Anatomic Variations in the Giraffe Conferring Protection from Intracranial Hemorrhage and Orthostatic Hypotension

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Abstract

Research Question:

Can our understanding of human cerebral hypertensive and hypotensive disorders be improved by utilizing the giraffe as a model to study vascular adaptations?

Background/Significance/Rationale:

Humans can suffer hemorrhagic strokes at blood pressures over 220/110, causing widespread death and disability throughout the world. In other populations, when blood pressures drop to 90/60 through dysregulation of the autonomic nervous system, patients may experience palpitations, dizziness, and syncope. These extreme changes in blood pressure can result in extreme morbidity and limitations in quality of life. The giraffe, on the other hand, can sustain these extreme variations in blood pressure throughout the day via changes in body position, yet dysautonomia or strokes are not commonly seen in these animals. This investigation aims to publish the first brain MRI of the giraffe on an infant and adult giraffe and will study the gross anatomic structures. The eventual goal of this project is to translate many of the cerebral and cardiac adaptions of the giraffe into discovery of therapeutics and protective measures for strokes and dysautonomia states in humans.

Methods:

To investigate the unique cerebrovascular giraffe adaptations, we propose a comparative analysis of 1) the gross anatomic structures of the giraffe neck vasculature and 2) a brain MRI of both infant and adult giraffe. Via partnerships with zoos across the county, giraffe specimen was selected after death from natural causes. A post-mortem dissection was performed 30 minutes after time of death to identify anatomy. Two other giraffes, one infant and one adult, were imaged one week from time of death to obtain brain MRIs.

Results:

The post-mortem dissection revealed a non-collapsible common carotid artery that progressed into the external carotid artery, followed by bifurcation into the maxillary and lingual artery. An internal jugular vein was also present, which was collapsible in nature. The vertebral venous plexus was unable to be identified, though further efforts will be committed to identify the structures from fixed vertebral sections. A brain MRI without contrast from the infant and adult giraffe was significant for a unique carotid rete originating from the external carotid artery.

Conclusion:

The study confirms a non-collapsible common carotid artery and a collapsible internal jugular vein, like humans. The external carotid artery perfuses the brain via the maxillary artery. The brain MRI identified a net-like structure originating from the maxillary artery, called the carotid rete, that is unlike human anatomy. This structure likely reduces resistance to blood flow in the brain and normalizes the blood pressure compared to what has been documented near the aorta.

Research Question

Looking at a giraffe, one may wonder how a creature 14 feet in length is able to sustain perfusion to the brain while preventing edema in its limbs. The giraffe is often seen in two separate positions, with its neck bent down (as if to drink water) and upright (standing straight). With this change in confirmation comes significant deviations in its blood pressure. One might wonder, how does this animal tolerate such deviations in its blood pressure? What mechanisms are present to prevent the giraffe from experiencing an intercranial hemorrhage, something often seen in humans with significantly high blood pressure. We hope that with exploring these mechanisms, we can translate these adaptations to improve the characterization of human hypertensive and hypotensive disorders.

The giraffe heart and neck are separated by 1.7m. When the animal assumes a standing position, several challenges are apparent: 1) pumping blood up against gravity to maintain cerebral perfusion without venous pooling in the extremities and 2) avoiding positional orthostasis and the potential for intracranial hemorrhage. In this study, we will closely study the giraffe heart, vasculature, and the adaptations that prevent pathologies resulting from varying deviations in the blood pressure from positional changes. By using the giraffe as a novel model to study cerebral perfusion, the vertebral venous plexus, and neurovasculature adaptations, we will gain greater insight into the determinants of human cerebral hypertensive and hypotensive disorders.

To investigate the unique cerebrovascular giraffe adaptations, we propose a comparative analysis of 1) the gross anatomic structures of the giraffe neck vasculature and 2) a brain MRI of both infant and adult giraffe.

Introduction, Significance, and Rationale

Stroke is the second largest cause of death in the world and is one of the leading causes of disability [1]. As life expectancy increases worldwide, the prevalence of stroke is expected to increase as well. Intracerebral hemorrhage (ICH) is the second most common subtype of stroke, following ischemic stroke, and is accountable for nearly 10-20% of stroke incidences, [2] occurring in approximately 2 million people per year worldwide [3]. This hemorrhage is associated with a 30 day mortality rate between 32-50%, [4] while a 6 month functional independence is only present in 20% of the patients that survive the hemorrhage. [5] An ICH can occur following the rupture of a cerebral parenchyma vessel, often from complications of pre-existing lesions, like abnormal vasculature or malignancies. More commonly, though, ICHs are idiopathic, and are termed primary ICH. It is known that the disease presents with a strong correlation with age, with individuals aged 85 and over having a 10-fold increase in annual risk of ICH compared to those who are between ages 45-54 years [6]. Furthermore, multifactorial risk factors, such as hypertension, smoking, alcohol use, diabetes, cerebral amyloid angiopathy, anticoagulant use, as well as genetic risk factors are being used to increase the predictability and diagnostic value of ICH [7]. Medical and surgical clinical trials have failed to demonstrate definitive therapies that improve functional outcomes after an ICH. Current medical management primarily involves hemostatic therapy, with additional correction of the coagulopathy if the ICH is anti-coagulant related, blood pressure management, and neuroprotective therapy [8]. Surgical interventions are focused on hematoma evacuation to reduce mass effect and neurotoxicity from red blood cell lysis and delay in thrombin release [8]. Still, the trauma of surgery leaves the patient vulnerable to rebleeding and can lead to worsened outcomes. Despite many efforts, a proven physiological mechanism and an effective, specific treatment of ICH is lacking.

Similarly, dysautonomia, as seen in orthostatic intolerance, is another disease state that remains vastly unexplored. Postural orthostatic tachycardia syndrome (POTS) is the most common form of orthostatic intolerance [9]. The prevalence of POTS is unknown, but a study estimated a minimum of 170 cases per 100,000 people in the general population. Since the diagnosis is not immediate, these estimates are unreliable, therefore, the prevalence is expected to be higher. POTS impacts the younger population more frequently, with the minority of patients above age 40 [10]. The disease state has a higher incidence in females as compared to males [11]. The disease onset might be linked to trauma, surgery, infection, or stress. Its symptoms (palpitations, dizziness, possible syncope) often present when standing and are worsened with modest exertion, heat, and food ingestions. Due to the heterogenous nature of this condition, the pathophysiological mechanism is unknown, but has been proposed to be associated with alterations in neural control, humoral factors, vascular properties, intravascular volume, and physical deconditioning [12]. The current treatment regimen is multi-faceted and focused on managing cardiovascular autonomic dysfunction via raising the blood pressure and reducing peripheral pooling [12]. With this treatment, about 60% of the patients are able to return to their level of function before their symptoms onset within 5 years of diagnosis [13]. More specific treatment with definitive benefits can result once the mechanism of the disease is established.

The giraffe's cerebral vascular anatomy is similar, in many ways, to the human anatomy. It has a common carotid artery that supplies the brain and the head, respectively, and a cerebral venous system that drains into the jugular vein and vertebral venous plexus (VVP) [14].

Many have questioned the mechanism through which the giraffe maintains cerebral perfusion pressure (CPP). CPP is defined as the difference between the Mean Arterial Pressure (MAP) and Intracranial Pressure (ICP). The answer may lie within the vertebral venous plexus (VVP), a non-collapsible vein attached to the cervical vertebrae that plays a role in maintaining cerebral perfusion pressure (CPP) by creating negative pressure. Other hypotheses have considered the involvement of the external jugular vein and the carotid artery. The external jugular vein is unlikely to produce negative venous pressure as it is collapsible, and therefore, has shown to play no part in maintaining CPP. The carotid artery, though non-collapsible, does not maintain CPP through subatmospheric (or negative) pressure at its highest point, shown by previous models [15]. Furthermore, because its diameter is wider than the VVP (1.2cm vs 3.2mm, respectively), it is hypothesized that it's resistance is lower compared to the VVP, further suggesting that the VVP plays a larger role in maintaining CPP. Another hypothesis suggested a vascular siphon perfusing the brain, a mechanism proposed in sauropod dinosaurs with long necks [16]. This mechanism would theoretically reduce the work of the heart by neutralizing the force of gravity. However, there have been wide objections that such negative pressure would cause the collapse of cerebral veins. This theory has further been debunked in inverted U-shaped models depicting giraffe circulation. It may be possible, though, that a surrounding column of connective tissue and viscous flow pressure could prevent the collapse of the intracranial vessels, as predicted by Badeer and Hicks (1996) for sauropods [17]. It has been found that the origin of the arterial and venous blood pressure is very complex and not dictated by one single mechanism. Further investigation needs to be performed in this area.

Another proposed mechanism of maintaining giraffe CPP is the presence of increased blood pressure accompanied by cardiac hypertrophy [18]. Although the giraffe heart was not found to be larger than expected, significant left ventricular (LVW) and interventricular (IVW) wall hypertrophy were found [19]. This process was found to be gradual as the giraffe matured from infanthood to adulthood, correlating the wall thickness linearly to the growth of the neck length.

This is important, as neck length and blood pressure are correlated [20, 21], suggesting that the hypertrophied ventricle normalizes wall tension [22].

Research Materials and Methods

To investigate the unique cerebrovascular anatomic adaptations of the giraffe, we propose a comparative analysis of 1) the gross anatomic structures of the giraffe neck vasculature and 2) a brain MRI of both infant and adult giraffe. Via partnerships with zoos across the county, giraffe specimens were enrolled in this study after death from natural causes. A post-mortem dissection was performed 30 minutes after time of death to identify anatomic structures within the proximal neck at the c5-c6 level. Two other giraffes, one infant and one adult, were imaged one week from time of death to obtain brain MRIs. A 3-tesla magnet was used to perform both brain MRIs with sagittal and axial views.

Results

Gross Anatomy:

The dissection was performed at the level of c5-c6 by an anatomist to identify the common carotid artery, internal jugular vein, and other major vasculature that may originate from these structures. The internal jugular vein was found to run lateral to the esophagus and noted to be collapsible (Figure 1). The common carotid artery was identified as a non-collapsible structure that lacked an internal carotid branch (Figure 2). The common carotid artery proceeds to become the external carotid artery before bifurcating into the maxillary artery and lingual artery (Figure 3). The lingual artery continued beyond visualization into the jaw anteriorly, while the maxillary artery gave off an occipital artery branch and continued superiorly. An internal carotid artery was not visualized. Due to the complexity of the vertebral bodies, the vertebral venous plexus was not able to be identified and isolated.

Figure 1: Internal jugular vein was found to be collapsible lateral to the esophagus

Figure 2: The common carotid artery, a non-collapsible structure, transitions into the external carotid artery

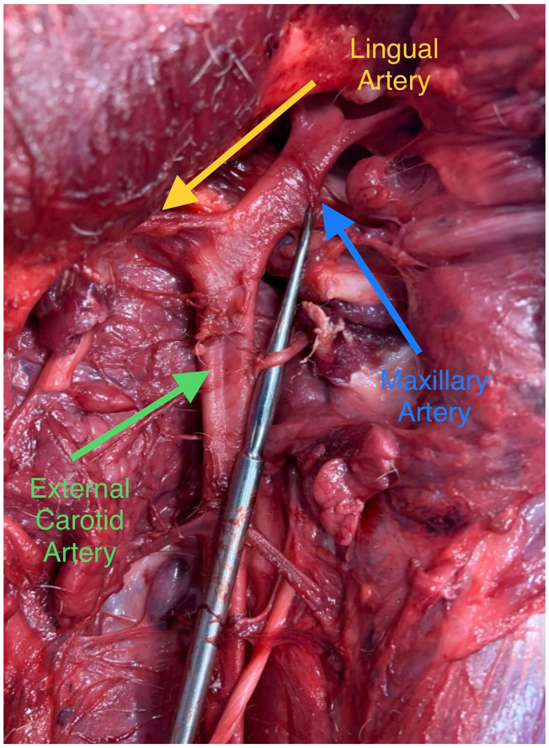

Figure 3: The external carotid artery gives rise to the lingual, maxillary, and occipital artery

Brain MRI

Two brain MRIs were performed, one on an infant giraffe and one on an adult giraffe. Imaging was performed within one week of the specimen's expiration. Arteries, specifically the common carotid, external carotid, maxillary artery, occipital artery, and lingual artery, identified in the gross dissection, were verified by the MRIs (Figure 4). The MRI was significant for a net-like structure, called the carotid rete, which originates from the maxillary artery in both the infant and adult giraffe and is found in the cavernous sinus (Figure 5). Additionally, another rete was found near the maxillary artery, termed arteria anastamotica. The internal carotid was not present in either MRI. Due the lack of brain perfusion, many structures were difficult to identify on brain MRI, including the vertebral venous plexus.

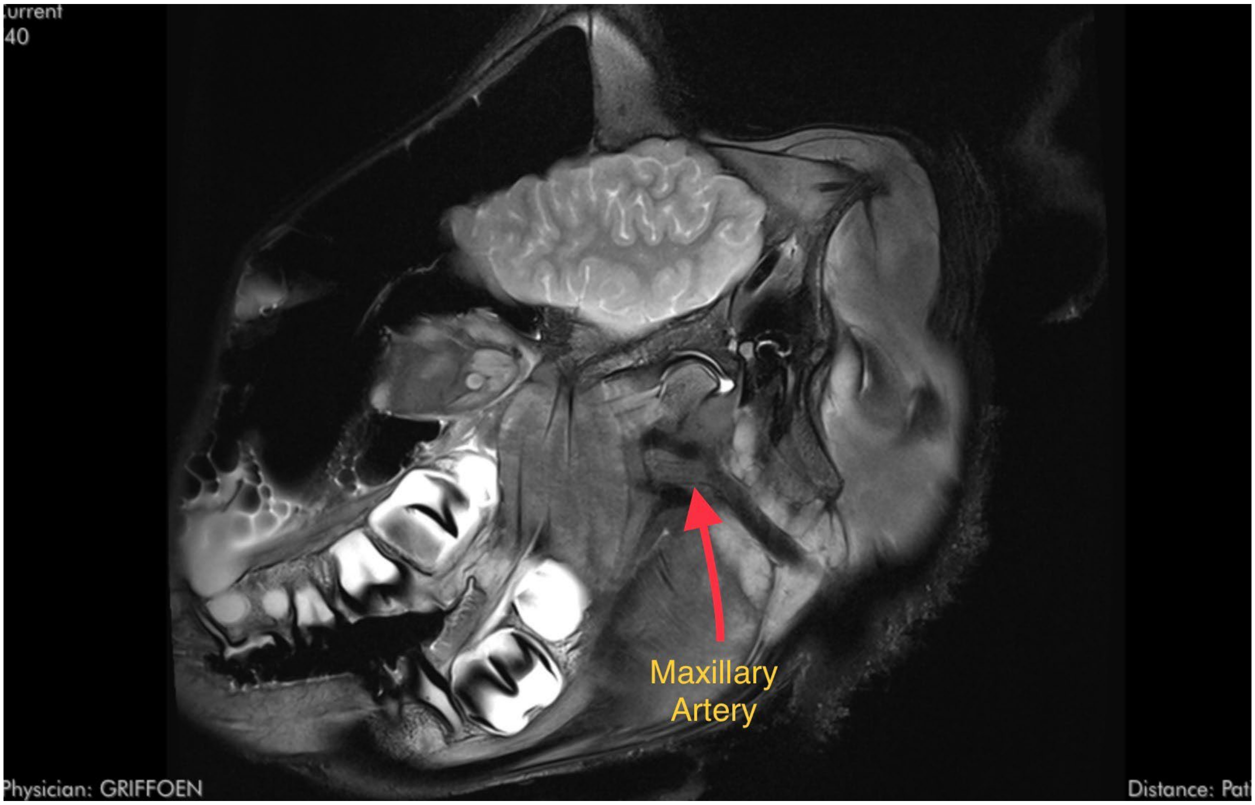

Figure 4: The maxillary artery originates from gives rise to the carotid rete, lowering the intracerebral blood pressure

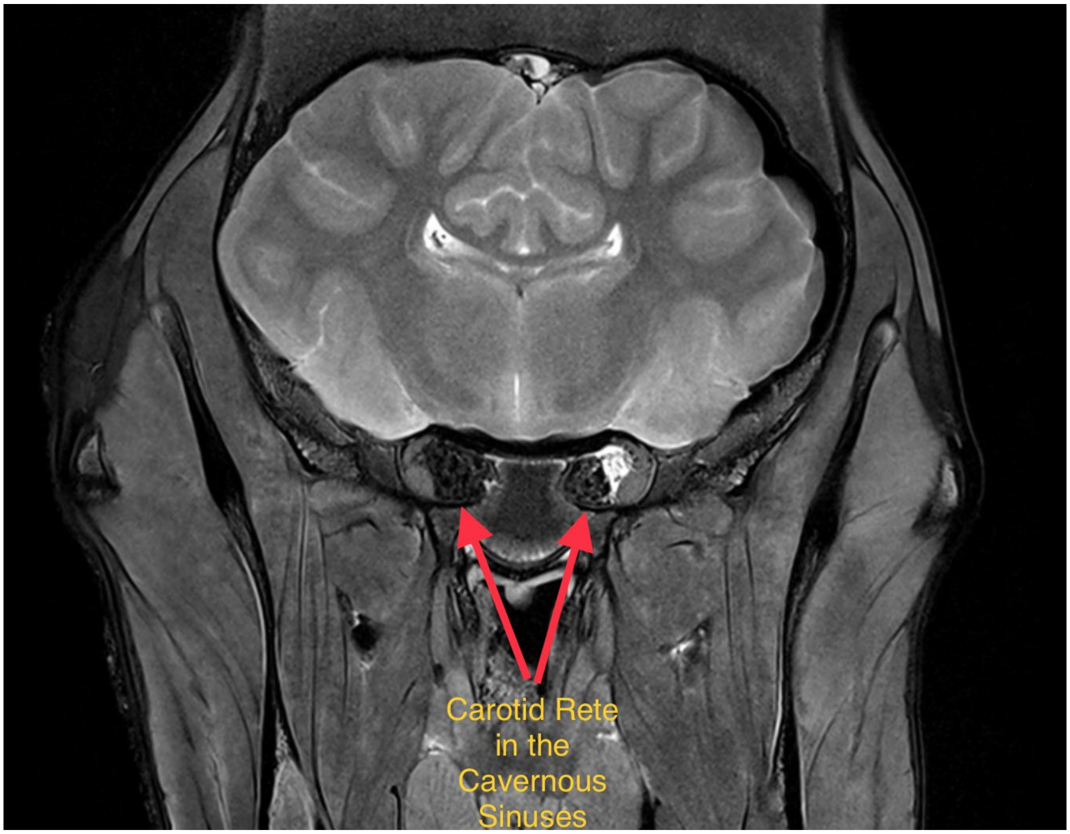

Figure 5: The carotid rete, a net-like structure that helps normalize cerebral pressure, is found in the cavernous sinuses originates from the maxillary artery

Discussion and Innovation

The gross dissection of the giraffe confirmed a non-collapsible common carotid artery from which originated the external carotid artery. Of note, an internal carotid artery was not identified in the gross dissection like that found in humans. The external carotid artery gave rise to the occipital artery, lingual artery, and the maxillary artery, which was confirmed by the giraffe brain MRI. The maxillary artery proceeds to form the carotid rete, a net like structure that reduces blood flow resistance leading to our hypothesized lower cerebral blood pressure (Figure 6). Furthermore, another rete, termed arteria anastamotica, was found near the maxillary artery, that likely also contributes to the reduction in resistance to blood flow.

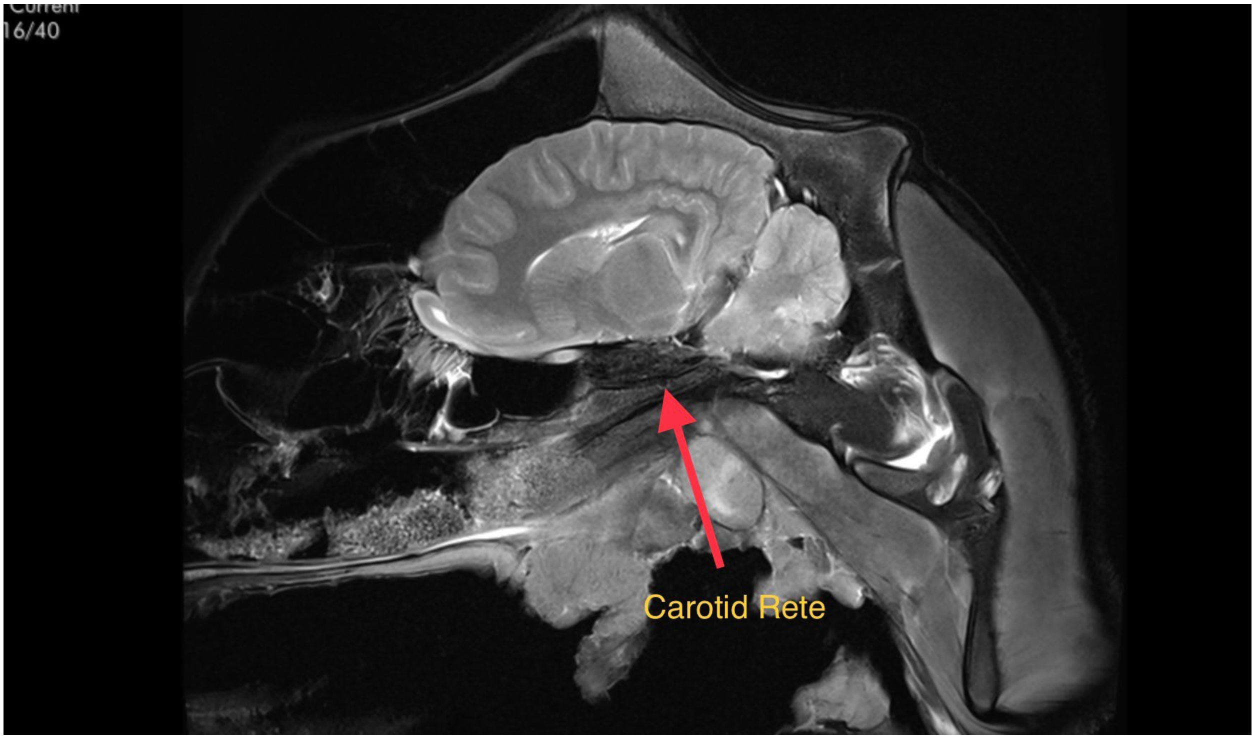

Figure 6: Sagittal view of the giraffe brain MRI showing the carotid rete

Compared to humans, where the common carotid bifurcates into the internal and external carotid arteries, the giraffe common carotid transitions to become the external carotid before bifurcating into the maxillary artery and lingual artery. A common variation is trifurcation of the external carotid artery to also include the occipital artery [23]. In humans, the internal carotid artery supplies blood to the brain through its major branches-- the ophthalmic artery, posterior communicating artery, and anterior choroidal artery. The external carotid artery, in contrast, is somewhat larger than the internal carotid artery and supplies blood to structures within the neck, extracranial head, and face. The major branches of the external carotid artery include the superior thyroid, ascending pharyngeal, lingual, facial, occipital, posterior auricular, superficial temporal, and maxillary artery [24].

By comparison, non-fetal giraffes do not have an internal carotid artery like other artiodactyls. The internal carotid artery, originating from the common carotid, is present in utero; however, this branch is obliterated prior to parturition [23]. Hence, the common carotid transitions into the external carotid artery, which supplies blood to the brain, neck, extracranial head, and face. The external carotid gives off three major branches in the giraffe—the lingual, maxillary, and occipital artery. The maxillary artery provides most of the brain's blood supply. It splits into a meshwork of arteries, called the carotid rete, that is housed within the cavernous venous sinus. This network reduces resistance to blood flow, normalizing the blood pressure. Hence, blood pressures near the aorta of 300/120 are likely not the blood pressure in the brain due to diffuse splitting of the maxillary artery. This is best explained by principles of physics. Circuits in parallel reduce resistance. This model is applied to the giraffe brain anatomy, such that the "parallel circuits" or the carotid rete significantly reduces resistance leading to a likely normal blood pressure. This finding highlights an adaptation that allows the giraffe to evade extreme hypertension, preventing strokes in this mammal. It also explains, that because humans do not have this carotid variation, strokes are experienced at a higher rate due to extreme elevations in blood pressure.

Another adaptation that may add to continuous cerebral perfusion evading orthostasis is the non-collapsible vertebral venous plexus. Due to intricacies of this structure, the VVP was unable to be isolated within the gross dissection and brain MRIs and further exploration needs to be performed to identify its tissue structure. The current hypothesized mechanism states that the VVP acts as a non-collapsible suction that holds negative pressure, generating potential for continuous cerebral perfusion.

Limitations of the study included the inability to acquire a brain MRI of a living giraffe. The data would show how the vasculature perfuses different regions of the brain. Unfortunately, acquiring such imaging poses unique challenges of its own. First, an MRI machine is not suitable for the size of even an infant giraffe. Second, an MRI requires the subject matter to remain still for extended periods of time. This poses challenges for animals as sedation techniques must be utilized to acquire the desired position and sedation may falsely lower blood pressure. Lastly, transportation barriers exist to move a giraffe from the zoo to an advanced imaging facility with an MRI machine. Moving a specimen of that size requires many resources, especially in a sedated state. Other limitations of this study include the power of the investigations. Due to sample constraints, the sample of this study was limited to three giraffes, though the investigation hopes to increase its sample size in the coming years.

Future Directions

Given the identification of the carotid rete, future work needs to be performed to explore the areas of the brain that it perfuses. Sedation of the specimen may be used to conduct the imaging, however, other modalities such as engineering perfusion models deceased giraffes may be of benefit too. Much can be learned from a perfusion study, especially with direct comparisons to human brain MRI scans. With the use of artificial intelligence, the imaging may be superimposed to recognize other structural differences that allows the giraffe to evade hypertension.

The next step of this project will also help address vascular adaptations against hypotension in addition to the hypothesized VVP mechanism. When raising its neck from a head-down position, one may expect that the giraffe will experience some degree of hypotension leading to syncope. In a study released in 2021, wild-type mice were compared to mutated mice with FGFR1 gene found in the giraffe [25]. The study showed that mutated mice, compared to wild-type mice experienced less adverse cardiac events. The study's next steps are to test the proximal and distal segments of the internal carotid artery for expression of FGFR. Higher expression of FGFR in the proximal segment common carotid artery compared to the distal segment are expected as quicker vasoconstriction and vasorelaxation may be needed based on neck positioning to make the vasculature adaptable to extremes in blood pressure.

Furthermore, genomic studies in the giraffe are largely unexplored. Much like the FGFR component of the study, it is plausible to hypothesize that genes within the vasculature of the giraffe allow for quick blood pressure adaptations based on positional changes. Further work exploring such key components, possibly in the HOX and NOTCH pathways can provide insight into how the vascular giraffe physiology is similar or different from humans. This project hopes to use immunochemistry staining to detect fibroblast growth factor receptors (FGFR) expression in the proximal and distal common carotid artery.

Conclusions

Dissection/Anatomy: The rigid structure of the common carotid artery confirms the non-collapsible nature of the vessel that transports blood from the heart to the brain. The non-rigid structure of the internal jugular confirms its collapsibility. However, confirmation of the tissue integrity of the vertebral venous plexus, a venous non-collapsible structure, was not identified due to anatomic complexity. Further work will be performed to isolate this structure.

Brain MRI: The infant and adult giraffe brain MRI found a novel carotid rete that reduced blood flow resistance in the brain and allows the giraffe to likely have normal blood pressure in the brain compared to the extreme blood pressure noted near the aorta. This adaptation showcases how giraffe populations can evade hemorrhagic strokes secondary to severe hypertension.

FGFR staining: The next portion of the study hypothesizes that higher expression of FGFR is present in the proximal segment of the common carotid artery as quicker vasoconstriction and vasorelaxation may be needed based on neck positioning to maintain stable blood pressure.

Compliance

Due to extensive work with deceased giraffe specimen, this project required an IACUC that was reviewed and approved by TCU and remains valid for 3 years. The project also helped partner institutions construct their IACUC to enroll into this project.

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