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Endovascular Transmural Access to Carotid Artery Perivascular Tissues: Safety Assessment of a Novel Technique

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Abstract

Background—Recent advancement in endovascular devices have allowed access and targeting of perivascular tissues of the peripheral circulation. The perivascular tissues of the cervical and cranial circulations have many important structures of clinical significance, yet the feasibility and safety of such approach has not been demonstrated. We evaluate the safety of a novel endovascular transmural approach to target the perivascular tissues of the common carotid artery in swine.

Methods—A Micro-Infusion Device was positioned in the carotid arteries of 3 Yorkshire pigs (6 carotid arteries total), and each carotid artery was punctured ten times in the same location to gain access to the perivascular tissues. Digital subtraction angiography (DSA) was used to evaluate for vessel injury or contrast extravasation. Magnetic resonance imaging and angiography (MRI and MRA) was used to evaluate for evidence of cerebral ischemia or vessel injury. Post-mortem tissue analysis was performed to assess for extravascular hematoma and intravascular dissection.

Results—None of the tested carotid arteries demonstrated evidence of vessel injury (dissection or perforation) or intravascular thrombosis. MRI performed post repeated puncture was negative for neck hematoma and brain ischemia. Post-mortem tissue analysis of the carotid arteries showed mild adventitial staining with blood, but without associated hematoma and without vessel dissection.

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Contributorship Statement

Wi Jin Kim, Hasitha Milan Samarage, Anthony C. Wang, Jeremiah Johnson and Geoffrey P. Colby had substantial contributions to the concept and design of the work and the interpretation of the data for the work. Wi Jin Kim, Hasitha Milan Samarage, David Zarrin, Keshav Goel, Kambiz Nael and Geoffrey P. Colby had substantial contributions to the acquisition, analysis and interpretation of the data for the work. All authors were significantly involved in drafting and revising the work. All authors reviewed and approved the final version of the work and agree to be accountable or aspects of the work.

Conflicts of Interest: None

Conclusion—Repeated puncture of the carotid artery to gain access to the perivascular tissues using a novel endovascular transmural approach is safe in a swine model. This represents a novel approach to various tissues in close proximity to the cervical and cranial vasculature.

Introduction

In recent years, there has been a significant expansion of novel endovascular devices and techniques to access non-vascular tissues and pathologies. With respect to the nervous system, innovative endovascular devices have been introduced to influence tissues or spaces outside the vessel. Oxley and colleagues have introduced the Stentrode, a stent-electrode recording array, to measure brain recordings from a cortical vein in sheep in 2016[1] and from the superior sagittal sinus in humans.[2] Heilman and colleagues have described an endovascular transdural cerebrospinal fluid (CSF) shunt as a potential new method of CSF diversion to the venous system for communicating hydrocephalus in 2019.[3]

In the peripheral vasculature, endovascular approaches for drug delivery to peri-vascular tissues have been reported. This includes targeting vessel adventitia for the treatment of peripheral arterial disease,[4,5] and perivascular renal artery denervation for refractory hypertension.[6]

The cervical and cranial spaces offer unique therapeutic targets given the high density of anatomic structures that control important body functions. However, direct access to these targets is often limited by invasive surgical techniques. The cervical and cranial vasculature provide pathways to achieve close proximity to both neural and non-neural structures, many of which reside in deep areas that are otherwise difficult to access. We sought to investigate the safety of a novel endovascular transmural technique in the cervical carotid artery in swine.

Methods

Animal Care

Ethical 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 (ARC-2020-193-AM-005). All procedures were conducted in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care International guidelines.

Anesthesia and Digital Subtraction Angiography (DSA)

Three Yorkshire pigs (Sus scrofa) (6 carotid arteries) of either gender between 40-50kg were used. Animals were pre-sedated with intramuscular Telazol and transitioned to inhaled isoflurane for intubation and intravenous (IV) access. Diagnostic angiography procedures were performed using a Siemens Artis Zeego C-Arm. DSA was performed in a standardized fashion as previously described[7] using a Medrad Mark V ProVis injector to deliver 6mL of Omnipaque (iohexol) 300 through the guide catheter (Infinity), 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).

Endovascular Transmural Approach to Peri-vascular Space

Through a femoral arterial sheath, an Infinity guide catheter (Stryker Neurovascular) was introduced and advanced over a select catheter and glidewire. The right or left common carotid artery was catheterized under roadmap guidance and the Infinity catheter tip was positioned in the mid common carotid artery proximal to the branch point of the ascending pharyngeal artery. A 3-6mm size Micro-Infusion Device (Figure 1; Devices provided by Mercator MedSystems, San Leandro, CA) was inserted into the Infinity catheter and navigated over a microwire into the common carotid artery. Radio-opaque markers at the distal and proximal ends of the balloon were used to position the balloon near the ascending pharyngeal artery branch point. The radio-opaque triangle markers were used to direct the needle in the postero-medial direction. The same position was used for each carotid to keep consistent between multiple punctures, vessels, and animals (Figure 2F). Under fluoroscopy, the balloon was inflated to fill the width of the vessel, causing the microneedle to puncture the vessel wall (Figures 2B-G). The balloon was inflated for 60 seconds, and this process was repeated for a total of ten times on each common carotid artery. DSA imaging was obtained after each vessel puncture to assess for evidence of vessel injury (contrast extravasation or dissection) or intraluminal thrombus. Three minutes were allowed to pass prior to the next inflation and vessel puncture. This procedure was performed bilaterally in each animal, in a total of 3 animals (6 sides).

Magnetic Resonance Imaging and Magnetic Resonance Angiography

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) images were obtained before the endovascular procedure to establish a baseline. The same MR imaging was performed after ten endovascular transmural carotid punctures bilaterally. Imaging was obtained approximately two to three hours after repeated punctures of the right carotid artery and approximately one hour after repeated punctures of the left carotid artery. MRI and MRA were obtained using Siemens 3T Magnetom Prisma Fit (Munich, Germany). Fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) of the brain were obtained to evaluate for intracranial hemorrhage or ischemic stroke. Time-of-flight and contrast-enhanced magnetic resonance angiography (MRA) of the neck vessels were obtained. Additionally, high-resolution vessel wall imaging (HR-VWI) of the neck vessels were obtained before and after contrast using a 3D fat-saturated T1 SPACE (Sampling Perfection with Application optimized Contrast using different flip angle Evolution) sequence. A total of 30-40 mL of gadolinium contrast (Gadobutrol, Bayer Healthcare Pharmaceuticals Inc) was injected intravenously depending on the weight of the animal.

All MR images were reviewed by an experienced clinical neuroradiologist (author KN), who was blinded to which images were collected before or after the endovascular procedure. Brain MRI images were evaluated for ischemic stroke or hemorrhage. MRA images were evaluated for presence of filling defects (to suggest thrombus or emboli in carotid or distal cerebral arteries), luminal irregularity, dissection flap or luminal stenosis to suggest arterial

injury. HR-VWI was used to assess the arterial wall for hemorrhage, wall thickening or enhancement.

Post-Mortem Dissection

After euthanasia of the animal in accordance with the institution's protocol, bilateral neck dissections were performed to visually evaluate the common carotid artery and perivascular tissues. Photographs of the common carotid artery at the location of the vessel puncture site were obtained once the carotid sheath was opened and the carotid artery was exposed. The segment of carotid artery corresponding to the puncture site (on each side and in each animal) was harvested for a more detailed examination. The vessels were opened in a longitudinal fashion to evaluate for any visible damage to the vessel intima.

Results

Repeated use of the Micro-Infusion Device in the swine common carotid did not result in evidence of vessel wall damage as evaluated by DSA in all animals. There was no evidence of contrast extravasation, dissection, flow limiting vasospasm, or thrombus formation (local or distal) in any of the carotid arteries after ten sequential carotid punctures. In 3 sides, there was presence of mild local, non-flow limiting vasospasm, most prominent after the tenth inflation (Figure 2H), which resolved without any intervention or treatment after approximately five minutes (Figures 2I).

MR imaging performed after bilateral Micro-Infusion Device procedures (ten punctures to bilateral carotid arteries) did not reveal any ischemic stroke or intracranial hemorrhage (Figures 3A, 3B, 3C). There was also no evidence of thrombus, significant luminal stenosis, vessel contour irregularity, or dissection flap on post-procedural MRA studies (Figures 3D, 3E, 3F). Subtle wall thickening (Figures 3H, 3J) and mild wall enhancement (Figures 3 I-K) was observed in three of six punctured carotid arteries, in post-procedural carotid wall compared to pre-procedure baseline.

Post-mortem neck dissection revealed intact common carotid artery without evidence of neck hematoma on all 6 sides. Mild blood staining of the adventitia where the carotid was repeatedly punctured was observed in all samples as seen in Figure 4E. There was no appreciable damage, disruption, or blood staining of the structures surrounding the carotid. Inspection of the carotid intima did not show any evidence of dissection flap (Figure 4F, 4G). There were no clear appreciable holes/openings on the endoluminal surface, apart from expected lumens of normal arterial branches.

For one experiment, systemic hypertension was pharmacologically induced with phenylephrine after bilateral repeated vessel punctures (ten punctures on each side) in an attempt to stress the vessel wall after repeated punctures. Systolic blood pressure of 170mmHg was obtained before performing diagnostic DSA. These studies also did not show any evidence of contrast extravasation or vessel damage.

In a separate experiment, a surgical neck dissection was performed to expose the common carotid artery prior to puncture with the endovascular Micro-Infusion Device. Under direct

visualization, endovascular transmural injection of saline was performed through the carotid artery and into the surrounding tissues (Figure 4A-D). No bleeding or adventitial staining was observed after deflation of the balloon and restoration of normal carotid antegrade blood flow (Figure 4D).

Discussion

Carotid puncture is not new to the field of endovascular intervention. Historically, percutaneous direct carotid puncture was utilized frequently for purposes of cervical and cerebral angiography.[8] This technique lost favor as endovascular catheter technology improved and paved the way for safer catheter navigation from femoral and radial approaches.[9] In modern times, direct percutaneous carotid puncture is used infrequently, but it can be used for neurointervention[9] and cardiac intervention[10] when alternate routes are unavailable or deemed higher risk. The risks of percutaneous transcartoid intervention have been studied in small case series[11,12,13], but they are generally not well known given the limited experience in the medical literature. Hybrid surgical-endovascular transcarotid procedures, the most well-known being Transcarotid Artery Revascularization (TCAR), has growing popularity and been demonstrated to be reasonably safe.[14] Direct carotid puncture has also been described for successful endovascular treatment of cerebral aneurysms.[15]

While large injuries to the carotid artery can obviously have devastating consequences, smaller punctures are often inconsequential. Oliver and colleagues reported inadvertent arterial puncture (presumed carotid puncture) occurs in up to 9.3% of attempted internal jugular central venous line placements using an 18-gauge introducer needle.[16] No patients had neurological or vascular complications within 24 hours of this event. Prior studies have also reported 0 to 23% incidence of inadvertent arterial puncture during internal jugular central venous line placement as well [17,18,19] However, these studies are limited in scope as they did not include detailed assessments of vascular or cerebral injury.

In our study, the carotid artery was punctured in a reverse fashion, from inside to outside the vessel, in contrast to what is widely reported in the literature. This is a novel technical approach to the carotid perivascular tissues, and is the first such report in the medical literature. The Micro-Infusion Device utilized in this study has a 34-gauge microneedle, which is significantly smaller than historical needles for carotid angiography or other modern access systems for transcarotid intervention. Given the small size of the microneedle, we hypothesized that micropuncture could be performed repeatedly and without significant negative consequence to the vessel wall.

Swine was the chosen animal model for this study because of its wide use for cardiovascular studies. Swine arterial morphology is one of the most similar to that of humans among numerous non-primate animal models.[20] However, swine arteries are smaller and more fragile than human vessels,[21] and this allowed for robust testing of the safety of microneedle puncture. Ten punctures in the same region for each vessel were selected for the experimental design as this number seemed much higher (more “aggressive”) than what would presumably be performed in a relevant clinical scenario. The puncture site location in this study (common carotid artery just proximal to the origin of the ascending pharyngeal

artery) was chosen based on other studies that demonstrated the sympathetic chain and superior cervical ganglion being positioned nearby.[8,22]

Vessel injury, flow limiting vasospasm, or neck hematoma was not observed utilizing various imaging modalities and direct post-mortem tissue analysis. While our post-mortem evaluation did show adventitial blood staining in the approximate location of the microneedle punctures, this was not considered clinically significant given the lack of associated hematoma. Real time visualization of the puncture and micro-infusion did not demonstrate any bleeding from the puncture site (Figure 4) despite an active circulatory system.

While there was no evidence of clinically significant vessel wall injury, MRI did demonstrate increased enhancement of the common carotid artery vessel wall at the location of the vessel puncture and localized fat stranding (Figure 3J, 3K). This enhancement likely represents the perivascular/adventitial blood staining on the common carotid artery that was observed in the post-mortem dissection (Figure 4E). The localized fat straining around the vessel may be due to surrounding local inflammatory changes, either from the needle puncture or the concurrent balloon inflation. We speculate that these changes are due to the aggressive nature of our testing, and such changes may be much milder or absent with a single or smaller number of punctures. Similar descriptions of vessel wall enhancement have been described in the clinical setting after mechanical thrombectomy from an ischemic stroke.[23,24,25] These studies suggest that unlike significant complications of mechanical thrombectomy, such as vessel dissections and thrombus, isolated vessel wall enhancement does not have associated morbidities and insignificant clinical implication at this time.[16, 21, 26] The lack of significant injury was confirmed by our post-mortem dissection, which did not reveal any evidence of vessel injury or associated neck hematoma.

Endovascular approach to the perivascular tissue using the Micro-Infusion Device in the peripheral vasculature is under investigation for various clinical applications. Dexamethasone Therapy Examining Reduction of Inflammation after Thrombus Removal to Yield Benefit in DVT (DEXTERITY) is a clinical trial whereby steroids are delivered to the perivascular tissue of the deep veins of the lower extremity with a goal of limiting inflammation and re-thrombosis after deep vein thrombosis recanalization.[27] Perivascular drug delivery is also under investigation in the Temsirolimus Adventitial Delivery to Improve Angiographic Outcomes Below the Knee (TANGO) trial, in which temsirolimus is delivered to the adventitia of popliteal or tibial arteries after revascularization with the goal of limiting intimal hyperplasia and inflammation.[28] To our knowledge, our study represents the first exploration of these techniques in the cervical/cranial space.

Our findings demonstrate safety of a novel endovascular transmural approach to the cervical/cranial perivascular spaces, and open the possibility of using this approach for clinical indications. We envision many clinical applications for this approach, one of which is to target structures in close proximity to the carotid artery for drug delivery. Potential targets include components of the autonomic nervous system, such as the sympathetic chain and the vagus nerve. Several studies have shown the utility of blocking sympathetic innervation to the cerebrovasculature to augment cerebral blood flow and perfusion in animal models

of cerebral vasospasm.[8,24] Hence, the endovascular transmural technique could be used to locally inhibit the sympathetic chain as a potential treatment for vasospasm. This is one active area of our research.

Limitations to our study include the obvious anatomic differences between swine and humans. Specifically, while the rete mirabile is thought to primarily have a role in temperature regulation, it may also help to maintain cerebral blood flow and act as a filter for any small emboli.[29] This may provide protection against ischemic insults in the swine that may not be present in humans. Thus, the lack of stroke or ischemic insults seen in our study on MRI might not be truly indicative of expected results in humans. Another limitation is that the swine in our study were not pre-treated with systemic heparinization or antiplatelet therapy prior to testing, although heparinized saline was administered as continuous flush through all catheters. We chose this experimental design to closely mimic a human patient with subarachnoid hemorrhage. As such, our results may underestimate the rate of extravascular hemorrhagic complications were systemic anticoagulation and/or antiplatelet therapy utilized. Finally, our model does not account for carotid artery pathologies (for example, atherosclerosis or fibromuscular dysplasia) that may be present in humans. These co-morbidities introduce variables that may affect safety. While our study includes a small sample size, we believed that our experimental design, showing lack of clinical complications despite aggressive testing of the Micro-Infusion Device, was sufficient and more meaningful than showing the results of conservative use of the Micro-Infusion Device in a larger sample size.

Conclusion

Repeated endovascular transmural micropuncture of the carotid artery in swine is safe and does not lead to complications of vessel injury, intravascular thrombus, extravascular hematoma, or stroke. The results of our study open the possible clinical use of a novel minimally invasive endovascular technique to target perivascular structures around the carotid artery and other cervical and cranial vasculature in humans.

Acknowledgments

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Key Message

What is already known on this topic

Development of new endovascular devices and techniques have pushed the boundaries of endovascular utility for treatment of various diseases and opened new minimally invasive clinical applications.

What this study adds

This study demonstrates the safety of a new endovascular transmural approach to target the cervical and cerebral perivascular structures in a swine model.

How this study might affect research, practice or policy

The safety of this minimally invasive endovascular technique opens new possibilities for the delivery of targeted therapeutics to important perivascular structures of the cervical and cranial spaces.

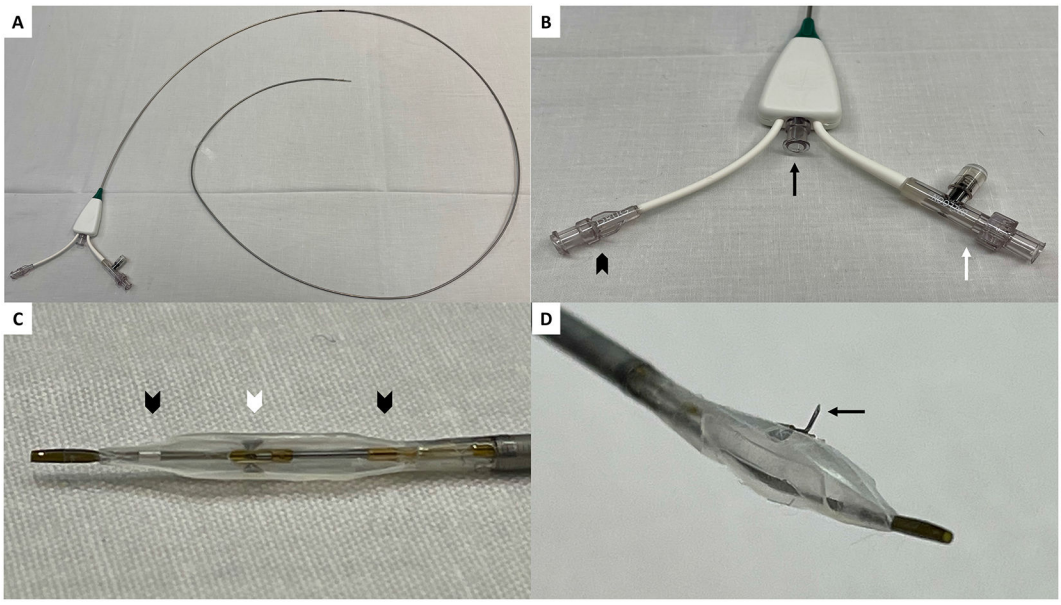

Figure 1: Micro-Infusion Device

(A) 3-6mm diameter Micro-Infusion Device (Mercator MedSystems, San Leandro, CA). (B) Operator end of the Micro-Infusion Device. Black arrow = wire and flush port. Black arrowhead = micro-infusion port. White arrow = balloon port with pressure pop-off valve. (C) Distal end of the device with balloon deflated. Black arrowheads = radio-opaque markers at the proximal and distal ends of the balloon. White arrowhead = location of the micro-needle with markers for orientation. (D) The micro-needle is visible and engaged with the balloon inflated. Black arrow = microneedle.

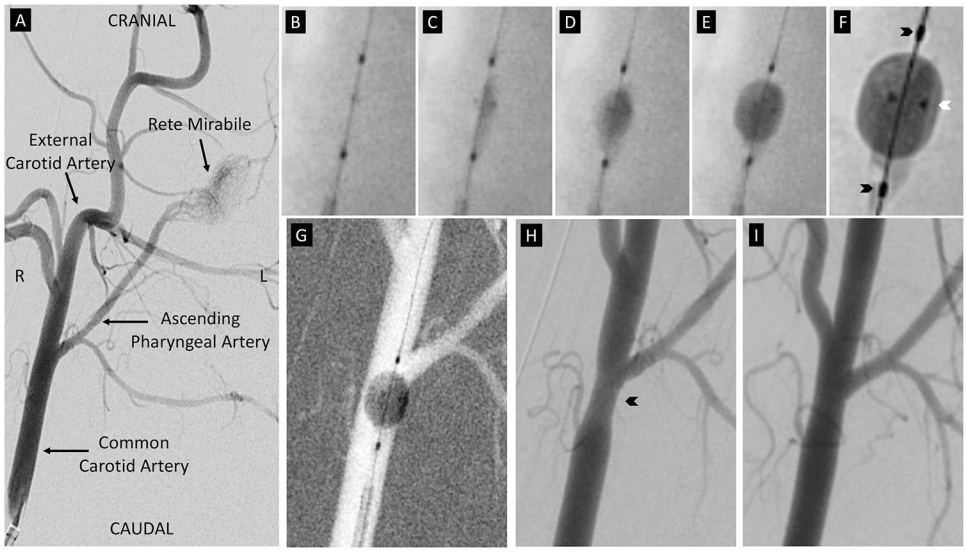

Figure 2: Representative intra-procedure images of Micro-Infusion Device positioning and endovascular transmural puncture.

(A) Baseline right common carotid artery DSA in swine demonstrating neck vasculature in the proximity of ascending pharyngeal artery branch point, which marks the approximate location of repeated common carotid artery puncture. (B-E) Gradual inflation of the Micro-Infusion Device balloon. (F) Fully inflated balloon of the Micro-Infusion Device. Black arrowheads = distal and proximal radio-opaque indicators. White arrowhead = location of needle with orientation indicators. (G) Image of inflated Micro-Infusion Device with roadmap background. (H) DSA immediately after the deflation and removal of the Micro-Infusion Device. Arrowhead shows mild, non-flow limiting, local vasospasm at the prior location of the Micro-Infusion Device balloon. (I) DSA five minutes after the deflation and removal of Micro-Infusion Device, showing resolution of vasospasm seen in (H).

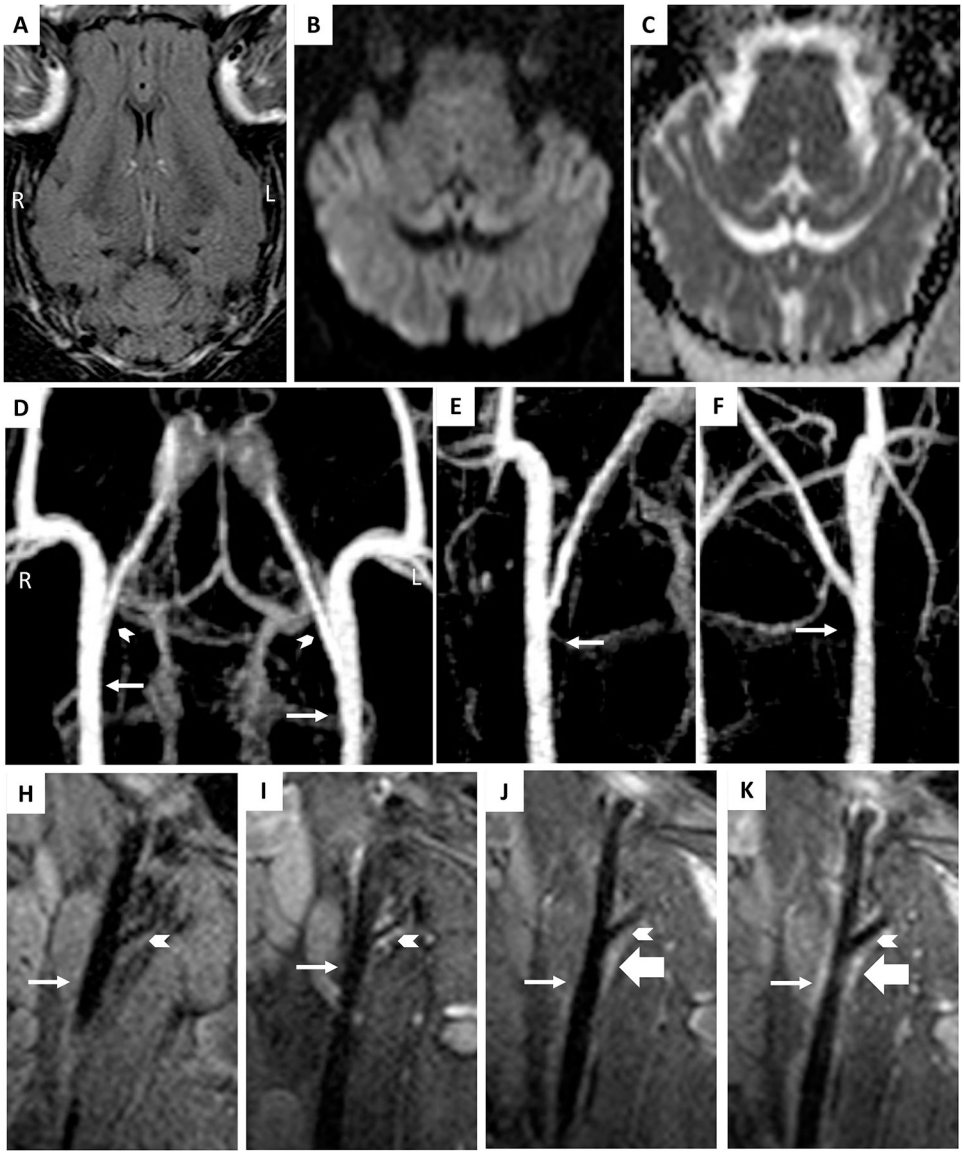

Figure 3: Representative Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) to assess for stroke, neck hematoma, and vessel injury.

(A) Normal appearing Fluid attenuated inversion recovery (FLAIR) axial view of the swine brain after ten punctures of the common carotid artery using the Micro-Infusion Device bilaterally. (B,C) Normal appearing Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) coronal view of the swine brain after ten punctures of the common carotid artery using the Micro-Infusion Device bilaterally. (D) Baseline MRA neck (AP view) showing bilateral carotid arteries (arrow = intended location of vessel puncture) and the ascending pharyngeal artery branches (arrowhead = ascending pharyngeal artery branch). (E-F) Post ten times puncture intervention MRA neck AP view rotated to better show postero-medial aspect of (E) right common carotid and (F) left common carotid. Arrows show approximate location of vessel punctures. (H,I) Baseline High-resolution vessel wall imaging (HR-VWI) without (H) and with (I) contrast. White arrow = common carotid artery. White arrowhead = location of ascending pharyngeal artery. (J,K) Post ten

times puncture intervention HR-VWI without (J) and with (K) contrast. Arrow = common carotid artery. Arrowhead = location of ascending pharyngeal artery. Large arrows = approximate location of vessel puncture with very mild local wall contrast enhancement.

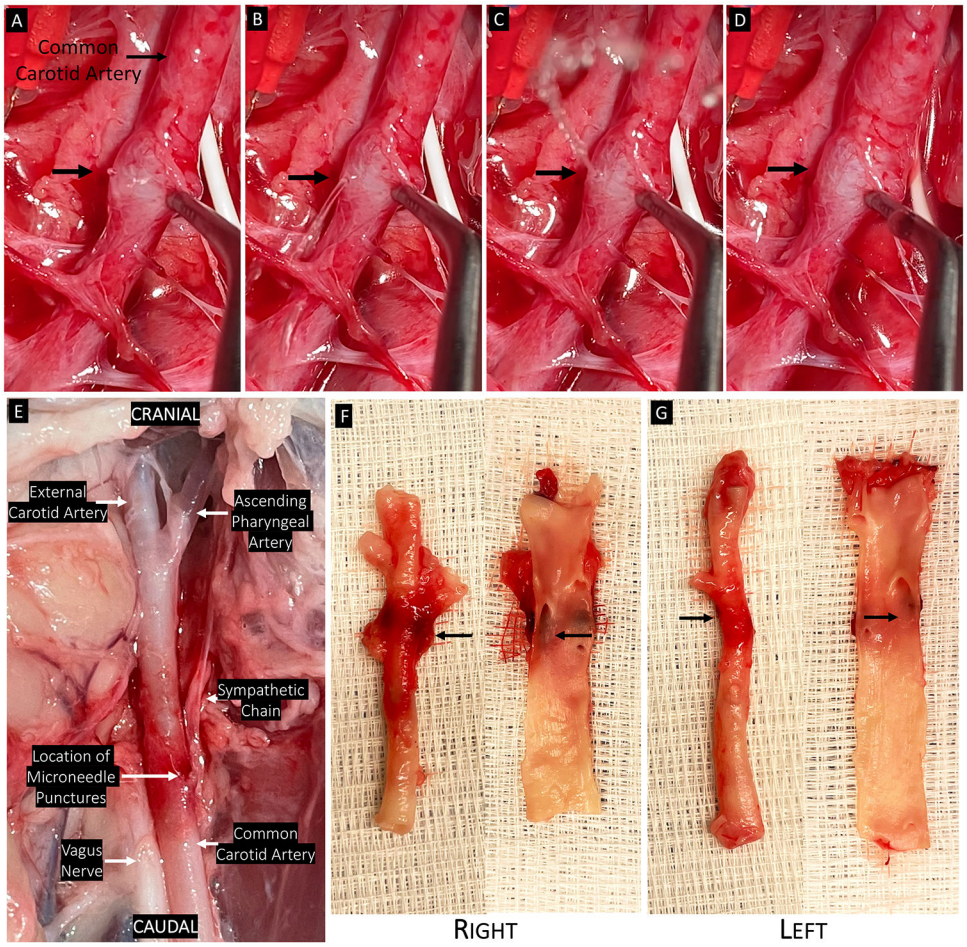

Figure 4: Endovascular Transmural Carotid Micropuncture with Saline Microinfusion and Representative Post-Procedure Carotid Analysis.

Following neck dissection to surgically expose the common carotid artery, endovascular access to the common carotid artery was obtained. The Micro-Infusion Device was then positioned and transmural micropuncture performed. (A) Beginning of transmural saline injection through Micro-Infusion Device micro-needle. (B-C) Transmural saline injection from transmural microneedle. The puncture site and saline microinfusion is marked by arrows. (D) Post injection after balloon deflated and intravascular flow restored, shows absence of active bleeding or adventitial blood staining at the site of vessel puncture (black arrow). (E) Right swine neck dissection showing right common carotid artery, ascending pharyngeal artery branch and adventitial staining at the location of microneedle punctures. Harvested segments of (F) right and (G) left common carotid arteries following repeated micropunctures. Adventitial blood staining (shown in black arrows) is visible on the intact vessels (left image) and opened vessels (right image). No dissection or other gross intimal injury is visible on the opened vessels.