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Is Cervical Anterior Spinal Artery compromised in Cervical spondylotic myelopathy patients? – dual energy Computed tomography analysis of Cervical Anterior Spinal Artery

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Abstract:

Objective: Cervical myelopathy is a common acquired cause of spinal cord dysfunction in elderly. It is postulated that hypoxic/ischemic environment secondary to chronic spinal cord compression plays an important role in the pathogenesis of myelopathy. This study aims to assess the altered blood flow to spinal cord in Cervical spondylotic myelopathy patients using Dual-Energy Computed Tomography. To our knowledge, this is the first study to utilize DECT in identifying comprised Anterior Spinal Artery blood flow in CSM patients.

Methods: Fifty patients with single disc level CSM and 10 volunteers without CSM performed DECT of the cervical spine to analyze and compare the ASA. The neurological status of each CSM patient was evaluated pre-operatively, at post-operative day five, one month and six months using the Japanese Orthopedic Association (JOA). All the CSM patients underwent Single-level ACDF and at post-operative day five, each patient had another DECT. The Anterior Spinal Artery prior to surgery and after surgery in CSM patients were compared. The blood flow in terms of iodine content at a specific region of interest (ROI) was measured in the axial CT of the volunteers group and in the pre-operative and post-operative axial CT of CSM patients. Correlations between change in blood flow and clinical improvement at each follow-up points were statistically analyzed.

Results: The iodine content in the volunteer were 14.2800 ± 1.89527 at C3/C4 disc level, 14.8280 ±1.83820 at C4/C5 disc level and 15.5000 ±2.41048 at C5/C6 level. In the CSM patients, the pre-operative iodine content measured was 10.2621± 2.37396 in C3/C4 disc level compression, 12.1438±1.63447 in C4/C5 disc level compression and 14.0620±2.44390 in C5/C6 disc level compression and at the post-operative iodine content measurement changed to 13.78±2.77 for C3/C4 disc level, 14.16±1.90 for C4/C5 disc level and 15.14±2.62 for C5/C6 disc level. The JOA score was 13.650 pre-operatively, 14.010 at 5 days post-operatively, 14.630 at 1-month post-operative and 15.000 at post-operative 6-month. The 1-month and 6-month correlation ratio between the JOA and change in blood flow was statistically significant, with an r value of 0.746 (p<0.05) and 0.760 (p<0.05) respectively.

Conclusions: This study provided an evidence for the benefit of DECT as a radiographic tool for identifying the compromised Cervical Anterior Spinal Artery in Cervical Spondylotic Myelopathy patients. We believe that the DECT is the one of the best radiographic tool available that provide an objective screening tool to detect compromised blood flow in cervical spondylotic myelopathy patients.
Introduction:

Cervical spondylotic myelopathy (CSM), wherein the spinal cord is compromised within the vertebral canal by degenerative changes, is the commonest acquired cause of spinal cord dysfunction among those aged over 55 years[1]. Teresi, L.M., et al. Identified 26% of general subjects over 64 years old with spinal cord compression on Magnetic Resonance Imaging[2]. It has been widely accepted that the pathophysiology of Cervical Spondylotic Myelopathy involves static factors, which results in acquired or developmental stenosis and dynamic factors, which involves repetitive injury to the cervical spinal cord[3, 4].

The signs and symptoms are widely dependent on the relative degree to which the posterior, dorsolateral and ventrolateral columns, the ventral horns and the cervical nerve root of the spinal cord are involved[2]. However, there is still a lack of understanding why some patient develops severe symptomatology, while others have few or no symptoms despite of radiographic evidence confirming similar degrees of compression. Histologic examination of spondylotic myelopathy patient’s spinal cord revealed flattening of the cord, swelling of myelin and axons, demyelination in the posterolateral and anterolateral columns, neuronal loss in the anterior horns and gliosis[5]. As a basis of reasoning, it was assumed that the chronic degenerative changes can compress major feeding arteries of the cervical spine, resulting in pathologically reduced blood flow and compromised spinal cord perfusion[5]. Cadaveric study that supports this theory has demonstrated a curved and stretched anterior spinal artery and branches of lateral pial plexus around the degenerative spondylo-osteophytes[6]

In light of ongoing concerns about altered blood flow in cervical spondylotic myelopathy, a radiographic tool to detect compromised blood flow in Cervical spondylotic myelopathy patients in clinical would be valuable. Attempts to detect altered Anterior Spinal Artery blood flow have been reported previously using the present-day availability of Computed Tomography Angiography(CTA), have been unsuccessful[7]. The concept of Dual-Energy Computed tomography (DECT) involves in the acquisition of two datasets utilizing different X-ray energy spectra[8, 9]. The knowledge about the potential for material decomposition by dual energy method have been known since the late 1970s, however clinical implementation of this technique was limited on early generation CT scanners[10, 11]

The goal of the present study was to utilize Dual-Energy Computed Tomography as a screening tool to: 1) identify and compare the blood flow in cervical anterior spinal artery in CSM patients and volunteers without cervical spondylotic myelopathy; 2) discuss the effect of surgical decompression for cervical spondylotic myelopathy on Cervical Anterior Spinal Artery; 3) Acknowledge and highlight the changes in blood flow of cervical anterior spinal artery after surgical
treatment with the improvement in the Japanese Orthopedic Association (JOA) score of CSM patients.

Material and methods:
Study populations:

Cervical spondylotic myelopathy patients:

Between June 2016 and April 2017, a total of 50 patients were prospectively included in our study. The inclusion criteria for this study was: 1) Patient presented with typical symptom of cervical myelopathy that were not alleviated after at least 6-month conservative treatment; 2) Obvious single disc-level cervical spinal cord compression as shown by magnetic resonance imaging studies; 3) Patient agreed to receive surgical treatment and cooperate with follow-up visits after surgery. These patients included 29 males and 21 females with an average age of 56.24 years. Magnetic Resonance Imaging (MRI) and myelography findings were consistent with Cervical myelopathy secondary to single-segmental cervical spondylotic stenosis. Each patient had myelopathy confirmed by a physical examination and cord compression was presented at C3/C4, C4/C5 or C5/C6 disc levels. Patients with severe spondylosis that limited resolution of the measurement parameters, ossification of the posterior longitudinal ligament or high-level shoulders were not enrolled due to possible artifacts. Other exclusion criteria for the study was: 1) patients unable to cooperate when performing Dual-Energy Computed Tomography scan; 2) metal denture that could not be removed; 3) patients with cardiovascular disease history, including hypertension; 4) patients with pulmonary disease history who could not follow breath hold commands; and 5) patients with renal dysfunction (renal failure or creatinine levels >150μmol/L).

Neurological status of each patient was evaluated prior to surgery, 5 days post-operative, 1-month post-operative and 6-month post-operative according to the Japanese Orthopedic Association (JOA) score. All the CSM patients included in this study, underwent Dual-Energy Computed Tomography scan prior to decompression. 5-days after surgery, the patients underwent another Dual-Energy computed tomography scan to analyze and compare the changes in Cervical Anterior Spinal Artery blood flow after decompression.

Surgical procedure:

Each patient underwent a single disc level anterior cervical discectomy and fusion (ACDF). Through a right anterior cervical approach, the disc compressing the spinal cord was removed. With completion of the discectomy, the posterior
longitudinal ligament was exposed and subsequently removed with a #1 or #2 Kerrison rongeur. A blunt hook was gently inserted to the neural foramen and central canal to ensure adequate decompression. To prevent the vertebrae from collapsing and to increase stability, a prosthetic cage (synthes GmbH, Cervicos, Switzerland) is used to fill the open space. An appropriate sized titanium plate (DePuy Spine, Inc. Slim-Loc, USA) is screwed on the rostral and caudal vertebral bodies to increase stability during fusion.

Asymptomatic Subjects:

Between May 2017 and July 2017, a total of 10 healthy volunteers with a mean age of 53 years were enrolled. Each volunteer had a Magnetic Resonance Imaging scan to rule out any cervical spine spondylotic stenosis. The subjects with a history of cardiovascular disease, a poor liver or renal function, a history of brain or spinal surgery, comorbid neurological disease such as cerebral infarction or neuropathy, symptoms related to sensory or motor disorders (e.g. numbness, clumsiness, motor weakness and gait disturbances) or the presence of severe neck pain were excluded.

The 10 volunteers underwent Dual-Energy Computed Tomography scan to analyze the cervical anterior spinal artery blood flow. The study protocol was approved by the first affiliated hospital of Wenzhou medical university ethics board for health science research involving human subjects. Informed oral and written consent was obtained prior to recruitment for DECT.

Dual-Energy Computed Tomography technique, image processing and measurement:

Computed Tomography scanning was performed using a 64-row American GE discovery Energy Spectrum CT 750HD CT instrument in the GSI scanning mode. The scan range was from the inion down to the edge of the seventh Cervical spinous process.

A fixed dose of 350mg/mL iodinated contrast agent (iohexol) was injected at the rate of 5.0mL/s, followed by a 30mL saline flush with a double-syringe power Empower CTA injector (ACIST, Eden Prairie, MN, USA). The arterial enhanced scan was performed 25 seconds after the plain scan. In both phase, Conventional tube current was 260mA, with an instantaneous highspeed switch tube voltage of 80,140 kVp. Both phases used Pitch 0.969:1, Rotation speed:0.8/r, DFOV of 25cm, with Slice thickness: is 5mm and Interlamellar spacing of 5mm. All the data file obtained was transferred to ADW4.6 workstation (GE Healthcare, Waukesha, WI,
The plain scan and arterial enhanced scan of each image were examined and processed in the iodine display mode. From the processed image, quantitative information of tissue attenuation and iodine uptake (in Hounsfield units or milligrams per milliliter) can be obtained from a single region of interest manually placed on the color coded iodine map[12, 13].

The region of interest was identified by and synchronous phasor measurement in MPR mode was performed to measure the iodine value in the anterior spinal artery and vertebral artery (VA) at each level for the asymptomatic volunteers. For CSM patients, the iodine value of ASA and vertebral artery was measured at the level of spondylotic compression. To ensure the validity of the results, the evaluation was performed by two different radiologists.

Statistical analysis

All data were analyzed using SPSS software (version 24, SPSS Inc. Chicago, Illinois). The iodine content was described as mean ± standard deviation. We used the paired t-test to identify the differences in pre-operative and post-operative blood flow and changes in JOA. The Pearson’s correlation analysis was used to investigate the relationship between the change in ASA blood flow and change in JOA at each follow-up point. To test internal and external validity of all measurements, imaging studies was measured by another radiologist to assess, the intra-observer and inter-observer reliability. The level of significance was set at P < 0.05.

Result:

The study included 50 Cervical Spondylotic Myelopathy (CSM) patients (29 males and 21 females) with an average age (and standard deviation) of 56.24±10.435 (range: 31 to 72) and 10 volunteers without Cervical Spondylotic Myelopathy (7 males and 3 females) with an average age (and standard deviation) of 53 ± 9.24(range: 31 to 64 years). The average length of symptoms in CSM patients were 10.26±2.44 months. The demographic features and radiological parameters are shown in Table 1. The JOA score (Table 1) for the CSM patients were 13.650 pre-operatively, 14.010 at 5 days post-operatively, 14.630 at 1-month post-operative follow-up and 15.000 at post-operative 6-month.

The Cervical Anterior Spinal Artery and vertebral artery was identified (figure...
1 and figure 2) from the processed lateral and axial CT image in both groups. The measurement of iodine content (mean ± SD) from the region of interest at the level of compression on axial CT were averaged in the CSM patients. In the volunteers, iodine content at each disc level was measured and averaged. The measurements of both groups were analyzed and compared (Figure 3). The pre-operative ASA iodine content (100mg/ml) in patient with C3/C4 disc level compression was 10.26 +2.37, 12.14+1.63 in C4/C5 disc level compression and 14.06+2.44 in C5/C6 disc level compression. The pre-operative VA iodine content (100mg/ml) at C3/C4, C4/C5 and C5/C6 segments in CSM patients was 161.59 ± 13.45, 162.48 ± 7.98 and 162.21 ± 5.18 respectively. In the asymptomatic volunteer, the ASA iodine content(100mg/ml) was 14.2800 ± 1.89527 at C3/C4 disc level, 14.8280 ±1.83820 at C4/C5 disc level and 15.5000 ±2.41048 at C5/C6 level and VA content at C3/C4, C4/C5 and C5/C6 was 161.84 ± 5.66, 162.49 ± 6.13 and 161.35 ± 5.40 respectively. No statistical correlation (p-value:0.64) was found between the ASA iodine content and the length of symptoms.

Table 1: Characteristics of asymptomatic volunteers and CSM patients

Table 2: ASA and Iodine value for asymptomatic patients

The difference in VA iodine content between asymptomatic volunteers and pre-operative CSM patients at each disc-level was statistically insignificant (with a P-value of 0.24 for C3/C4 disc level, 0.59 for C4/C5 and 0.34 for C5/C6) whereas the difference in ASA iodine content between the two groups showed a statistical significant (with a P-value of 0.018 for C3/C4 disc level, 0.017 for C4/C5 and 0.039 for C5/C6).

Figure 1: lateral CT showing identified ASA

Figure 2: Axial CT showing identified ASA

Figure 3: graphical analysis comparing pre-operative Iodine content and control iodine content

At post-operative day 5, the iodine content was measured and compared in each patient (figure 4). The value changed to 13.78±2.77 at C3/C4 disc level, 14.16±1.90 at C4/C5 disc level and 15.14±2.62 C5/C6 disc level. The change between pre-operative and post-operative ASA iodine content was statistically significant (P-value: <0.001 at each segment) however, the difference in between asymptomatic volunteer ASA iodine content and the ASA iodine content in CSM patient post-operatively was insignificant (p-value: 0.83 for C3/C4 disc level, 0.511
for C4/C5 disc level and 0.17 for C5/C6 disc level. The difference between pre-operative and post-operative VA iodine content was statistically insignificant (p-value: 0.96 for C3/C4 disc level, 0.79 for C4/C5 disc level and 0.15 for C5/C6 disc level).

Table 3: VA and ASA iodine content in CSM patients.

The intra-observer and inter-observer reliability were both excellent with a value of 0.947 and 0.960 respectively.

Figure 4: graphical analysis comparing pre-operative iodine content and control iodine content

Ratio correlations between change of blood flow and JOA score at different follow up was tested to show how changes in blood flow affects the clinical outcomes over time were tested. The 1-month (figure 6) and 6-months (figure 7) ratios correlated strongly and significantly with the change in blood flow. The post-operative day 5 ratio (figure 5) (r=0.242, p=0.09 (P>0.05)) had weaker correlations with the change in blood flow.

Figure 5: correlation ratio between the change of JOA at post-operative day 5 and change rate of iodine content

Figure 6: correlation ratio between the change of JOA at post-operative 1-month and change rate of iodine content

Figure 7: correlation ratio between the change of JOA at post-operative 6-months and change rate of iodine content

Discussion:

Chronic degenerative changes in the cervical spine causes an interruption in the blood supply to the spinal cord which may be a significant component in the initiation and progression of Cervical Spondylotic Myelopathy[14]. The cadaveric study conducted by Breig, A et.al[6], supports the suggestion of compromised Anterior Spinal Artery blood flow by degenerative changes in cervical spine to axonal pathways including corticospinal tracts. Clinical attempts to identify compromised ASA in CSM patients have been unsuccessful previously[7].

In this study, using the Dual-Energy Computed Tomography, we successfully demonstrated significant decrease of Anterior Spinal Artery blood flow in the spinal cord of Cervical spondylotic Myelopathy patients. Basic science research work showed that hypoperfusion of the spinal cord in combination with chronic compression could induced myelopathy[15]. An increased in spinal cord tissue pressure due to chronic compression raises capillary and venous pressure, resulting
in a net decrease in perfusion pressure. This would precipitate a decrease of blood flow as proven by our data. The chronic hypoxic/ischemic environment damages neurons and oligodendrocytes, eliciting an inflammatory response[16]. On the other hand, the chronic compression induced ischemic environment results in endothelial loss, thereby disrupting neurovascular unit and leading to compromised blood-spinal cord barrier (BSCB)[16]. Permeability and inflammation of BSCB have been demonstrated in the chronic stages of CSM patients[17]. Moreover, it is suggested that during the late stages, inflammatory Fas ligand (FasL) signaling can lead to apoptosis of neurons and oligodendrocytes[17, 18] which might be responsible for the upper limb dysfunction, spasticity and gait disturbances seen in Cervical Spondylotic Myelopathy patients.

Surgical decompression has proved to be an effective treatment option in CSM patients[19] and experimental model[3], that not only halt the progression of the symptoms, but can also promote meaningful functional recovery. Evidence have suggested that decompression treatment blocks the inflammatory induced FasL pathway which decreases the level of cellular apoptosis activity, thereby improving the functional outcomes in CSM patients [3, 16]. In our study, we found a strong correlation between the change in Anterior Spinal Artery blood flow and the clinical outcome at 1 month and 6 months. However, at post-operative day 5, a weak correlation was observed. An explanation for the notably poor statistical ratio could be a slow healing process after decompression, due to an ongoing apoptotic reaction with demyelination of corticospinal tracts at site away from the primary injury. An experimental study conducted by Karadimas et.al, demonstrated an ongoing apoptosis of oligodendrocytes at area of 5mm surrounding the primary compression site 10 weeks following decompression[16].

The ready availability of conventional Computed Tomography Angiography as used previously[7], can only provide qualitative assessment and not quantitative assessment of the Anterior Spinal Artery. Major improvements in CT hardware have gratified the prerequisites for the clinical application of Dual-Energy Computed Tomography imaging. By exploiting the attenuation profile of different materials when expose to two energy spectra[8, 9], DECT enables the evaluation of vascular anatomy and perfusion in one imaging sessions. Using the iodine display techniques of DECT with a three material decomposition analysis, the iodine contribution to an image can be selectively identified[12] from the absorption characteristics and generating virtual non-contrast-enhanced images[20]. This approach provides both attenuation information in Hounsfield units and iodine concentration in milligrams per milliliter[20].

The generated image is comparable to the image quality of conventional non-enhanced acquisition[20, 21]. However, it is suggested that a dual energy scan
with reconstructed VNC image results in a reduction in radiation dose by up to 50% compared with multiphasic single energy CT protocols[20, 21]. DECT is not prone to the inherent motion and/or breathing artifacts that can occur with a conventional multiphasic CT protocol[12, 13]. Accumulating evidence suggest that DECT may contribute to the alleviation of metal related artifacts thus improving the image quality[22, 23] which is a common and challenging task with conventional CT imaging[22]. Therefore, the DECT can help practitioners to assess quantitatively and qualitatively the Cervical Anterior Spinal artery even in the presence of metal implants.

In this study, we demonstrated a change in anterior spinal artery blood flow after decompression surgery in Cervical Spondylotic Myelopathy patients using Dual-Energy Computed Tomography. Attempt to correlate the change in blood flow with the Japanese Orthopedic Association (JOA) score found a strong statistical significance at post-operative 1 month and post-operative 6 month. This suggest that decrease of the blood flow at the site of compression may contribute to the development of myelopathy. The DECT can be used as a screening tool to identify compromised blood flow in CSM patients. It can help in qualitative and quantitative measurement of the pre-operative and post-operative blood flow in CSM patients. We are planning additional studies to evaluate the utility of Dual-Energy Computed Tomography in differentiating the outcome between anterior and posterior decompression.

Limitation and weakness:

The change in ASA blood flow as measured by DECT in CSM patients could be used as a predictor of outcome reflecting an underlying pathological event. However, this cannot be confirmed until the affected neurons are directly evaluated. This is not possible as it would involve an invasive operation and damaging the white matter itself. Instead, animal models of CSM may prove to be useful in understanding the basic mechanisms of neuronal death or dysfunction after a lack of blood flow in hopes of devising a to that can predict the surgical outcome.

Acknowledgement:

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References:


Table:

- Table 1: Characteristics of asymptomatic volunteers and CSM patients
- Table 2: ASA and iodine value for asymptomatic patients
- Table 3: VA and ASA iodine content in CSM patients

Figure caption:

- Figure 1: Lateral CT showing identified ASA
- Figure 2: Axial CT showing identified ASA
- Figure 3: Graphical analysis comparing pre-operative iodine content and control iodine content
- Figure 4: Graphical analysis comparing pre-operative iodine content and control iodine content
- Figure 5: Correlation ratio between the change of JOA at post-operative day 5 and change rate of iodine content
- Figure 6: Correlation ratio between the change of JOA at post-operative 1-month and change rate of iodine content
- Figure 7: Correlation ratio between the change of JOA at post-operative 6-months and change rate of iodine content
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<th>Asymptomatic volunteers</th>
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<td>C4/C5</td>
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Cervical myelopathy is a common acquired cause of spinal cord dysfunction in elderly. It is postulated that hypoxic/ischemic environment secondary to chronic spinal cord compression plays an important role in the pathogenesis of myelopathy. This study aims to assess the altered blood flow to spinal cord in Cervical spondylotic myelopathy patients using Dual-Energy Computed Tomography. To our knowledge, this is the first study to utilize DECT in identifying comprised Anterior Spinal Artery blood flow in CSM patients.
Abbreviation lists:

CSM: cervical spondylotic myelopathy
DECT: Dual-energy computed tomography
ASA: anterior spinal artery
ACDF: Anterior Cervical Discectomy and fusion
VA: vertebral artery