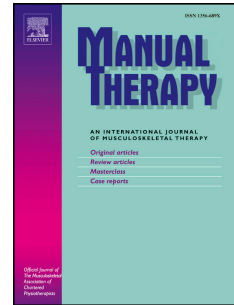


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The effect of end-range cervical rotation on vertebral and internal carotid arterial blood flow and cerebral inflow: A sub analysis of an MRI study

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## The effect of end-range cervical rotation on vertebral and internal carotid arterial blood flow and cerebral inflow: A sub analysis of an MRI study

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## ABSTRACT

### Introduction

Cervical spine manual therapy has been associated with a small risk of serious adverse neurovascular events, particularly to the vertebral arteries. Sustained end-range rotation is recommended clinically as a pre-manipulative screening tool; however ultrasound studies have yielded conflicting results about the effect of rotation on blood flow in the vertebral arteries. There has been little research on internal carotid arterial flow or utilising the reference standard of angiography.

### Objectives

To evaluate the mean effect of cervical rotation on blood flow in the craniocervical arteries and blood supply to the brain, as well as individual variation.

### Design

This was an observational study.

### Method

Magnetic resonance angiography was used to measure average blood flow volume in the vertebral arteries, internal carotid arteries, and total cerebral inflow, in three neck positions: neutral, end-range left rotation and end-range right rotation in healthy adults.

### Results

Twenty participants were evaluated. There was a decrease in average blood flow volume in the vertebral and internal carotid arteries on contralateral rotation, compared to neutral. This was statistically significant on left rotation only. Ipsilateral rotation had no effect on average blood

flow volume in any artery. Total cerebral inflow was not significantly affected by rotation in either direction.

#### Conclusions

It appears that in healthy adults the cerebral vasculature can compensate for decreased flow in one or more arteries by increasing flow in other arteries, to maintain cerebral perfusion.

Sustained end-range rotation may therefore reflect the compensatory capacity of the system as a whole rather than isolated vertebrobasilar function.

ACCEPTED MANUSCRIPT

## INTRODUCTION

Manual therapy to the neck, in particular rotational manipulation, has rarely been associated with serious adverse events related to the craniocervical vasculature, including arterial dissection and stroke (Thiel, Bolton et al. 2007). Because the majority of cases occur in relatively young, healthy people with no known cardiovascular risk factors (Thomas, Rivett et al. 2011), these complications are difficult to predict. Current clinical screening guidelines include the provocative positional test of sustained end-range rotation as the minimum pre-manipulative physical screening procedure (Rivett, Shirley et al. 2006, Rushton, Rivett et al. 2014) to detect vertebrobasilar ischaemia (VBI). The onset of VBI in response to neck rotation suggests some compromise to vertebral artery blood flow which may be an indication of increased biomechanical stress on the vessel (Refshaug 1994). This could increase the risk of dissection. However, the validity of the provocative positional tests to predict a patient's risk of stroke from neck manipulation remains controversial, largely because of contradictory findings arising from various ultrasound flow studies of the craniocervical arteries (Zaina, Grant et al. 2003, Mitchell 2009, Sultan, Hartshorne et al. 2009, Bowler, Shamley et al. 2011).

Blood is supplied to the brain via the craniocervical arteries; internal carotid (ICA) and the vertebral arteries (VA), communicating via the Circle of Willis (Moore and Dalley 2006). Given their intimate anatomical relationship with the upper cervical vertebrae, the VAs in particular are subject to motion and deformity on neck movements, especially rotation (Wuest, Symons et al. 2010). Attempts to quantify blood flow changes in the VAs on neck rotation, with the premise that large changes in flow might indicate greater biomechanical stress on the artery, have yielded conflicting findings. Some studies showing reduced flow on contralateral rotation, some with ipsilateral and others no change in either direction, sometimes despite positive VBI tests (Thiel, Wallace et al. 1994, Haynes 1996, Rivett, Sharples et al. 1999, Haynes and Milne 2001, Mitchell

2003, Sakaguchi, Kitagawa et al. 2003, Zaina, Grant et al. 2003, Mitchell, Keene et al. 2004, Sultan, Hartshorne et al. 2009, Bowler, Shamley et al. 2011, Quesnele, Triano et al. 2014). Of the few studies that have examined blood flow in the ICAs, similarly conflicting findings have emerged (Sultan, Hartshorne et al. 2009, Bowler, Shamley et al. 2011). This ambiguity has raised questions over the relevance and continued use of sustained end-range rotation positioning as a screening tool (Childs, Flynn et al. 2005, Thiel and Rix 2005). Direct assessment of blood flow using velocimetry has been suggested as a more valid and objective screening procedure (Haynes 2002).

One explanation for the conflicting findings may lie in methodological variance. The majority of these studies utilise ultrasound imaging which is highly operator dependent (Zwiebel 2000, Rivett, Sharples et al. 2003). Few studies have utilised angiography, which is the reference standard for investigation of the craniocervical arterial system (Rodallec, Marteau et al. 2008).

Only a few small studies have been identified which utilise magnetic resonance angiography (MRA), to examine blood flow in different neck positions. In an elderly cohort with existing cerebrovascular disease (Weintraub and Khoury 1995), sustained end-range rotation, up to 13 minutes, produced significant decrease in flow volume in the contralateral VA and provoked VBI symptoms. In contrast, two small studies of healthy young adult males demonstrated no difference in VA flow with neck rotation (Mawera, Hillen et al. 1998, Quesnele, Triano et al. 2014). A recent examination of both VA and ICA blood flow response to neck movement in healthy adults (Thomas, Rivett et al. 2013) similarly found no significant difference in flow for a number of neck positions, including rotation.

Another potential limitation of previous studies may be the use of blood flow velocity as the primary outcome measure, as this fluctuates widely depending on proximity of sampling to the

vessel wall (Freed, Brown et al. 1998). Average blood flow volume may be a more stable and perhaps more clinically relevant measure as it reflects the amount of blood delivered to the brain, rather than simply the velocity at which it moves.

This study examined the response of the craniocervical vasculature to cervical rotation using MRA. Specific research questions were:

1. What is the effect of end-range cervical rotation on blood flow volume in the vertebral arteries and the internal carotid arteries?
2. What is the effect of end-range cervical rotation on total cerebral blood inflow volume?
3. Does a large decrease in flow in one vessel affect total blood flow to the brain?

## METHODS

### Design

This was an observational study using MRA to measure blood flow changes in the vertebral and internal carotid arteries with neck rotation, compared to the neutral neck position. The study utilised a subset of the data of Thomas et al (Thomas, Rivett et al. 2013) which compared mean effects on blood flow in different pre-manipulative positions. This study looked in greater detail at the effects on rotation and individual variation. Ethics approval was obtained from the local Human Research Ethics Committee. A power calculation prior to the study was not possible due to the lack of published studies using MRA, however the collected data was used to perform a post hoc power analysis.

### Participants

Healthy volunteers aged 18 to 65 years with no history of neck pain or headache, were included in the study. Exclusion criteria were inflammatory joint disease, history of serious cervical spine

trauma; any congenital disorder recognised as being associated with hypermobility or instability of the upper cervical spine; diagnosed VBI; claustrophobia or discomfort in confined spaces; or any other contraindication identified by the local health authority MRI safety screening questionnaire. All participants provided informed consent.

### Procedure

Imaging took place at the Radiology department of a large metropolitan tertiary hospital. Participants were positioned in supine lying in the bore of the scanner with their head enclosed by a phased array head coil (Figure 1). A space of approximately 4 cm separated the coil from the participants' head on all sides, and participants were asked to report any restriction to head rotation. Participant's neck movements were observed by the researcher to ensure rotation was not impeded by the head coil and were asked to report any adverse symptoms during scanning at each end-range rotation position and upon return to neutral.

In the neutral neck position, each participant first underwent time of flight (TOF) MRA to produce an image of the anatomy of the craniocervical vasculature. TOF and phase-contrast are MRA sequences used to visualise flow and demonstrate anatomy of vessels without the need for contrast (Rodallec, Marteau et al. 2008, Provenzale 2009). The imaging was reviewed post hoc for the presence of any vascular anomalies or anatomical variants.

For the experimental component of the study, blood flow data were collected in three neck positions:

1. Neutral – head positioned in the midline
2. Left rotation – head actively rotated to the left, to end of range
3. Right rotation – head actively rotated to the right, to end of range.

For each position, data collection with the scanning protocol took approximately two minutes.



### Outcome Measures

The primary outcome measure was average blood flow volume (mL/sec). This was collected for the right and left ICAs, and the right and left VAs. In addition, total cerebral inflow (TCI; mL/sec) was determined from the sum of the average flow volume in all four vessels.

Participant characteristics including age, gender and VA dominance were also collected. For this study VA dominance was defined as an average blood flow volume in one VA of more than twice that of the contralateral VA, with the head in neutral position (Seidel, Eike et al. 1999, Jeng and Yip 2004).

Blood flow volume in each of the four individual arteries was measured using a phase-contrast flow quantification sequence. This is a robust technique with reported errors  $< \pm 5\%$  (Evans, Iwai et al. 1993) (Laffon, Valli et al. 1998, Power, Maier et al. 2000). All participants were imaged on a 3T superconducting magnet (Siemens Magnetom Verio, Siemens AG, Erlangen, Germany).

Participants were scanned with T1 weighted sagittal and axial images and 2-dimensional time of flight angiography. A retrospective cardiac-gated phase contrast flow quantification sequence was used (repetition time=29 milliseconds, echo time=7 milliseconds, flip angle=30°, slice thickness=6 mm, matrix=192 x 512, field of view=200, and number of excitations=1). A velocity encoding value of 100 cm/s was used. The selected imaging plane was at the level of the C1 vertebra and atlas loop of the VA, this being the site of most reported manipulative injuries of the VA (Frisoni and Anzola 1991, Hurwitz, Aker et al. 1996, Haldeman, Kohlbeck et al. 1999).

### Data Processing

Blood flow measurements were analysed using the proprietary software Syngo Argus (Siemens AG, Erlangen, Germany). To analyse blood flow, a region of interest was placed around each

artery for each of the neck positions. This is a circle drawn around the lumen of the artery which allows measurement of blood flow volume (mL) per second within this region. To assess the effect of neck position on blood flow, average blood flow volume (mL/sec) was used as the primary test variable and was analysed in neutral and each rotated position for each artery.

#### Data Analysis

Data was analysed using Stata statistical software (Version 12, StataCorp, College Station, Texas). Descriptive statistics were used to summarise age, gender and vertebral artery dominance data. Average blood flow in all four individual arteries and total cerebral inflow (TCI) for the neutral position and each of the rotated neck positions was analysed with descriptive statistics and tested for normality. The difference in mean average blood flow volume in each artery between each rotated position and neutral was analysed using paired t-tests.

### RESULTS

#### Group Data

Twenty participants with a mean age of 33.1 years (SD=11.9; range 21-59) were included in the study (10 females). Five (25%) participants had a dominant left VA (including two with reverse flow in the right VA), while two (10%) had a dominant right VA. No vascular anomalies or anatomical variants were identified. No participants developed any signs or symptoms of VBI at any point during measurement.

Flow volume data for each artery and each position was normally distributed. Measurements of average blood flow volume (mL/sec) for the ICAs, VAs and TCI for the neutral, left rotation and right rotation positions are presented in Table 1.

On left rotation, compared to neutral, there were statistically significant decreases in average flow volume of 0.35 mL/sec (13.66%) in the right ICA ( $p < 0.01$ ), and 0.20 mL/sec (27.93%) in the right VA ( $p = 0.02$ ). There were no other statistically significant changes in flow volume for any other artery in any position. There was no significant difference in TCI in rotation to either side compared to neutral. TCI with proportional contribution from individual arteries for each neck position is illustrated in Figure 2.

#### Individual Data

Eight individual arteries, from seven participants, had a greater than 50% decrease in average blood flow volume in a rotated position, compared to neutral (Figure 3). Of these, one was an ICA (R) while seven were VAs (4 L, 3 R); and seven of these eight decreases in flow occurred with contralateral rotation. Fourteen individual arteries had an increase in blood flow volume of more than 50% between neutral and a rotated position. Of these, one was an ICA (L) while thirteen were VAs (8 L, 5 R); and ten of the fourteen large increases in flow occurred with ipsilateral rotation.

Of these eight cases with a large decrease in flow in one artery, the impact on TCI was variable (Figure 4). In one case (Figure 4a), the decrease in blood flow volume in one artery was accompanied by an increase in flow in the other three arteries, producing an overall increase in TCI on rotation, compared to neutral, of 0.675 mL/sec (27.7%). In four cases (Figure 4b), the decrease in one artery was accompanied by an increase in one or two of the other arteries, to produce a small decrease in TCI. In three cases (Figure 4c), blood flow volume decreased in all four individual arteries on rotation, to produce a large cumulative decrease in TCI of up to 3.9 mL/sec (42.6%) compared to neutral.

#### Power

The standard deviations for each artery due to the sum of measurement and position sources of variation were 0.40 for the VA and 0.54 for the ICA. The post-hoc power calculation was based on a comparison of the neck positions (neutral and rotation) with an independent samples t test. For the VA, for a 50% change in average flow volume between neutral and either rotated neck position, power was 0.97; for a 36.4% change from the neutral position, power was 0.80. For the ICA, for a 50% change in flow volume, power was 1, and for as low a value as 16.4% change, power was still 0.80.

### DISCUSSION

This study is one of a few to use MRA to measure the response of average blood flow volume in all four craniocervical arteries to rotation of the neck, in healthy adults. The results suggest that rotation does produce some changes in flow in the vertebral and internal carotid arteries, but that in general, it does not have any overall effect on total cerebral inflow in those with normal cerebral vasculature.

End-range cervical rotation appears to produce a decrease in flow volume in the contralateral vertebral and internal carotid arteries. Although this trend was demonstrated for both directions of rotation, statistical significance was only achieved for left rotation. This may be a reflection of VA dominance, with five dominant left VAs but only two dominant right VAs amongst participants. The results mirror earlier ultrasound findings of decreased flow velocity in the contralateral VA on rotation (Haynes, 1996; Rivett et al., 1999; Mitchell, 2003; Sakaguchi et al., 2003; Mitchell et al., 2004) and, adding to limited previous data on ICA blood flow change, a decrease in flow in the contralateral ICA. However, there was no evidence to support the opposite relationship – no significant increase in flow in either the VA or ICA was demonstrated with ipsilateral rotation. The results of this study in healthy participants, combined with the

findings of previous research suggest that a decrease in both VA and ICA blood flow could be considered a normal response to contralateral end-range rotation of the neck and that large changes in flow appear idiosyncratic for individuals and may not indicate biomechanical stress on the vessel. In that case, direct measurement of craniocervical blood flow as a clinical screening procedure for VBI as suggested by some authors (Haynes 2002, Kerry, Taylor et al. 2008) may produce a high number of false positive results. However, this may be different in those with abnormal vessels.

Total cerebral inflow generally appears to be unaffected by end-range cervical rotation. Although total flow decreased slightly with rotation, the changes were very small and did not approach statistical significance. Given that previous research only considers flow in one or more individual craniocervical artery, this finding may be an important contribution to our knowledge in this area. It suggests that the cerebral vasculature may be able to compensate for flow decreases in one or more individual arteries by increasing flow in other arteries, to maintain adequate cerebral perfusion during neck movement. This stable response in total cerebral inflow to rotation is also reflected in the fact that no participants developed any symptoms of cerebral ischaemia. This finding may indicate that VBI screening involving sustained end-range rotation tests the compensatory capacity of the craniocervical vasculature as a whole, rather than the structure or function of the VAs in isolation.

Within this study cohort, large individual differences in blood flow volume in the craniocervical arteries were demonstrated. This is one of only a few studies to report specifically on individual data within a healthy population. Blood flow in the VAs appears to be more variable between individuals than that of the ICAs – of the 22 individual arteries that demonstrated a change in flow volume of more than 50% on rotation, just two were ICAs. The impact of these large decreases in flow volume in one artery on total cerebral inflow was variable. In one individual, a reduction in

flow volume in one artery on rotation was accompanied by an increase in flow in each of the other three arteries, to produce an overall increase in TCI. In others, decreased flow in one artery was balanced by increased flow in one or two of the other arteries, so the decrease in TCI was mitigated. In others still, all four arteries demonstrated a reduction in flow volume to produce a cumulatively large decrease in TCI. However, none of these changes – even large decreases in total cerebral inflow of more than 40% – led to the development of symptomatic posterior circulation ischaemia in this sample. This may reflect the presence of a well-developed collateral circulation in these individuals (outside of the four major craniocervical arteries), or may simply indicate that during sustained rotation of the neck in supine lying there is sufficiently low cerebral metabolic demand that a substantial decrease in blood flow is tolerable.

Importantly, all participants in this study had normal cerebrovascular anatomy. An intact Circle of Willis can reasonably be assumed to be crucial to the ability of the cerebral vasculature to compensate for a reduction in flow in one, or more, individual craniocervical arteries. The presence of anatomical anomalies such as VA hypoplasia, prior VA injury and previous VBI symptoms are all recognised risk factors for the development of vertebrobasilar complications following neck manipulation (Mann and Refshauge, 2001). In the clinical setting, in the absence of angiography to determine the presence of anatomical anomalies, taking a comprehensive history and physical VBI screening involving sustained cervical rotation, with careful and thorough exploration of symptoms, may well be the most appropriate way to assess risk of adverse event following manual treatment of the neck as endorsed by recent authors (Rushton, Rivett et al. 2012, Rushton, Rivett et al. 2014). Some authors dispute the validity of the provocative positional tests to predict individuals at risk (Rushton, Rivett et al. 2014), however physical screening arguably still has a place to detect those with abnormal cerebral vasculature and who may suffer from rotational VBI and pre-syncope during positions of end –range rotation.

The strengths of this study arise from the use of MRA, which allows simultaneous assessment of the four major craniocervical arteries. Most previous studies utilise ultrasound, which is highly operator-dependent as it requires real-time identification of the vessel and measurement of parameters. MRA offers a more complete picture of blood flow to the brain in response to movement, through simultaneous consideration of all four arteries and subsequently TCI, than the isolated study of individual arteries. Additionally, MRA offers more detailed imaging and evaluation of blood flow characteristics than ultrasound (Laffon, Valli et al. 1998, Paciaroni, Caso et al. 2005). Future studies could repeat this methodology in patients with an absent cervical or cerebral vessel or those with ischaemic symptoms; practically however this may present some ethical challenges.

There were some limitations to this study. Firstly, use of the MRI scanner necessitated positioning in supine lying. While this reflects common clinical practice in manual treatment of the neck, there is evidence that craniocervical arterial blood flow is higher in supine lying than in upright positions (Mitchell 2009). It may be valuable to repeat this study protocol with upright positioning, as the impact of rotation on blood flow may be more apparent due to the effect of gravity. Secondly, cervical rotation range of movement in this study was not formally assessed. However, visual observation and questioning by researchers confirmed that all participants reached end-range so it is unlikely that this threatens the validity of the findings. Similarly, the movement examined in this study was active rotation – it may be of value in future studies to assess whether passive rotation results in a greater range of motion, greater changes in blood flow, and/or provocation of symptoms. Finally, participants' eyes remained open for the duration of the study. It has been suggested that rotation of the head with eyes open may be confounded by increases in blood flow in the posterior cerebral arteries due to stimulation of the visual cortex (Rossitti and Volkmann, 1995), and this was not controlled for in this study.

In conclusion, although rotation of the neck may produce a decrease in blood flow volume of the contralateral vertebral and internal carotid arteries, total blood supply to the brain is generally maintained. In healthy people with an intact Circle of Willis, decreased flow in one artery may be compensated for by other arteries, to maintain adequate cerebral perfusion. Changes in flow volume, even large changes, do not necessarily lead to symptomatic ischaemia. However, it should be considered that large flow changes could act as a surrogate marker for increased biomechanical stress of the arterial wall which may be clinically undesirable, and that symptomatic ischaemia may well manifest in those individuals with abnormal vascular structure. Therefore, the patient interview combined with the physical examination, which may include VBI screening tests, with careful and thorough exploration of symptoms, may be a more useful predictor of risk of vertebrobasilar complication following manual treatment of the neck than direct measurement of blood flow changes in these vessels.

## CAPTIONS

- Table 1: Mean average blood flow volume (mL/sec) in the individual craniocervical arteries and total cerebral inflow for neutral, left rotation and right rotation positions. Difference in average flow volume between rotated positions and neutral (mL/sec [% change] and p-value).
- Figure 1: Participant positioning in scanner with a standard neck coil in situ.
- Figure 2: Mean total cerebral inflow (mL/sec) showing proportional contribution from individual arteries for each neck position: neutral, left (L) rotation and right (R) rotation.
- Figure 3: Individual change (%) in average blood flow volume for left rotation and right rotation compared to neutral for all participants (n=20).
- Figure 4: Difference in mean average blood flow velocity (mL/sec) and TCI between rotated positions and neutral, for selected individuals with a large decrease in flow in one artery.



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Table 1:

	Neutral	L Rotation	Difference (%)	p-value	R Rotation	Difference (%)	p-value
<b>R ICA</b>	2.57	2.22	-0.35 (-13.7)	<0.01*	2.61	0.04 (1.7)	0.66
<b>L ICA</b>	2.71	2.66	-0.05 (-1.8)	0.68	2.56	-0.15 (-5.5)	0.16
<b>R VA</b>	0.73	0.53	-0.20 (-27.9)	0.02*	0.80	0.07 (9.8)	1
<b>L VA</b>	0.98	1.12	0.15 (15.0)	0.14	0.87	-0.11 (-11.0)	0.11
<b>TCI</b>	6.98	6.52	-0.46 (-6.5)	0.18	6.84	-0.14 (-2.0)	0.68

*R ICA: right internal carotid artery; L ICA: left internal carotid artery; R VA: right vertebral artery; L VA: left vertebral artery; TCI: total cerebral inflow*



ACCEPTED

