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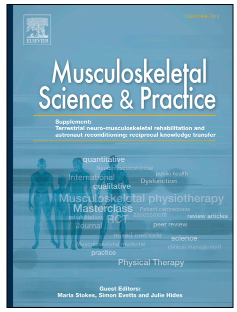

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Shear wave elastography of the cervical arteries: A novel approach to the assessment of cervical arterial wall stiffness. An investigation of psychometric properties and intra-rater reliability

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ABSTRACT

Background

Cervical arterial dissection, can occur spontaneously and is a rare but catastrophic adverse event associated with neck manipulation. Pathophysiology involves altered integrity of the arterial wall increasing its vulnerability to minor trauma. Those at risk are difficult to detect. Previous screening investigated blood flow but altered mechanical properties as stiffness of cervical arterial wall could provide a more valid indication of arterial integrity or even early dissection.

Objectives

To investigate suitability and intra-rater reliability of shear wave ultrasound elastography to measure mechanical properties of the cervical arterial wall. Suitability was assessed by ability to track arteries along their length and measurement accuracy.

Design

Observational and intra-rater reliability study.

Methods

Internal carotid (ICA) and vertebral arteries (VA) of healthy participants were examined with shear wave elastography. Shear wave velocity (m/s) indicative of wall stiffness was measured with the head in the neutral position: proximally (C3-4) and distally (C1-2) where injuries have been more commonly reported. Proximal measures were repeated to assess intra-rater reliability.

Results

Thirty healthy participants (13 female), mean age of 29 (± 12.8) years were imaged. Mean VA wall stiffness (3.4 m/s) was greater than ICA (2.3 m/s) ($p<0.000$). Intra-rater reliability for ICA was ICC 0.81 (CI 0.52 to 0.92) and for VA ICC 0.76 (CI 0.38 to 0.9). Standard error of measurement was 0.16 for ICA and 0.34 for VA.

Conclusions

Shear wave ultrasound elastography appears a suitable and reliable method to measure cervical arterial wall stiffness, justifying further research into its use for screening arterial integrity.

Keywords: Cervical artery; shear wave elastography; vertebral artery; cervical arterial dissection

INTRODUCTION

Cervical arterial dissection (CAD) can occur spontaneously and is a common cause of stroke in persons under 55years, peaking between 30-40 years. It is a rare but catastrophic complication of neck manipulation. The arteries are vulnerable due to mobility at the atlanto-axial level where most injuries have been reported {Biller, 2014 #442. The vertebral artery (VA) has an angular course between C1-2 and is relatively fixated along C1 and the internal carotid artery (ICA) is in close proximity to structures such as the styloid process(Haneline and Rosner, 2007, Kawchuk et al., 2008). Pathophysiology usually involves altered integrity of the cervical arterial walls, rendering them more susceptible to minor trauma{Debette, 2014 #420}. Screening methods have focused on blood flow to detect signs of vertebrobasilar insufficiency (VBI) or Doppler ultrasound to measure flow rather than potential risk factors for CAD (Thomas, 2016). Both methods have limitations to determine those at risk. Apparent VBI symptoms may have other causes and VA blood flow is inherently variable and usually compensated by other cervical vessels (Thomas et al., 2014). Modelling suggests that people with CAD have up to 58% stiffer cervical arteries than healthy individuals(Calvet et al., 2004) of similar age. Therefore, altered cervical arterial wall mechanical properties might provide a valid indication of arterial susceptibility or even early CAD, particularly in younger people. Shear wave elastography may provide a means of evaluating arterial wall stiffness. While the strain on cervical arteries induced by neck manipulation is reportedly low based on cadaveric studies of older subjects (Herzog, 2010, Piper et al., 2014) and arteries stiffen normally with age, altered integrity of the cervical arterial wall particularly in younger people might be a risk factor for CAD.

Elastography is a relatively new technology, which uses shear wave propagation through tissues to measure differences in compliance, which might indicate pathology (Ianculescu et al., 2014). Ultrasound or magnetic resonance imaging can be used. A radiofrequency pulse is focused on a specific region of interest (ROI) inducing a shear wave in targeted tissues, the velocity of which gives a measure of stiffness. Stiffer tissues allow faster propagation. Shear wave elastography is used successfully in liver, breast and thyroid tissues to detect tumors, with some use in carotid arteries to detect atherosclerotic plaques (de Korte et al., 2016). Elastography imaging in vascular applications is in the early stages and usually focused on the carotid artery (Couade et al., 2010, Maurice et al., 2015). Li et al (Li et al., 2016) found the common carotid was stiffer in older patients with acute ischemic stroke, probably consistent with atherosclerotic change. Limitations such as anisotropy, variations due to cardiac cycle and difficulties of wave dispersion in tubes challenge accurate estimation of stiffness (a shear modulus) (Maksuti et al., 2017).

The Siemens VTIQ system can focus the RF pulse using multiple beam-lines, rendering velocity of the propagating shear waves less dependent on arterial wall thickness when compared to other elastography techniques (e.g. supersonic imaging) (Tozaki et al., 2013). This may make it possible to examine small blood vessels such as VA or ICA even in the more tortuous and clinically relevant distal atlanto-axial region.

Stiffer arterial walls might increase an individual's susceptibility to environmental triggers as minor trauma. If cervical artery stiffness can be reliably measured, normal values for the ICA and VA could be established. This would provide opportunities to compare stiffness between healthy individuals and those with CAD, to increase understanding and recognition of arterial susceptibility and allow comparisons between proximal and more vulnerable distal sites where CAD more commonly occurs.

This study aimed to investigate the suitability of shear elastography to measure properties of the ICA and VA walls in healthy individuals. Specifically, we investigated:

1. Psychometric properties:
    - Intra-rater reliability;
    - Measurement error;
    - ability to detect real difference
2. Characteristics of arterial wall stiffness in terms of:
    - Artery (ICA vs VA);
    - Site (proximal vs distal);
    - Age

METHODS

Design

This was an observational and intra-rater reliability study conducted from April 2015 to April 2016. Institutional ethical approval was obtained No. 2015000326. All participants gave written informed consent.

Participants

Healthy individuals aged 18-65years were recruited from university staff, students and associates via advertisement and personal contact. Inclusion criteria were no current neck pain, headache or restriction to neck movement, blood pressure and BMI within normal limits. Exclusion criteria included any cardiovascular risk factors (smoking, hypertension, oral contraception, hypercholesterolaemia) which could potentially confound ultrasound findings(Li et al., 2016); any connective tissue disease which might influence arterial stiffness; recent major illness or surgery; neurological conditions; positive positional tests for VBI as determined by response to sustained neck rotation (Thomas et al., 2018). Healthy individuals rather than persons with neck pain were recruited in the first instance as the aim was to determine whether the method had merit. It was inappropriate to subject persons with neck pain to an unproven procedure.

Demographic details, information on general health and past medical history were collected using a standard form to ensure all inclusion criteria were met and participants were in good health. Seated blood pressure was measured on the right arm with an automated sphygmomanometer(OMRON, Hoofddorp, The Netherlands), and was repeated in supine for reliability and to identify any postural effects on blood pressure which might confound results.

Measurement of arterial wall stiffness using elastography

Participants received a single session of ultrasound for 45 minutes, conducted in a quiet, dark room by an ultrasonographer with 25 years of experience. Ultrasound images were acquired with a Siemens Acuson S3000 Virtual Touch™ Imaging Quantification system(VTIQ) (Erlangen, Germany) optimized for vascular applications, using a 9 MHz (9L4) linear transducer.

Image processing

VTIQ provides quantitative measures of shear wave velocity (m/s) and qualitative colour-coded maps (elastograms), with high velocities indicative of stiffer tissues displayed in red and slower, less stiff tissues in blue. Data is formed by a pulse sequence comprised of up to 256 beam lines for each RF pulse. A '*shear wave quality mode*' identifies whether the shear wave is of sufficient magnitude with adequate signal to noise ratio to accurately estimate velocity within the ROI; values >5-10% variation from mean values are disregarded(Ianculescu et al., 2014). This system was used as the image processing should facilitate imaging of small vessels to ensure accurate velocity measures, as the ROI may include part of the vessel lumen, which could confound results. Higher velocity values correspond to a stiffer arterial wall(Doherty et al., 2013).

Procedure

Participants lay supine with their head supported in a neutral position. For convenience, the right vessels were imaged with the probe positioned longitudinally to the artery. Estimation of arterial wall stiffness was based on the velocity of the shear-wave propagating through the far wall of the vessel. Using the far wall accessed the target ROI through a fluid interface to limit reflection at tissue interfaces. We used one wall as an indication of stiffness of the whole artery. Both ICA and VA were measured at a proximal site (C3-4 level just distal to the carotid bulb-standard position) and a distal site at the atlanto-axial level (region more vulnerable to dissection)(Figure 1a &b).

The carotid bulb was located using B-mode ultrasound, and the right proximal ICA identified immediately distal at the level of C3-4. Doppler ultrasound was applied using a standard protocol with the transducer positioned longitudinally and at 60° to the vessel. The ICA was confirmed by its distinctive low-resistance waveform(Freed et al., 1998). Shear wave *velocity mode* was then selected. The focal depth was adjusted to position a ROI over the intima of the vessel wall level at C3-4. A radiofrequency pulse was applied at 90° to the vessel wall. Shear wave velocity (m/s) was recorded from three voxels (Figure 2a,b) positioned along part of the arterial wall with highest quality image (established by the '*quality mode*' function). The average was used in analysis. Cardiac gating was not used as averaged velocity measures accounted for any tissue variation. The ICA is a low resistance vessel so cardiac cycle variation should be small(Maksuti et al., 2017). The transducer was moved as far distally as possible along the artery to the C1-2 level and measures were repeated.

For the VA, the transducer was angled posteriorly, maintaining 90° angle, to identify the vessel between the cervical transverse processes. The artery was confirmed with Doppler ultrasound. Shear wave velocity measures were obtained from the VA wall at C3-4 and C1-2 levels. Velocity measurements were repeated on a subgroup of 20 participants on the same day at the proximal sites of both ICA and VA to assess the intra-rater reliability of stiffness measures. At the completion of the test sequence, the ultrasonographer repeated the proximal measures. She was blind to the outcomes of the first measurements. The second measures were taken approximately 45 minutes later.

Statistical analysis

Descriptive statistics were calculated for all outcomes. Measures of proximal and distal ICA and VA wall stiffness were tested for normality. Intra-rater reliability was calculated using intraclass correlations (ICCs $_{2,1}$) where ICCs >0.75 were indicative of good reliability and those <0.75 poor to moderate(Bruton et al., 2000, Shrout and Fleiss, 1979). Bland Altman plots were constructed for ICA and VA to show the mean difference in stiffness between the two measurement occasions. Standard error of measurement (SEM) and ability to detect the smallest real difference (SRD) were calculated as follows: ($SEM = s\sqrt{1 - r}$) where s is SD and r is intra-rater reliability, and ($SRD = 1.96 \times SEM \times \sqrt{2}$)(Portney and Watkins, 2009). Arterial stiffness measures were compared between ICA and VA and between proximal and distal sites for each artery with paired samples T-tests. The significance level was set at $p<0.05$. Data was analysed using IBM SPSS for Windows (release 25).

RESULTS

Participant characteristics

Thirty healthy participants (13 female) mean age 29.8 (± 12.8), range 20-62 years were studied; 20 aged <30 years, and 10 >30 years. Blood pressure and BMI were within normal ranges (World Health Organisation, 2000) and BP remained stable between positions. All were in good health with no major CV risk factors. None exhibited signs of VBI.

Both proximal and distal sites of the ICA and VA were identified clearly with elastography and high quality elastograms established by shear wave quality maps and velocity measures could be obtained (Figures 2a,b). No significant arterial abnormalities or anatomical variants were identified.

Psychometric properties of elastography

Intra-rater reliability between for repeated measures for both the ICA and VA were good (Table 1). Though confidence intervals were wide, Bland Altman plots showed mean differences between measures were within 2 standard deviations (Figure 3a &b). The SEM was 0.16 for ICA and 0.34 for VA and the SRD was 0.46 for ICA and 1.00 for VA.

Characteristics of arterial wall stiffness

Table 2 presents the arterial wall stiffness measures for ICA and VA. Data for each artery and site were normally distributed. The VA was significantly stiffer than the ICA. There was no difference between proximal and distal sites for ICA (Table 3). Mean stiffness was similar across age groups with the exception of the VA which was 0.7 (95% CI 0.1 to 1.4) m/s stiffer in those over 30 years.

DISCUSSION

This study demonstrated that it was possible to obtain high quality measures of ICA and VA wall stiffness using shear wave elastography. Both arteries could be tracked and stiffness reliably measured especially in the more vulnerable atlanto-axial segments where dissection has been commonly described. The ICA was easily identified by the carotid bulb and tracked distally past the angle of the mandible. The VA was easily identifiable using the landmark shadows of the cervical transverse processes. Tracking the artery towards the atlanto-axial region was more challenging in some participants due to vessel tortuosity, but shear wave velocity measures were obtained from all but one participant. While a few studies have investigated the ICA, measures of VA are novel. Elastography for vascular applications is an emerging area, but the results of this study suggest it may be worth pursuing in future studies as a measure the mechanical properties of cervical arteries(Ramnarine et al., 2014). Elastography could potentially enable detection of vascular susceptibility, although validation in larger groups and clinical populations needs to be undertaken.

Psychometric properties

Intra-rater reliability of measures was good, with ICCs for both arteries >0.75. This suggests elastography at least in the hands of an experienced ultrasonographer is able to provide accurate estimates of vessel stiffness. Measurement error was low for ICA but somewhat larger for VA, probably consistent with the smaller artery size. Similarly, smallest real difference was low for ICA but higher for VA. Larger groups and clinical populations will be required to determine clinically important cut off scores potentially indicating that the artery wall might be ‘at risk’.

Arterial wall stiffness characteristics

The ICA was less stiff than the VA, consistent with its larger size. The greater stiffness in the VA probably reflects its relatively restricted course through the cervical transverse foramen and its smaller size, which may have implications for the effect of head movement and minor trauma. Stiffer cervical arteries might be more vulnerable to trauma (Callaghan et al., 2011, Schlemm et al., 2017), whereas less stiff arteries may be more vulnerable to aneurysm (Li et al., 2016). In our healthy individuals, wall stiffness was similar between proximal and distal sites. This might be different in clinical groups particularly those with CAD and might be a potential identifiable risk factor (Callaghan et al., 2011). One might expect that distal segments of the VA would be stiffer due to greater movement and angular course of the artery at C1-2, so greater differences in stiffness might be indicative of wall pathology but this will need exploring in clinical groups.

Wall stiffness was independent of age in this study but trended towards greater VA stiffness in older individuals. Increasing arterial stiffness with age is recognised (Lee and Oh, 2010) but CAD occurs more frequently in younger people and is not associated with atherosclerosis. Thus, increased stiffness in younger people might be important for determining risk of CAD (Calvet et al., 2004).

Previous shear wave research of carotid arteries has largely focused on identifying plaque and assessing vulnerability to rupture (de Korte et al., 2016, Ramnarine et al., 2014). The current study adds additional information about the arterial wall itself, which may provide a useful indicator of arterial susceptibility.

Strengths and limitations

VA and ICA stiffness was successfully measured using shear wave elastography and demonstrated good utility in identifying and tracking both vessels to the alanto-axial region. Application of a RF pulse does not complicate a vascular ultrasound investigation, making it feasible for less experienced operators. Psychometric properties of elastography were good. While confidence intervals for reliability were somewhat wide, the actual numbers are still small and Bland Altman plots showed measurement variation was within acceptable limits. Some natural variation might be expected nonetheless, and further more detailed exploration of psychometric properties such as inter-rater reliability will be required. The ROI for elastography measurement was slightly larger than the intimal layer of the vessel wall. It extended into the lumen, which could have affected the accuracy of velocity measures. However, the 'shear wave quality mode' disregards any measures which vary >5-10% allowing us to take measures only from areas of high quality.

Shear wave elastography measurement of arteries can be criticised with limitations of anisotropy, dispersion of shear waves in tubes and variations due to the cardiac cycle. We addressed these potential limitations by taking the average of 3 velocity measures at each site as well as measuring 2 separate sites on each artery. Additionally, the ICA and VA are low resistance vessels and do not vary greatly between systole and diastole. We reported shear wave velocity as a measure of arterial stiffness, as this was the VTIQ system output, rather than estimating shear modulus, which is influenced more by vessel diameter.

Future studies are needed to determine side differences in ICA and VA stiffness and the impact of neck rotation and extension as these movements may place greater strain on the arteries. Likewise, research is required on clinical populations to determine any differences in vascular stiffness which might indicate a susceptibility to trauma and a risk factor for CAD.

CONCLUSION

Shear wave elastography appears to be a suitable method to examine VA and ICA stiffness, which warrants further investigation. Preliminary evaluation of psychometric properties suggest acceptable reliability and measurement error and estimates of smallest real difference can be obtained. The study is a useful first step to inform future research exploring the use of elastography to assess arterial wall properties, which may inform the assessment of arterial integrity.

CAPTIONS

TABLES AND FIGURES

Figure 1a Location of proximal and distal sites on internal carotid and vertebral artery examined with elastography

Figure 1b Ultrasound set-up showing participant and probe position

Figure 2a Elastogram of the distal internal carotid artery (ICA).

Figure 2b Elastogram of the distal vertebral artery (VA).

Footnote: Voxels (yellow boxes) lined along the distal wall provide stiffness measures in V_s, where V_s is the velocity (m/s) of propagated shear-wave through the vessel wall. A higher V_s value corresponds to a stiffer vessel wall.

Figure 3a Bland Altman plots for internal carotid artery (ICA) showing mean (solid line), upper and lower limits of agreement (LoA)

Figure 3b Bland Altman plots for vertebral artery (VA) showing mean (solid line), upper and lower limits of agreement (LoA)

Table 1 Mean (SD) of initial and repeat measures of arterial wall stiffness (m/s) at the proximal site of the ICA and VA and reliability (ICCs) , measurement error and smallest real difference (SRD) for a subgroup of 20 participants

Table 2 Mean (SD) arterial wall stiffness (m/s) for ICA and VA by age and mean difference (95%CI) between arteries (p value for group)

Table 3 Mean arterial wall stiffness (m/s) for proximal and distal sites of ICA and VA and mean difference (95% CI) between sites

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Table 3 Mean arterial wall stiffness (m/s) for proximal and distal sites of ICA and VA

Tables

Table 1: **Mean (SD) of initial and repeat measures of arterial wall stiffness (m/s) at the proximal site of the ICA and VA and reliability (ICCs), measurement error and smallest real difference (SRD) for a subgroup of 20 participants**

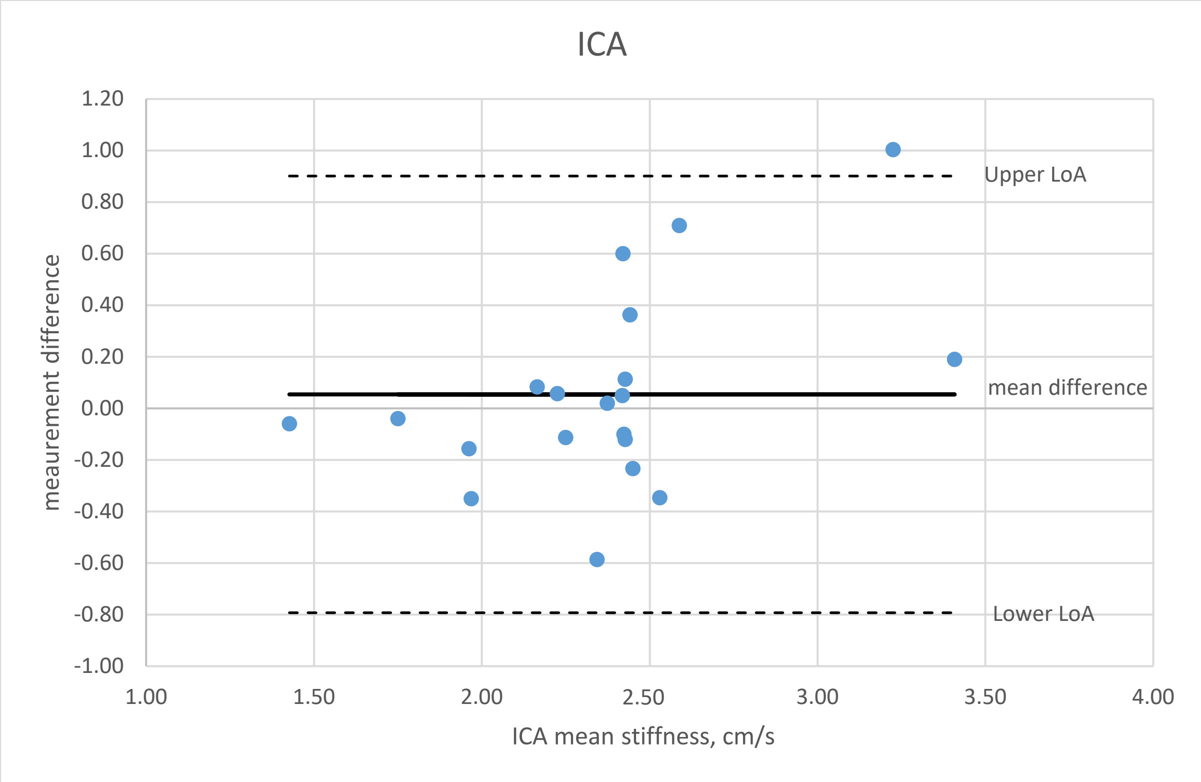
Artery	Initial	Repeated	ICC	Measurement error	SRD
ICA	2.4 (0.6)	2.3 (0.3)	0.8 (CI 0.5 to 0.9)	0.2	0.5
VA	4.0 (0.8)	3.8 (0.8)	0.8 (CI 0.4 to 0.9)	0.3	1

Table 2 **Mean (SD) arterial wall stiffness (m/s) for ICA and VA by age and mean difference (95%CI) between arteries (p value for group)**

Participants	R ICA	R VA	Difference between arteries	P-value
≤30 years	2.4 (0.6)	3.6 (0.6)	1.2 (-1.6 to -0.9)	0.00
≥31 years	2.4 (0.3)	4.4 (1.1)	1.9 (-2.8 to -1.1)	0.001
Total group	2.4 (0.49)	3.7 (0.89)	1.3 (1.6 to 1.1)	0.00*

Table 3: **Mean arterial wall stiffness (m/s) for proximal and distal sites of ICA and VA and mean difference (95% CI) between sites**

Artery	Proximal	Distal	Difference between sites	P-value
ICA	2.4 (0.5)	2.4 (0.5)	0.004 (-0.1 to 0.1)	0.95
VA	3.8 (0.8)	3.5 (0.9)	0.3 (-0.06 to 0.6)	0.1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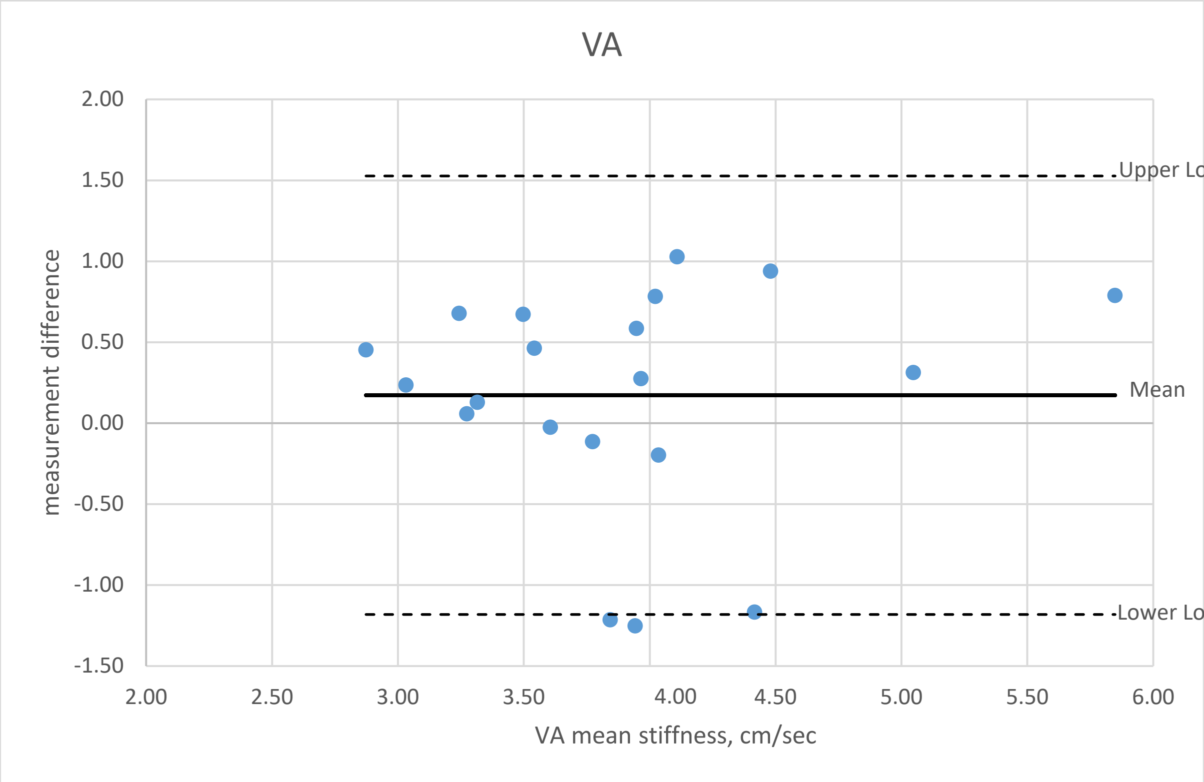
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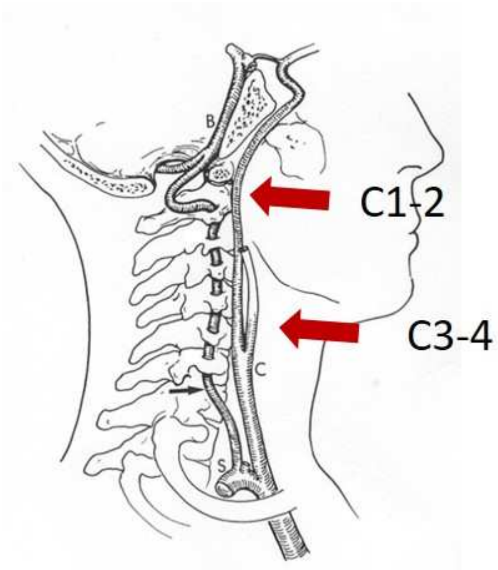
VA mean stiffness, cm/sec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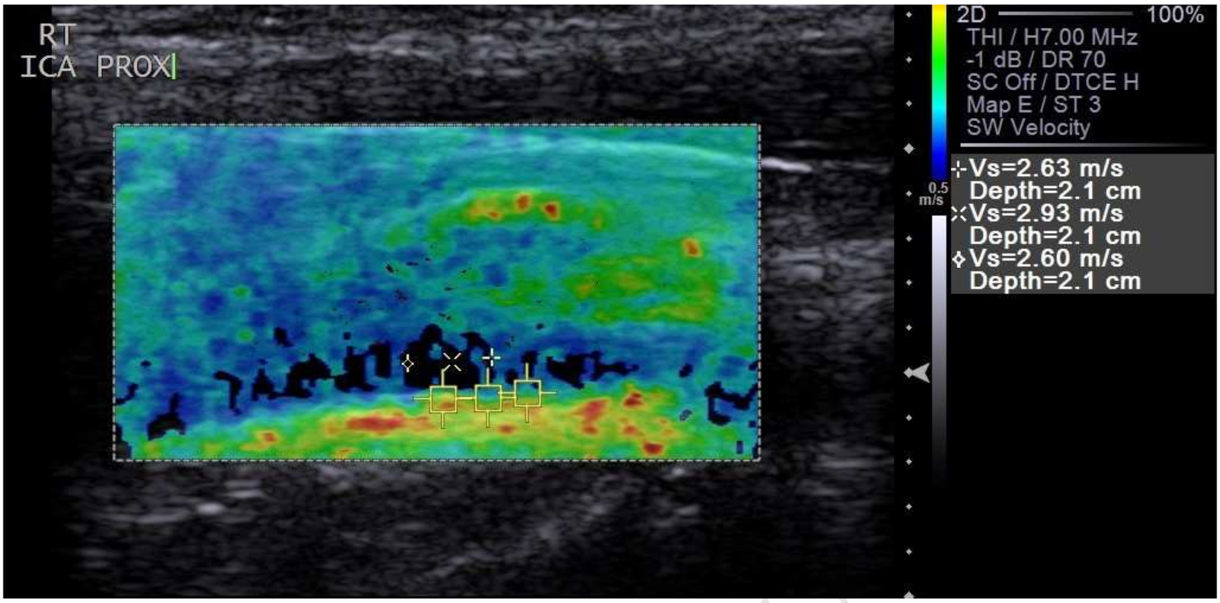
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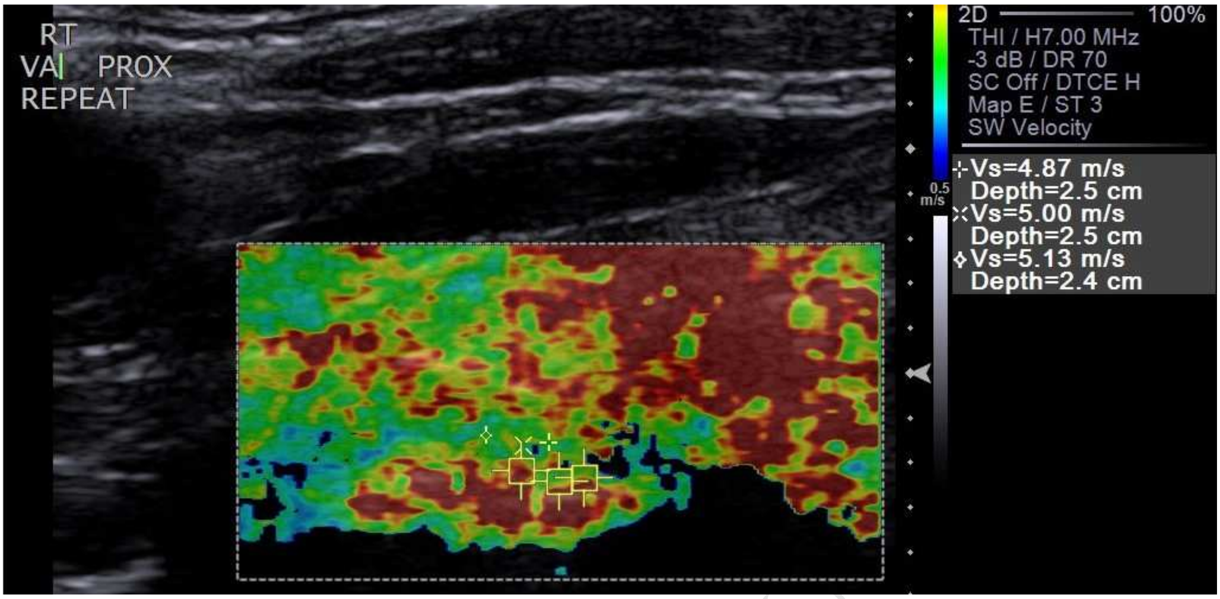

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Vs=4.87 m/s
Depth=2.5 cm
Vs=5.00 m/s
Depth=2.5 cm
Vs=5.13 m/s
Depth=2.4 cm