (presence of ptosis/Horner's syndrome)
- Visual disturbance (presence of blurred vision, diplopia, hemianopia)
- Speech disturbance (presence of dysarthria, dysphonia, dysphasia such as expressive or receptive)
- Balance disturbance (presence of dizziness, imbalance, unsteadiness, falls)
- Paraesthesia (presence, location such as upper limb/lower limb, face)
- Weakness (presence, location such as upper limb/lower limb).

Questions about clinical features not expected to be present will also be included as distractors. These questions will be about the presence of chest pain and cognition. Information will be initially sought in the medical records and additional details, including the time frame of onset of signs and symptoms, obtained from a structured patient interview (see Additional file 1: Appendix 1). The interview will be undertaken by a member of the research team as soon as the participant is medically stable.

Statistical analysis

The projected sample size is 100 dissection patients and 100 controls. The sample size is based on ten subjects per prognostic indicator, based on a review of the literature [2,18,25] Indicators evaluated will include mechanical trauma, recent infection, vascular anomaly, hypertension, hypercholesterolemia, smoking, diabetes, migraine, family history and oral contraception.

Demographic data, risk factors and outcome will be analysed using descriptive and comparative statistics. Risk factors will be analysed using simple logistic regression to generate odds ratios and p values. All factors with a p value >0.2 will be included in a multiple regression model with outcomes expressed as odds ratios with 95 % confidence intervals. Statistical analysis will be

performed with STATA statistical analysis software (version 11, Statacorp, Texas, USA).

Ethical approval for the study has been granted by the Hunter New England Human Research Ethics Committee.

Discussion

The proposed study will help to further define risk factors for CAD, in comparison to a control group, in a young population in whom CAD is most commonly described. The prospective nature of the study and the use of a structured interview will allow more detailed analysis of the preceding events and presenting clinical signs and symptoms than has previously been undertaken. Quantifying the burden of stroke for both dissection and non-dissection stroke patients may help inform decisions concerning the provision and extent of post-acute rehabilitative care.

In the case of recent minor mechanical trauma to the neck, the study may allow more detailed information to be gained on the nature of the trauma, forces involved and direction of movement of the neck. This may be helpful to identify typical traumatic events, such as a blow to the head or neck during a sporting or other commonly undertaken activity, which might be implicated in the onset of dissection.

The detailed characterisation of presenting clinical features of dissection in this prospective study may help to assist primary care practitioners to more readily identify this serious pathology in patients who present seeking conservative pain relief. Descriptive details of radiological features and infarct topography may assist better recognition of vertebral and internal carotid artery dissection in young stroke patients admitted to emergency departments.

Similarly, if mechanical trauma or infection or other risk factors are shown to be associated with CAD in this study, this might be useful to raise the index of suspicion amongst primary care practitioners of the potential diagnosis of CAD in the young to middle aged patient for example, who presents with sudden onset of headache and or neck pain and a recent history of mechanical trauma to the head or neck. This may help to both avoid inappropriate treatment in such people and prompt further investigation, potentially expediting medical intervention, in the case of a suspected dissection.

Additional files

Additional file 1: Appendix 1. Guide for patient interview regarding clinical features and possible risk factors.

Competing interests

The authors declare no conflict of interest.

Authors' contributions

All authors were involved in the design of the study. All authors read and approved the final manuscript.

Funding

The study forms part of the doctoral studies of Lucy Thomas and is not supported by any external funding.

Received: 4 March 2012 Accepted: 27 August 2012

Published: 3 September 2012

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doi:10.1186/1471-2474-13-164

Cite this article as: Thomas et al.: Risk factors and clinical presentation of craniocervical arterial dissection: A prospective study. *BMC Musculoskeletal Disorders* 2012 **13**:164.

STUDY 4

Physical Therapy

Journal of the American Physical Therapy Association and



de Fysiotherapeut

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Effect of Selected Manual Therapy Interventions for Mechanical Neck Pain on Vertebral and Internal Carotid Arterial Blood Flow and Cerebral Inflow

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PHYS THER. Published online June 27, 2013

doi: 10.2522/ptj.20120477

The online version of this article, along with updated information and services, can be found online at: <http://dx.doi.org/10.2522/ptj.20120477>

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