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Original Article

Comparison of atlanto-axial artery hemodynamics during cervical spine manipulation with doppler ultrasound in rhesus macaques

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Abstract: Background: The vulnerability of atlanto-axial vertebral artery (C1-C2 VA) to cervical spine manipulation (CSM), resulting in compromised blood flow and possible cerebrovascular accident, is well recognized. It needs to build animal model for further investigate the blood flow changes in the vertebral arteries during cervical spine manipulation (CSM). Methods: Peak systolic velocity (PSV), end diastolic velocity (EDV), resistance index (RI) and lumen diameter of bilateral VAs were measured using duplex Doppler ultrasound in 6 healthy rhesus monkeys with the cervical spine in eight cervical positions used in CSM. Results: The mean PSV and EDV of both VAs were decreased significantly in contralateral rotation, extension-ipsilateral and -contralateral rotation, and extension-ipsilateral and -contralateral rotation with traction ($P < 0.05$). A significant increase ($P < 0.05$) in RIs with left rotation and extension-left rotation-traction was demonstrated in right VA. Doppler waveforms revealed that blood flow followed a dampened systolic waveform during contralateral rotation and extension-contralateral rotation, and a near occlusion in combined extension-contralateral rotation with traction. Conclusion: The VA of rhesus monkey is subjected to forces that are sufficient to reduce blood flow velocity in positions involving in contralateral rotation, extension-ipsilateral and -contralateral rotations as well as combined extension- rotation with manual traction. The study of hemodynamics of the vertebral artery in rhesus monkey, which apply to biologic and mechanical research, is need to further conduct.

Keywords: Atlanto-axial joint, vertebral artery, Doppler ultrasound, rhesus macaques

Introduction

Cervical spine manipulation (CSM) is a therapeutic intervention and has increasingly administrated by physicians, physical therapists, and chiropractors around the world [1-6]. Some evidence in literature reviews to support the use of manipulation techniques for the treatment of neck pain and headache [7-11]. A conservative estimate of approximately 193 million of CSMs is performed each year in the United States and Canada [5-12]. This growing acceptance has, in turn, advocated the necessity to evaluate its potential side effects and complications that include cerebrovascular accidents such as stroke, paralysis, and even death [13-17], most commonly due to arterial dissection of the vertebral artery (VA) at atlanto-axial joint (C1-C2) [18-20]. It is estimated that the incidence of vertebral artery dissection (VAD) ranges from 1 to 1.7 in 100,000 person years in the United States [21], and the stoke resulting from VAD happened in 0.75 to 1.12 per 100,000 person years [22]. Despite this relatively rare occurrence, the clinical relevance of changes in VA blood flow associated with cervical spine movements have been the main focus of considerable researches.

Several studies were conducted that measure VA blood flow velocity using Doppler ultrasonography. However, the results of such studies have provided conflicting evidence, for instance, some studies suggested that there was diminished blood flow in the contralateral VA during cervical rotation whether extension was added or not [23, 24], whereas other authors have reported that flow velocity in VAs decreased significantly during both ipsilateral and contralateral rotation [25-27], or no changes [28-30]. Research findings for the sustained extension-rotation are equally equivocal with significant decreases in blood flow [31, 32], or no effect noted on VA blood flow [25, 27]. In addition, other positions such as extension and the application of manual traction have been limitedly investigated with no consensus conclusion on the findings [24, 27, 31].

On the basis of the inconsistency of the evidence, it is need to develop experimental animal model for investigate the blood flow changes in the vertebral arteries during cervical spinal manipulation or/and pre-manipulative testing of these vessels, for instance, clinical studies are usually complicated by uncontrolled variables such as age, gender, nutrition, hypertension, alcohol, tobacco, and drug abuse, data derived from clinical trials measuring blood flow velocity are difficult to interpret and generally require large sample size for relevant information [33, 34]. To investigate whether end-range cervical movements produce significant changes in VA blood flow velocity, resistance index, and lumen diameter, the rhesus macaque (Macaca mulatta), a member of the Old-world Primate, was selected as the study subject to provide some evidence on which to base the treatment of humans.

Materials and methods

Animals

A total of 6 adult rhesus macaques, 3 male, 3 female, approximate age 4.3 ± 0.6 yrs.; weight 4.5 ± 0.6 kg; height 51.5 ± 2.1 cm (Macaca mulatta, Chongqing Medical University Animal Research Center, Chongqing, P. R. China) were involved in the current study. All experimental protocol was approved by the Institutional Animal Care and Use Committee of Chongqing Medical University. Before participation in the experimental study all animals underwent a routine physical examination, ensured they are one group of healthy rhesus macaques without any neurological, cardiovascular and musculoskeletal diseases. A prior Doppler examination ensured that there was no any abnormality in cervical spine and neck vasculature. Animals were singled-housed in cages (121 × 68 × 81 cm) located in a clean and quiet single room. The lights were on 12 hours daily from 7:00 am to 7:00 pm, and the temperature was maintained at 22°C. A pelleted diet was fed twice daily (Lab Diet, Chongqing, P. R. China) with fresh fruits/vegetables, and water was available ad libitum.

Pre-test preparation

All rhesus monkeys were intramuscularly anesthetized with Xylazine Hydrochloride (0.1 mL/kg) and handled humanely for all procedures. Postoperative analgesia with Buprenorphine Hydrochloride (0.1 mg/kg) was given as needed. Postoperative evaluations for behaviors, food and water consumption, and urine and feces production were done. Under sterile circumstances the rhesus monkey were placed in supine position on an insulating mat, and the region of interest was washed and cleaned accordingly. A thorough examination of the cervical spine was performed prior to the Doppler test.

Cervical spine manipulation maneuvers

Eight spinal manipulation maneuvers were chosen that incorporate all of the maximum passive arthrokinematic facet motions and performed bilaterally with the animal placed in supine position. All cervical movements were performed by a single qualified physical therapist with extensive experience in manual therapy and joint manipulation. The procedure commenced with a 10 minutes rest period to allow for a period of hemodynamic stability. Systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg) and pulse rate (PR, beats/min) were measured in the resting position and during cervical manipulations with a digital Blood Pressure Monitor (model DS-145, ALPK2, Japan; ± 3 mmHg for BP and ± 5% for PR). Eight spinal manipulation maneuvers as follow:

Flexion 60°

For the C1-C2 facet joint flexion shown in **Figure 1B**, the examiner manually stabilized C1 with a bilateral laminar contact between the thumb and index finger of the stabilizing hand while placing the manipulating hand against the infe-

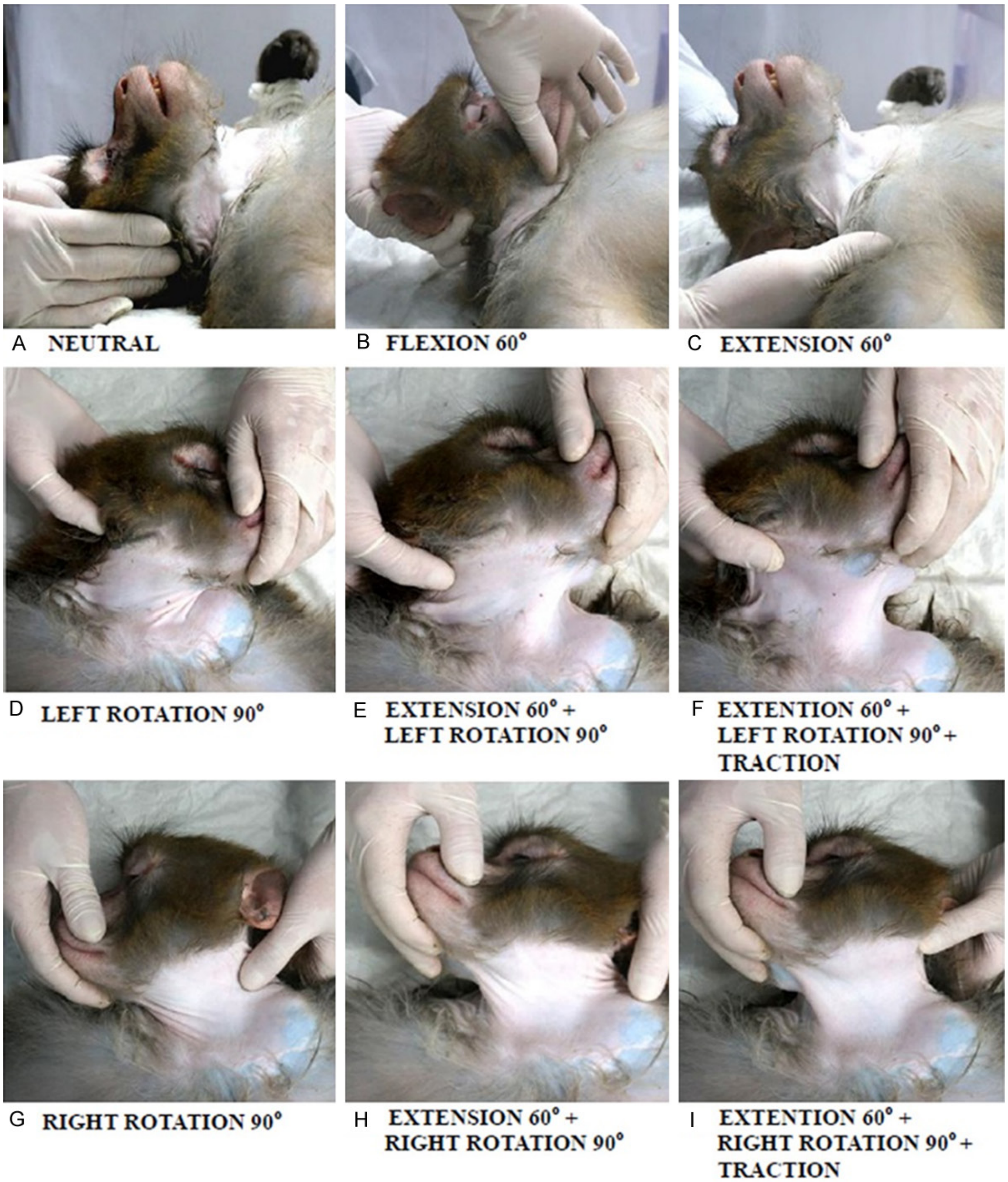

Figure 1. Cervical positions of rhesus macaque during duplex Doppler ultrasound examination.

rior nuchal line, and then passively introduced flexion to 60°.

Extension 60°

With the animal's head extending over the edge of the examination table, the examiner manually stabilized C1 with a bilateral laminar contact between the thumb and index finger of the stabilizing hand while placing the manipulating hand against the inferior nuchal line, and then passively introduced extension to 60° (**Figure 1C**).

Rotation 90°

The examiner encircled the animal's head, with index finger on the ipsilateral lamina of C1,

Table 1. Values of blood flow velocities and lumen diameters taken at the C1-C2 region of the right and left vertebral artery in rhesus monkeys

Position	PSV-LVA (cm/s)	PSV-RVA (cm/s)	EDV-LVA (cm/s)	EDV-RVA (cm/s)	RI-LVA	RI-RVA	LD-LVA (cm)	LD-RVA (cm)
N	16.71 ± 3.21	16.65 ± 5.45	7.43 ± 2.03	7.77 ± 2.16	0.56 ± 0.07	0.52 ± 0.08	0.10 ± 0.01	0.11 ± 0.02
F	14.24 ± 0.84	13.45 ± 1.25	5.70 ± 0.21	5.27 ± 1.35	0.60 ± 0.02	0.61 ± 0.09	0.08 ± 0.01	0.10 ± 0.01
E	14.69 ± 2.73	14.56 ± 2.76	5.42 ± 3.77	6.37 ± 3.77	0.66 ± 0.17	0.58 ± 0.15	0.11 ± 0.01	0.10 ± 0.01
LR	14.51 ± 1.86	11.90 ± 3.43*	5.93 ± 1.38	4.02 ± 1.34*	0.60 ± 0.09	0.65 ± 0.12*	0.11 ± 0.01	0.10 ± 0.02
RR	10.38 ± 1.15*	14.88 ± 4.00	4.50 ±0.83*	6.10 ± 1.56	0.57 ± 0.05	0.58 ± 0.04	0.10 ± 0.02	0.10 ± 0.01
ELR	10.67 ± 1.09*	11.07 ± 0.87*	4.54 ± 1.33*	4.86 ± 0.97*	0.58 ± 0.11	0.56 ± 0.08	0.10 ± 0.02	0.10 ± 0.02
ERR	9.75 ± 1.79*	11.6 ± 2.55*	4.02 ± 0.77*	5.91 ± 1.93	0.59 ± 0.03	0.51 ± 0.07	0.10 ± 0.02	0.10 ± 0.02
ELRT	10.47 ± 2.30*	9.48 ± 1.28*	4.20 ± 1.68*	3.03 ± 0.72*	0.61 ± 0.10	0.68 ± 0.09*	0.11 ± 0.02	0.10 ± 0.02
ERRT	9.49 ± 1.26*	10.96 ± 2.93*	3.19 ± 1.24*	4.22 ± 1.35*	0.66 ± 0.11	0.62 ± 0.07	0.10 ± 0.01	0.11 ± 0.01

Abbreviations: PSV-peak systolic velocity; EDV-end diastolic velocity; RI-resistive index; LD-lumen diameter; LVA-left vertebral artery; RVA- right vertebral artery. N-neutral; F-flexion; E-extension; LR-left rotation; RR- right rotation; ELR-extension-left rotation; ERR-extension-right rotation; ELRT-extension-left rotation-traction; ERRT- extension-right rotation-traction. All values are mean ± standard deviation, n = 6 rhesus macaque monkeys, *$P < 0.05$.

spanned the arch of C2 with the thumb and passively introduced 90° rotation either away from the US evaluation side or toward the US evaluation side (**Figure 1D**, **1G**).

Extension 60° and rotation 90°

With the animal's head extending over the examination table, C1 was first passively pre-positioned in 60° extension, and then was either 90° rotated away from the US evaluation side or rotated toward the US evaluation side (**Figure 1E**, **1H**).

Extension 60°, rotation 90° and traction

For the C1-C2 facet joint distraction, C1 was first passively pre-positioned with a combination of 60° extension and 90° rotation either away from the US evaluation side or rotation toward the US evaluation side; then the examiner passively distracted C1 with approximately 1/3 the animal's body weight to achieve 1-2 mm of vertebral separation in a cranial direction (**Figure 1F**, **1I**).

Ultrasonographic examination

A standard, duplex Doppler ultrasound device (Mylab 50, Esaoto Corporation, Genoa, Italy) was applied to measure peak systolic velocity (PSV, cm/s), end diastolic velocity (EDV, cm/s), resistance index (RI) and lumen diameters (LD, cm). The machine possesses a color flow mapping capability, and a high frequency 12-5 MHz broadband linear array transducer. All scanning was performed by a single qualified ultrasonographer with extensive experience in musculoskeletal US imaging and the examination of the extra-cranial vasculature. Measurement of PSV, EDV, RI and LD were recorded three times in each position for both left and right VAs using the same order of sampling. Each of the positions was sustained passively for at least 30 seconds. Ranges of motion (ROM, degree) for flexion, extension and left/right rotation were measured with a goniometer. The animal was then rested in a neutral position for 10 seconds and was observed for neurological signs before re-positioning for the next movement. Following the test procedure, the ultrasonographer reviewed all scans for any artery pathology or abnormal discrepancy.

Statistical analysis

The software package SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. The mean (± SD) blood flow PSVs and EDVs, RIs, and LDs were calculated for the right and left VA with the cervical spine in all the different positions. Hemodynamic stability was evaluated by comparing SBP, DBP, and PR measurements taken before and during the ultrasound examination, using paired samples t-tests. The consistency between measurements of ROM was also determined using paired samples t-test. One-way ANOVA with repeated measures on the PSV, EDV, RI, and LD measurements were performed to identify any statistically significant change between the neural position and each different head movement. Post hoc tests were calculated with

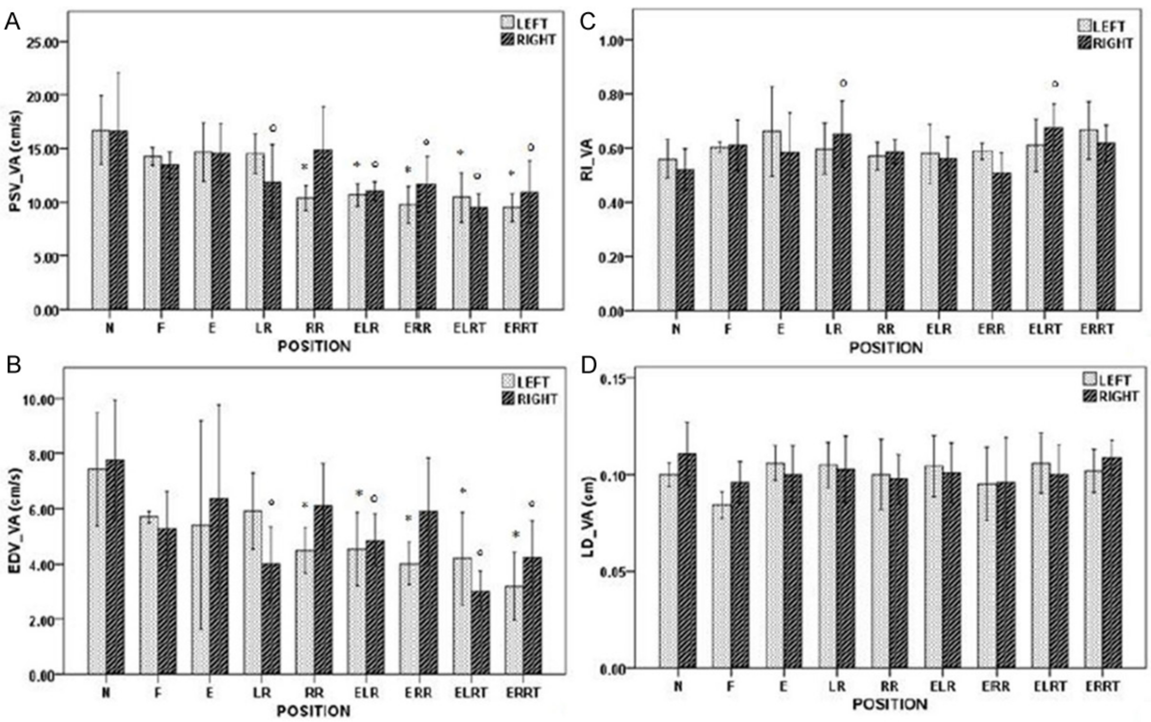

Figure 2. Changes in A. Mean peak systolic velocity (PSV); B. Mean end diastolic velocity (EDV); C. Mean resistance index (RI); and D. Mean lumen diameter (LD) of left and right vertebral artery in rhesus monkeys. *$P<0.05$ in LVA; °$P < 0.05$ in RVA.

Bonferroni correction for multiple comparisons ($P < 0.05$). One additional paired sample t-tests was used to identify any significant hemodynamic difference ($P < 0.05$) between the left and right VA in each different position. *P* values < 0.05 were considered to indicate a trend towardstatistical significance.

Results

Ultrasonographic examination was successfully performed in all positions on both left VA (LVA) and right VA (RVA). No animal showed any alteration in BP, PR, and ROM as a result of the experimental procedure that was statistically significant in relation to the findings of this study. No abnormalities were reported by the ultrasonographer upon reviewing the ultrasound scans.

Comparison of VA blood flow in various cervical positions

The mean (± SD) blood flow PSVs, EDVs, RIs as well as LDs for neutral and each of different cervical spine positions are shown in **Table 1**. Typical patterns of change in blood flow for both VAs are illustrated in **Figure 2**. The mean PSV of LVAs tended to decrease significantly in sustained contralateral rotation (RR) ($P < 0.05$), extension -left/right rotation (ELR, ERR) ($P < 0.01$), and extension-left/right rotation with the application of traction (ELRT, ERRT) ($P < 0.01$). The similar patterns of change was also found in RVA, a significant decrease in blood flow velocities with contralateral cervical spine rotation (LR) ($P = 0.01$), ELR and ERR ($P < 0.05$), ELRT and ERRT ($P < 0.01$) (**Figure 2A**). The mean EDV of LVAs and RVAs decreased significantly during contralateral rotation ($P < 0.05$), ELR and ERR ($P < 0.05$), ELRT and ERRT ($P < 0.01$) as compared with the neutral position (**Figure 2B**). A significant increase in RIs with left rotation (LR) ($P < 0.05$) and extension-left rotation-traction (ELRT) was demonstrated in RVAs ($P = 0.003$). For the LVA there were similar changes in the RIs, but were not significant (**Figure 2C**).

Comparison of VA blood flow between left and right VAs

On comparing the mean PSVs between the left and right VAs with the cervical spine in neutral position, no statistically significant difference

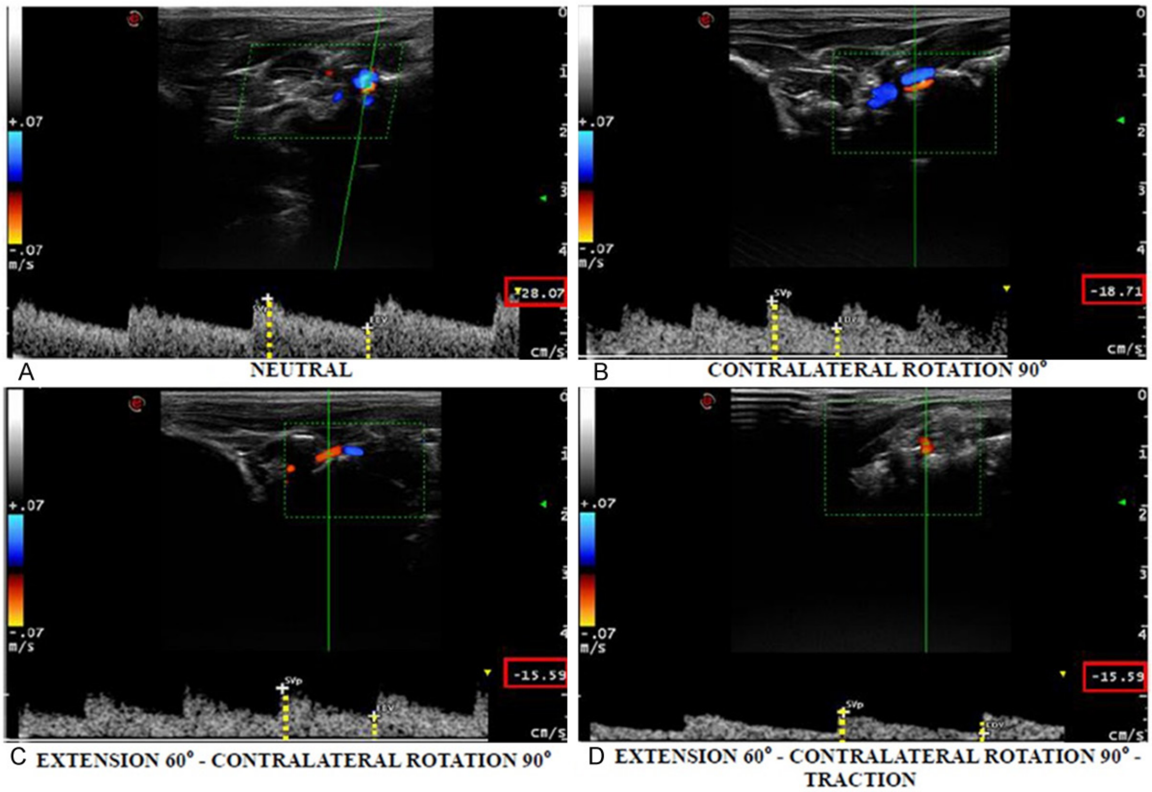

Figure 3. Ultrasound spectral images of blood flow velocities during different head positions.

was found between LVA and RVA (P = 0.769) and during the positioning sequence (P = 0.290). The similar no significant difference was also found between the mean EDVs of LVA and RVA in neutral position (P = 0.164) and in each different position (P = 0.262). RIs of LVA were not statistically different from RVA in neutral cervical spine position (P = 0.329) and no significant differences (P = 0.307) in each cervical position. In addition, no significant difference was found in the mean lumen diameters between the left and right sides in neutral position (P = 0.222) and during different cervical movements (P = 0.551).

Doppler waveforms of blood flow

Upon reviewing spectral Doppler waveforms of blood flow velocity measurements, the results revealed that blood flow followed a low resistance pattern in the neutral position, which is a wide peak systolic and high diastolic flow in the VA (**Figure 3A**); a dampened systolic waveform, which is an indication of a turbulence distal to the point of sampling during positions such as end-range contralateral rotation and extension-contralateral rotation (**Figure 3B**, **3C**); then the waveform indicated a near occlusion in combined extension-contralateral rotation with traction, where blood flow velocity was slower than the usual flow velocity in the neutral position, and diastolic flow velocity reached zero and extended beyond the baseline (**Figure 3D**).

Discussion

CSM can ease the neck pain and headache, however, it could cause some iatrogenic damages. Although the probability of the iatrogenic damages is very low, the adverse effect will be great in some case. Atlanto-axial joint is the most agility and weakest as well as the most dangerous movement segment as it has complex structures and special functions in occipito-cervical migration department. The characteristic of rotary motion of atlanto-axial joint initiated from atlas: 1) rotary motion from 0° to 30°, the axis remains immovable; 2) rotary motion from 30° to 60°, the axis begins move, but at a slower speed compared with atlas; 3) rotary motion from 60° to maximumrotation, rotation of atlas and axis have reached to maximum, the rotation of the neck occurs exclusively at segments below the axis. The segment of VAs adjacent to atlanto-axial joint is considered to be the most vulnerable to the stimuli to cervical vertebra, such as rotation, stretch and compression [35]. Sim et al. [36] suggested that the VA is elongated by approximately 5 mm during contralateral rotation with 50-90% of cervical rotation attributed to movement at the atlanto-axial joint. Therefore, the adversely influence of intracranial blood flow would occurrence during CSM, even likely deteriorate the symptom of verterbral-basilar artery ischemia, particularly if atherosclerosis or other vascular disorders simultaneous in VAs.

Recently, some scholars suggested that many of side effects (vertebral artery dissection, stroke, etc.) are unlikely to be the result of cervical manipulation. Even a drastic debate between David Cassidy and Benedict, argued whether abandon CSM for security reasons [37, 38]. It was documented that CSM is safe for normal and healthy VAs from a mechanical point [39]. Healthy adults who experience various head positions and CSM have no significant change in blood flow in the VAs using Duplex ultrasound with colour Doppler imaging [40]. Another research measured blood flow and velocity at the atlanto-axial artery using phase-contrast magnetic resonance imaging, and no significant change in blood flow have been found [41]. However, those results are inconsistent with previous study [26]. By the way, the relationship between vertebral artery lesion and CSM in humans is still difficult confirm as the integrity of vessel is typically unknown before using CSM. Some scholars focus on using animals to study the changes in VA blood flow associated with cervical spine movements or simulating a pre-existing vascular lesion within the VAs of animals prior to CSM application [42-44]. Comparison with adult pigs or dogs, rhesus monkey as a kind of non-human primates has the unique dominant position depend upon genetic and genomic similarity, anatomic and physiologic closeness to humans [45, 46]. Moreover, the 3D-CTA imaging data of cervical artery of rhesus monkeys, which was obtained from our prior subject, shown that vertebral artery of rhesus monkey was similar with anatomic structure of human. We speculate this investigation of atlanto-axial artery in rhesus monkey would have been capable of providing quantify VAs hemodynamics during CSM.

The findings of this present study demonstrated that the blood flow of the VAs of rhesus macaque was significantly affected by cervical positions especially involving with contralateral rotation, extension-rotation and a combined extension-rotation with manual traction. However, there was no significant reduction in blood flow during flexion and extension of the cervical spine. Variations in BP and PR were unlikely to contribute to the changes observed because these measurements were not significantly different in each different cervical position. Based on the anatomic structures with regard to the cervical arteries, the sustained rotation and extension-rotation tests have been clinically used to determine the presence of vertebrobasilar artery dysfunction. We found that full range of cervical rotation at C1-C2 stressed the VAs sufficiently to demonstrate reduction of blood flow. Although no significant difference was found between the diameters of the left and right VAs in either the neutral position or cervical spine rotation, mean PSV and EDV tended to decrease below resting values in the both left and right VAs during contralateral rotation. Extension-rotation has also been investigated extensively with controversial results, and combined extension- rotation mechanically stressed the contralateral artery more than rotation alone. It is possible that when attempting to combine full extension with rotation, the vertebral artery is more vulnerable to shear and tensile forces at the region, where it exits C2 and runs vertically and laterally to C1. Additional traction applied to the cervical spine while it is in an extended and rotated position produced the maximal mechanical stress to the contralateral VA as compared to any other position.

In addition, the RI increased significantly in right VA during left rotation and combined extension-left rotation-traction, suggesting that the resistance encountered by the blood flow was actually increased. This finding was consistent with the expectation of vessel narrowing and associated increased resistance to flow. The RI is based on the premise that diastolic velocity is likely to be reduced to a greater extent by higher resistance than is systolic velocity, leading to a rise in the index [32]. However, the measurements of this study indicate that both the PSVs and the EDVs of VAs are reduced in these positions, albeit the PSVs to a proportionally greater degree.

Limitations

As with any study, there are a number of limitations in the current study. First of all, the study is based on maneuvers of cervical spine manipulation, the order of movement progression was the same for all animals. This method was chosen in order to gradually adding further stress to the arterial system. However, because combined extension-rotation-traction was the last movements in the sequence and demonstrated the greatest flow decrease, it is not completely clear if the order of testing may have affected the results and further investigation is required before such claims can be justified. Also, a convenience sample of young, healthy, and asymptomatic monkeys was used in this study. Since no attempt was made to investigate whether positional maneuvers have a greater hemodynamic effect in those monkeys with symptomatic vertebrobasilar insufficiency, it is therefore not possible to generalize the results to the symptomatic population. In addition, although Doppler ultrasound has advantages in terms of patient comfort, non-invasiveness and relative time of performance in comparison to angiography, there are a number of potential problems associated with its use. For instance, the reliability of Doppler sampling is highly dependent on the skill of the technician to accurately locate and identify the VA, particularly when measuring in the extreme neck positions such as combined extension and rotation. Another major shortcoming of ultrasound is the lack of specificity, ultrasound often shows nonspecific hemodynamics signs of VA occlusion.

Conclusions

On the basis of the reference data presented in this study, the VA of rhesus monkey was subjected to forces that was sufficient to reduce blood flow velocity in positions involving in contralateral rotation, combined extension with ipsilateral and contralateral rotations, and combined extension-rotation with manual traction of the cervical spine seems to have a particularly significant effect in reducing the maximum blood flow in the contralateral VA. Given the comparison with the recently research of atlanto-axial artery hemodynamics during CSM in healthy human from other scholars [39, 40], the different results between rhesus monkey and humans implicate that furtherbiologic and mechanical research of vertebral artery in rhesus monkey need to investigate, even though rhesus monkey has lots of similarities in anatomic structure of vertebral artery.

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Disclosure of conflict of interest

None.

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