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Journal

Journal of vascular and interventional neurology, 13(1)

ISSN

1941-5893

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Publication Date

2022-06-01

Peer reviewed



Published in final edited form as:

J Vasc Interv Neurol. 2022 June ; 13(1): 35–41.

Superior cervical ganglion stimulation results in potent cerebral vasoconstriction in swine

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Abstract

Introduction: Sympathetic activity from the superior cervical ganglion (SCG) has been shown to cause cerebral hypoperfusion in swine, similar to that seen with clinical cerebral vasospasm. Although the mechanism of such perfusion deficit has been speculated to be from pathologic cerebral vasoconstriction, the extent of sympathetic contribution to vasoconstriction has not been well established.

Objective: We aimed to demonstrate that SCG stimulation in swine leads to significant cerebral vasoconstriction on digital subtraction angiography (DSA). Additionally, we aimed to show that inhibition of SCG can mitigate the effects of sympathetic-mediated cerebral vasoconstriction.

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- Geoffrey P. Colby MD PhD: corresponding author, director and coordinator for all aspects of the project

Financial Disclosures: Casa Colina Foundation research grant, NIH Research Education Programs (R25)

Previous Presentations: None

List of Commercial Products:

- Siemens Artis Zeego C-Arm (Siemens Healthcare™, Erlangen, Germany)
- Medrad Mark V ProVis (Medrad Bayer Healthcare Llc, Pittsburgh, Pennsylvania, USA)
- Syngo iFlow (Siemens Healthcare™, Erlangen, Germany)

Conflicts of Interest: None

Methods: Five SCGs were surgically identified in Yorkshire swine and were electrically stimulated to achieve sympathetic activation. DSA was performed to measure and compare changes in cerebral vessel diameter. Syngo iFlow was also used to quantify changes in contrast flow through the cerebral and neck vessels.

Results: SCG stimulation resulted in 35–45% narrowing of the ipsilateral ascending pharyngeal, anterior middle cerebral and anterior cerebral arteries. SCG stimulation also decreased contrast flow through ipsilateral ascending pharyngeal, internal carotid and anterior cerebral arteries as seen on iFlow. These effects were prevented with prior SCG blockade. Minimal vessel caliber changes were seen in the posterior cerebral, posterior middle cerebral and internal carotid arteries with SCG stimulation.

Conclusion: SCG stimulation results in significant luminal narrowing and reduction in flow through various intracranial arteries in swine. The results of sympathetic hyperactivity from the SCG closely models cerebral vasoconstriction seen in human cerebral vasospasm. SCG inhibition is a potential promising therapeutic approach to treating cerebral vasospasm.

Introduction

Cerebral vasospasm is a disease of pathologic narrowing of the cerebral vasculature leading to diminished cerebral blood flow, resulting in significant morbidity and stroke. Various modalities are used to assess for cerebral vasospasm, including clinical exam, elevated Lindegaard ratio on transcranial doppler flow velocity measurements,¹ or visualizing irregular caliber vessels on axial imaging, such as computed tomography angiography (CTA).² However, the gold standard method for diagnosing cerebral vasospasm is the observation of irregularly diminished cerebral vessel caliber on a digital subtraction angiography (DSA).³ Furthermore, the severity of vasospasm is determined using a widely accepted grading scale based on the degree of cerebral vessel luminal narrowing.⁴

Although the exact mechanism of cerebral vasospasm remains unclear, and it is likely multifactorial, sympathetic hyperactivity has been shown to be a significant contributor.^{5,6,7} Sympathetic innervation to the ipsilateral cerebral vasculature originates from the superior cervical ganglion (SCG).^{8,9,10} We have previously shown that, in a swine model, electrical stimulation of the SCG results in significant cerebral perfusion deficit.¹¹ However, a purely sympathetic mediated cerebral vasoconstriction has not been characterized in a large mammal model using DSA.

In this study, we aimed to show that sympathetic activation of the SCG is sufficient to induce true cerebral vasoconstriction. Furthermore, we demonstrate that prior pharmacologic blockade of SCG inhibits this sympathetic-mediated cerebral vasoconstriction.

Methods

Animal Care

Use of animals, associated housing/handling and all related experiments were reviewed and approved by the institution's Institutional Animal Care and Use Committee and Animal Research Committee and Division of Laboratory Animal Medicine. All procedures

were conducted in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care International guidelines.

Anesthesia/Neck Dissection/SCG Stimulation/SCG Blockade

Yorkshire pigs (*Sus scrofa*) of either gender between 40–50kg were used. Animals were anesthetized and bilateral carotid sheath contents were surgically exposed as previously described.¹¹ Anesthesia was transitioned to alpha-chloralose and the SCG were stimulated as previously described. An SCG was stimulated for 30 seconds prior to angiography imaging. For SCG blockade, a 29G needle was used to deliver 0.3mL of 2% Lidocaine HCL to the identified SCG. Ninety seconds were allotted after lidocaine administration prior to SCG stimulation, with subsequent angiography done 30 seconds after stimulation.

Digital Subtraction Angiography (DSA)

Diagnostic angiography procedures were performed using a Siemens Artis Zeego C-Arm. Through a femoral arterial sheath, a 5F diagnostic catheter was introduced and navigated over a guidewire to the intended vessels. The ascending pharyngeal artery was catheterized under roadmap guidance. DSA was performed in a standardized fashion using a Medrad Mark V ProVis injector to deliver 6mL of Omnipaque (iohexol) 300 through the 5F catheter, with a flow rate of 3mL/s and maximum pressure of 300psi. All images were obtained at the same magnification and view for each experiment set. All obtained images and series were transferred to, and stored in the institution's picture archiving and communication system (PACS).

Vessel Measurements

Vessel diameters were measured using tools on the institution's PACS system. Location of the vessel diameter measurements for various arteries are as shown in Figure 1. Diameters of ascending pharyngeal artery (APA), anterior cerebral artery (ACA), anterior middle cerebral artery (aMCA), posterior middle cerebral artery (pMCA), internal carotid artery (ICA) and posterior cerebral artery (PCA) were measured. All measurements were done under four times the original magnification to ensure accurate measurements of vessel diameter.

Contrast Flow Measurements

Angiography series were further analyzed with the commercially available and clinically utilized software, Syngo iFlow. Using the algorithm inherent to the software, a colorimetric map was generated to visualize time of maximum contrast intensity detection at various regions. (Figure 2A) Regions of interest (ROI) were selected along the APA, ICA and ACA, where vessel diameters were measured. Given the small calibers of MCA and PCA vessels, they were not reliably identified on the colorimetric maps and therefore, were excluded in these measurements. Contrast flow metrics were calculated and used as a surrogate for blood volume flow. ROIs were used to plot percent contrast intensity detected over time. Area under this generated curve was then calculated and used as a measure of total contrast flow through the vessel over the defined time interval (Figure 2B). Location and area of ROI was kept identical between different angiograms to ensure consistency.

The contrast flow in each ROI was normalized to contrast flow passing through the confluence of sinus (torcula) as the reference point. The torcula was chosen as the reference point because it was determined to be the vessel that consistently has maximum contrast flow, and is not affected by SCG stimulation, thereby comparable between angiograms. Using a reference point just distal to the catheter tip, for example would introduce variability depending on degree of vasoconstriction of the ascending pharyngeal artery and therefore not selected.

Statistics

To account for normal variation in vessel diameter between animals and laterality, vessel diameters were represented as a percent of the diameters measured at baseline (no SCG stimulation) and compared between groups. Two-tailed student's t-test was used to determine statistical significance between groups. The significant level for all tests was set at $p=0.05$.

Results

Five SCGs, from 3 animals, were used in our study. One SCG was excluded from data analysis secondary to difficulty identifying the ganglion and failure to confirm activation by ipsilateral mydriasis with electrical stimulation. There was significant vasoconstriction seen in both intracranial and extracranial arteries with SCG stimulation. (Figure 3)

SCG Stimulation causes vasoconstriction in ipsilateral APA, aMCA and ACA

SCG stimulation resulted in significant vasoconstriction of APA, aMCA and ACA (Figure 4A). Mean vessel diameter decreased by 44% in APA ($p=0.011$), 36.1% in aMCA ($p=3.89\times 10^{-3}$), and 47.3% in ACA ($p=2.46\times 10^{-3}$), with ipsilateral SCG stimulation compared to baseline. While other vessel diameters decreased with SCG stimulation, they did not meet statistical significance. When SCG was inhibited with lidocaine prior to SCG stimulation, there was no significant difference in vessel diameter compared to baseline (all p -values > 0.2) (Figure 4A).

SCG Stimulation decreases contrast flow in APA, ICA and ACA

SCG stimulation significantly reduced the contrast flow through APA, ICA and ACA (Figure 4B). Mean contrast flow decreased by 49.4% in APA ($p=0.038$), 31.7% in ICA ($p=0.035$) and 49.7% in ACA ($p=8.58\times 10^{-3}$) with ipsilateral SCG stimulation compared to baseline. When SCG was inhibited with lidocaine prior to SCG stimulation, there was no significant difference in contrast flow through the APA, ICA and ACA compared to baseline (all p -values > 0.3).

Discussion

To the authors' knowledge, this is the first study to demonstrate with DSA that sympathetic activation alone is sufficient to induce potent cerebral vasoconstriction in a large mammal vasospasm model. The SCG electrical stimulation procedure outlined above shows promise as a novel and easily reversible large-mammal animal model for cerebral vasospasm. The

degree of vasospasm in swine vasospasm models have been traditionally assessed using diametric measurements, with ICA caliber narrowing ranging from 16–34% in autologous blood injection models.^{12,13,14} In our study, ICA caliber reduced by an average of ~10% from baseline, with an accompanying 31.7% reduction in ICA perfusion comparable to findings from other swine SAH experiments.¹⁵ While further studies are warranted to better establish our protocol as a model for SAH-induced vasospasm, our results, in conjunction with our prior work showing cerebral perfusion deficits seen in SCG stimulation, offer a compelling, sympathetic-driven model of cerebral vasospasm in large mammals.

Our prior study demonstrated that SCG stimulation results in a holo-hemispheric cerebral perfusion deficit in swine.¹¹ However, this current study demonstrates in a more granular fashion that only some of the cerebral arteries had significant vasoconstrictive response to SCG stimulation. This discrepancy between greater perfusion deficit and more limited individual vasoconstrictive changes, may be due to significant vasoconstriction of the ascending pharyngeal artery. While there exists an artery named the “internal carotid artery” in swine, its anatomic location and orientation is vastly different from that of humans’. In fact, some argue that the ascending pharyngeal artery in the swine is a more similar structure to the human ICA, as they both branch off the common carotid artery and act as the main arterial feeder to intracranial structures.¹⁶ Hence, while some vessel calibers seem unaffected by SCG stimulation, the reduction in cerebral blood flow from narrowing of the ascending pharyngeal artery in swine may be sufficient to cause perfusion deficits. This is further supported by our observation of a significant reduction in contrast flow through the ICA (Figure 4B), despite overall unchanged vessel diameter, with SCG stimulation.

Another consideration for the variability in cerebral vasoconstriction seen with SCG stimulation may be due to variability in our ability to accurately identify and stimulate the entire SCG. In our prior study, we were able to induce ipsilateral mydriasis and ipsilateral cerebral perfusion deficit with stimulation of the sympathetic chain above or below the SCG, albeit usually with higher current per stimulus. Partial stimulation of the SCG might lead to variations in cerebral vasoconstriction based on the map of the SCG as it relates to the downstream vascular targets. Furthermore, while recent studies have shown differential regulation of anterior and posterior cerebral circulation in humans,^{17,18,19} there may be additional autonomic innervation of cerebral vessels in swine that remains yet to be elucidated. This may explain the lack of significant changes in vessel caliber for PCA and even pMCA vessels with SCG stimulation observed in the current study.

Similar to our prior work that showed greater CT perfusion deficit in the extracranial distribution, we observed a more significant vasoconstrictive effect on extracranial than intracranial vessels with SCG stimulation. As previously mentioned, swine have greater emphasis on extracranial vasculature compared to humans, to supply larger facial muscles and the snout. Accordingly, we suspect that swine have greater number of sympathetic efferents to the extracranial than intracranial vessels. This could also explain the potent vasoconstriction response of the ascending pharyngeal and anterior cerebral arteries seen with SCG stimulation, given the emphasized development of the snout and olfactory areas in swine. It is important to recognize that in swine, many extracranial arteries have been found to form anastomoses with intracranial arteries to contribute to the cerebral blood

supply.^{20,21,22} Given the significant vasoconstriction of the extracranial circulation in swine, our model may underestimate the role of SCG in altering intracranial vessel caliber in humans.

There is debate in the literature regarding the association between cerebral vasospasm and delayed cerebral infarction. Traditionally, cerebral ischemia and poor patient outcomes following subarachnoid hemorrhage have been attributed to arterial narrowing and cerebral vasospasm.^{23,24,25} However, it has been proposed that vasospasm may not be the main cause of delayed cerebral ischemia (DCI), and that alternative disease processes such as global ischemia, surrounding inflammation and cortical spreading depolarization may be more closely associated.^{26,27} Regardless of which specific phenomenon is responsible for DCI, sympathetic regulation of cerebral vasculature remains an important topic and potential therapeutic option for improving patient outcomes.²⁸

A newly emerging disease process that is relevant to our study is reversible cerebral vasoconstriction syndrome (RCVS). The term RCVS was coined by Calabrese et al in 2007²⁹ to encompass various cerebral vasoconstriction syndromes described since the 1970s.³⁰ RCVS is thought to be more frequent than previously predicted and has been associated with cerebral ischemia, edema, stroke and even non-aneurysmal subarachnoid hemorrhage.^{31,32,33,34,35} Recent studies have shown that the pathophysiologic mechanism of RCVS may be due to sympathetic overactivity.^{13,36,37,38,39} The findings in our study support this notion, as sympathetic activation clearly resulted in reversible cerebral vasoconstriction in a large mammal model. In this sense, our findings suggest that SCG blockade, through pharmacologic or other means, may be an effective treatment for patients suffering from RCVS in addition to cerebral vasospasm.

Limitations of our study include the small sample size. However, given the striking and obvious changes in vessel caliber seen with SCG stimulation, we were able to demonstrate statistical significance with this sample size. Our study may have been underpowered to detect more subtle changes in vessel diameters for other vessels, including PCA, pMCA and ICA. Additionally, we were unable to accurately determine changes in contrast flow in MCA and PCA vessels using the Syngo iFlow system as mentioned above. Further studies with higher magnification may have been used to better detect such changes in these smaller vessels. However, the generally small size of the cerebral vessels and the thickness of the swine cranium may limit proper visualization to detect these changes even with more magnified DSA imaging.

Conclusion

Our study demonstrates that sympathetic activation through SCG stimulation can induce significant vasoconstriction of intracranial vessels and reduction of blood flow in a large mammal swine model. In addition, SCG blockade is able to mitigate this effect and prevent this vasoconstriction. Sympathetic mediation through SCG inhibition is a potential promising therapeutic intervention for diseases involving pathologic cerebral vasoconstriction.

List of Abbreviations:

| | |
|-------------|---|
| DSA | Digital Subtraction Angiography |
| SCG | Superior Cervical Ganglion |
| PACS | Picture Archiving and Communication System |
| APA | Ascending Pharyngeal Artery |
| ACA | Anterior Cerebral Artery (ACA) |
| aMCA | Anterior Middle Cerebral Artery |
| pMCA | Posterior Middle Cerebral Artery |
| ICA | Internal Carotid Artery |
| PCA | Posterior Cerebral Artery |
| MCA | Middle Cerebral Artery |
| ROI | Region Of Interest |
| RCVS | Reversible Cerebral Vasoconstriction Syndrome |

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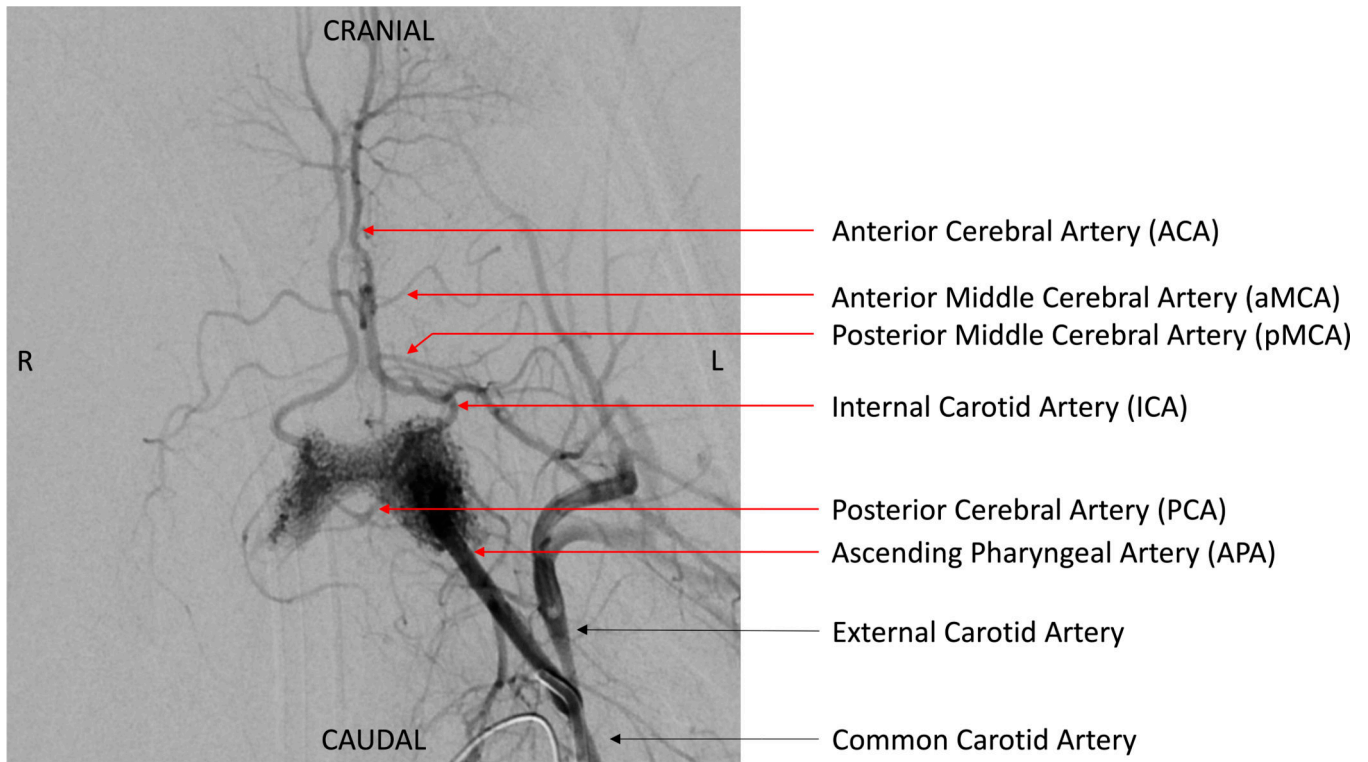


Figure 1: Representative Anterior-Posterior (AP) view of swine cerebral angiogram from the left ascending pharyngeal artery.

Red arrows: location of vessel diameter measurement. Black arrows: anatomic references. (ACA: anterior cerebral artery. APA: ascending pharyngeal artery. ICA: internal carotid artery. MCA: middle cerebral artery. PCA: posterior cerebral artery)

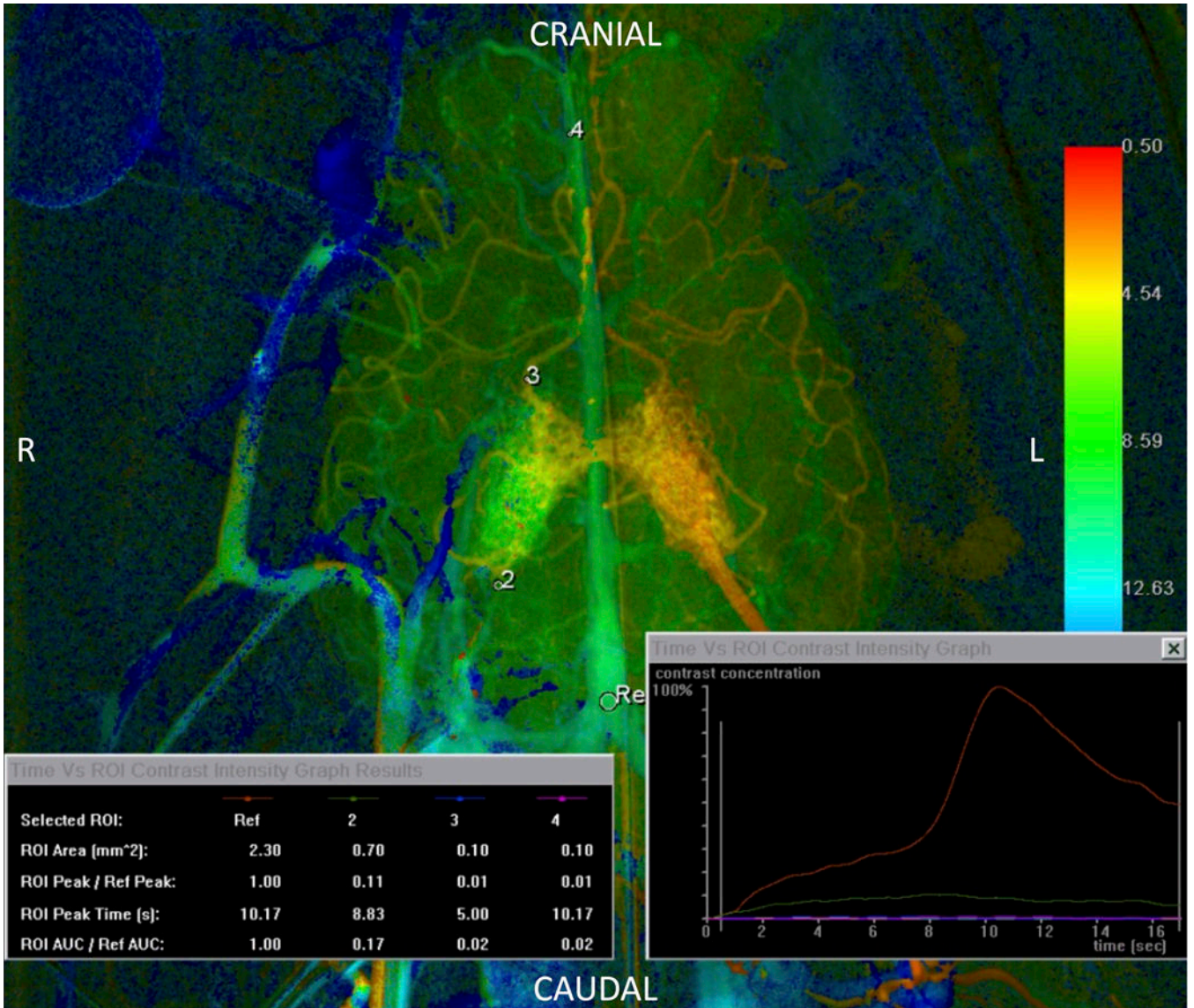


Figure 2: Representative Contrast Flow Measurements on Syngo iFlow of AP view of Swine Cerebral Angiogram.

Colorimetric map of maximum contrast detection at different times in a right sided contrast injection during right SCG stimulation. Representative ROI placements and analysis of area under the curve of at each ROI as a ratio of reference point. Red indicates early time of maximum contrast detection; blue indicates late time of maximum contrast detection. *ROI*: Region of interest. *AUC*: Area under curve.

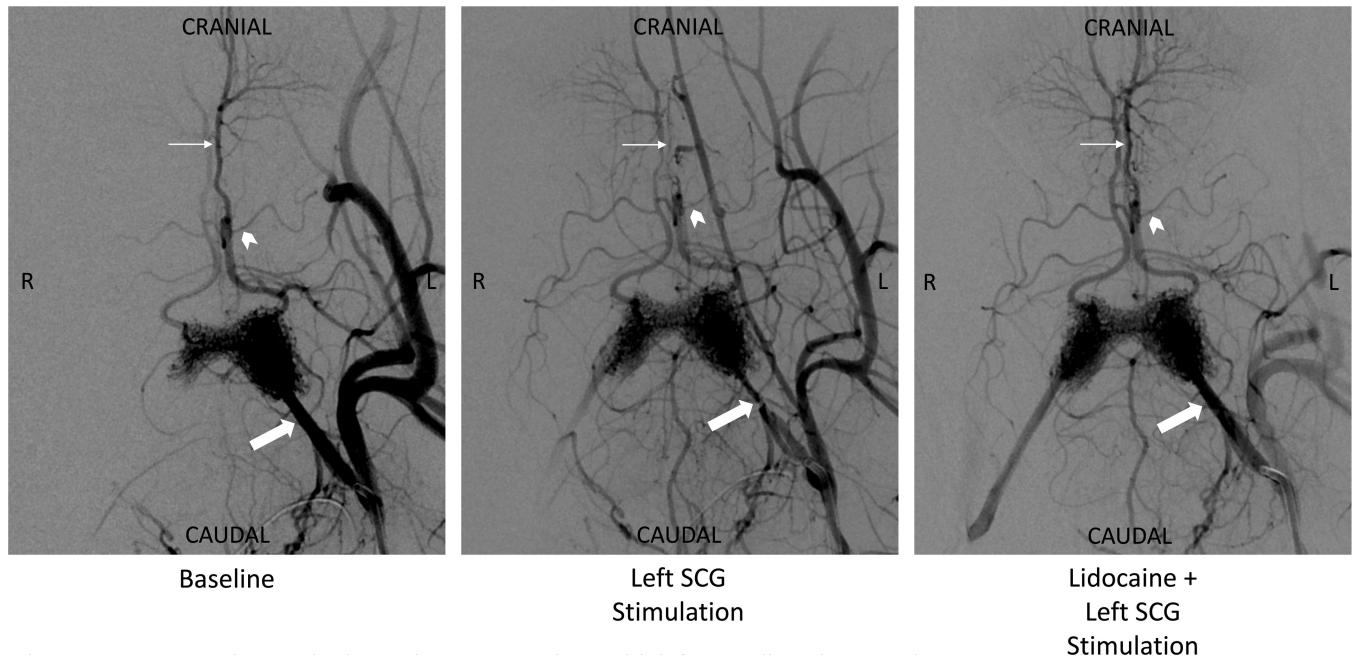


Figure 3: Representative cerebral DSA images (AP View) with left ascending pharyngeal artery contrast injection.

Baseline (left). Left SCG stimulation (middle). Prior lidocaine administration with left SCG stimulation (right). Small arrow (ACA), large arrow (APA), arrow head (aMCA) indicates arteries that showed significant changes in vessel diameter during SCG stimulation.

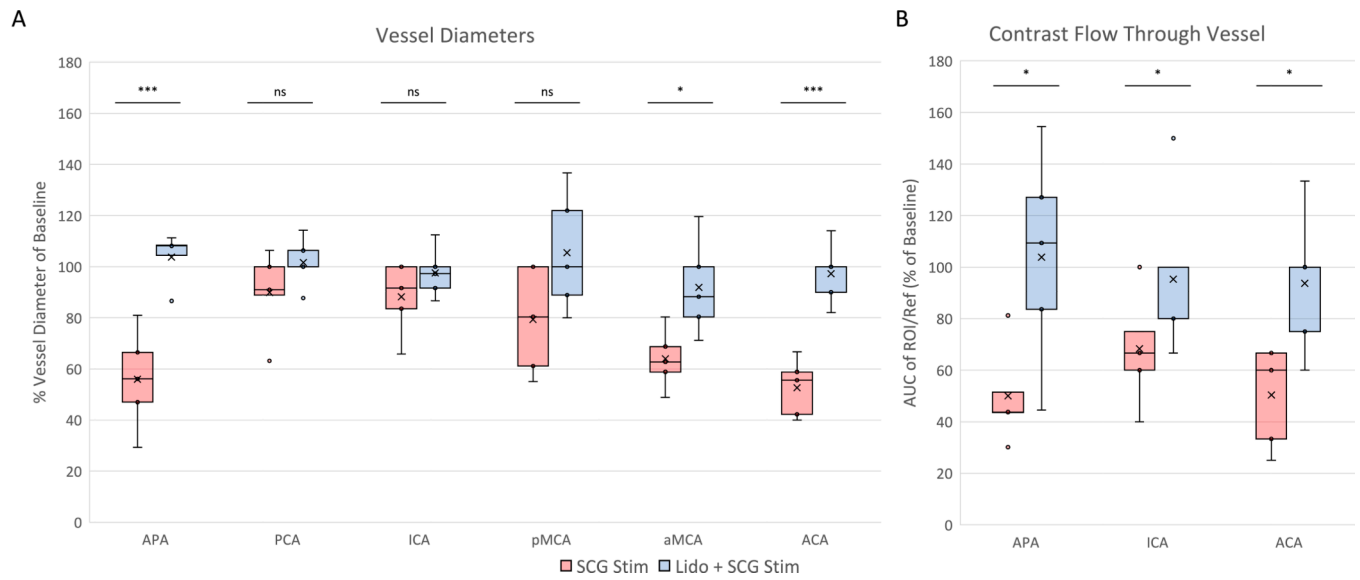


Figure 4: Box and Whisker plots of Vessel Diameter and Contrast Flow through Intracranial Arteries.

(A): Vessel diameters plotted as a percent of baseline (no SCG stimulation) vessel diameters.

(B): Contrast flow through vessels in relation to the flow through torcula, compared to baseline. Box indicates first to third quartile of data points. Whiskers indicate data set range within 1.5 times interquartile range from the box. Line within box indicates median. "X" within box indicates mean. Red (solid): SCG stimulation; Blue (solid): SCG stimulation with prior 2% lidocaine administration. (*: $p < 0.05$; ***: $p < 0.001$)