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The Circle of Willis Predicts the Antihypertensive Effects of Carotid Artery Stenting: 12 Month Follow Up

Stroke is one of the leading causes of death and morbidity in the United States. Various modifiable risk factors have been identified, which elevate the risk of stroke. Two such risk factors include hypertension and carotid artery stenosis.[1] Moreover, carotid artery atherosclerosis, even when asymptomatic or when subclinical stenosis is present, has been shown to increase the risk of future stroke.[2] As such, proper treatment of carotid artery stenosis and hypertension plays a critical role in the future reduction of stroke incidence.

Hypertension and carotid artery stenosis are not independent of each other. Multiple studies have shown a relationship between interventions for carotid artery stenosis, carotid endarterectomy (CEA) and carotid artery stenting (CAS), and hypertension. However, the data on this relationship is less than consistent. McKevitt et al. showed a reduction in patients' blood pressures immediately after CEA and CAS, but the blood pressure effects where not seen for patients treated with endovascular therapy, such as CAS, at 1 or 6 months.[3] Other studies have shown that the effects on blood pressure after CAS are long lasting and may lessen the requirement for antihypertensive medications.[4-6] Chung et al., reported that while both CEA and CAS have blood pressure lowering effects, the efficacy on lowering blood pressure may favor CAS.[7]

Despite previous published works, which are not consistent, the pathophysiologic mechanism behind blood pressure response in carotid artery stenosis patients has not been fully investigated. One such thought is that the integrity of the circle of Willis (COW) and an individual patient's reliance on leptomeningeal collateral vessels influences a patient's blood pressure response after CAS. Based on simple fluid dynamic principles, the use of the smaller caliber, higher resistance leptomeningeal vessels required by patients without a complete COW would necessitate a higher pre-intervention mean arterial pressure (MAP) to maintain cerebral perfusion. In 2017, the University of California San Diego Department of Neurosurgery published their pilot study investigating this matter. This pilot study found that there was a significant decrease in MAP or a decreased requirement for antihypertensive medications in patients who had an incomplete COW and thus, relied more heavily on the higher-pressure pial collateral vessels to maintain cerebral circulation. However, this study was limited to only a 3-month follow up period.[8]

The antihypertensive effects of carotid artery stenting (CAS) have been variable among previously published works.[3-7, 9]However, management and control of hypertension remains a clinical guideline for the reduction of stroke risk. The variability in blood pressure changes in studies has not been adequately evaluated, except for immediate perioperative changes secondary to temporary stimulation of carotid artery baroreceptors leading to transient hypotension.[9, 10] More interestingly, the longevity of blood pressure reduction after carotid stenting has been minimally evaluated without investigation into the physiologic mechanism for this change in blood pressure.

Methods

As outlined by this group's previous pilot study, this study will follow a similar design. This retrospective cohort study received IRB approval and met all institutional regulations without the potential for harm to patients, as there was no intervention performed based on this study. Patients were selected if they had a

carotid artery stent placed between November 2013 and April 2017, allowing for a one year follow-up period to fall within the study period, November 2013 to April 2018, for symptomatic carotid artery stenosis or as indicated by current guidelines.[8] Patients that did not meet the above-mentioned criteria or were younger than 18 years of age were excluded from this study. Eighty-eight patients met the above inclusion criteria.

The 88 patients where separated into two cohorts, those missing an anterior communicating artery (ACoA) and/or the ipsilateral posterior communicating artery (PCoA) and those with an intact COW. This was based on pretreatment vascular imaging or intraoperative cerebral angiograms. Vascular imaging was initially reviewed by a group of neurosurgery residents and medical students at UCSD. The available imaging was then reexamined by the principle author to verify that patients were correctly classified, resulting in reclassification of two patients. Twenty-six of the 88 patients (29.5%) were missing either an ACoA or ipsilateral PCoA and thus, were considered part of the pial-collateral dependent cohort. The remaining 62 patients (70.5%) were not missing either arteries being examined and thus, were part of the complete collateral circulation cohort. The patients' blood pressures were then examined at 4 time points, immediately pre-intervention, 3 months post stenting, 6 months post stenting, and 12 months post stenting, to determine their average mean arterial pressures (MAP) and to assess for changes in their hypertensive medications, which could alter their MAPs.

In the pial-collateral dependent cohort, 10/26 patients (38.5%) were lost to follow up at the 3-month time point, 16/26 patients (61.5%) were lost at the 6-month time point, and 17/26 patients (65.4%) were lost at the 12-month time point. Patients who were lost to follow up in the earlier time point but returned to follow up in the later time points were still included in the respective time group.

In the complete collateral group, 10/62 patients (16.1%), 32/62 patients (51.6%), and 30/62 patients (48.4%) were lost to follow up at the 3-month, 6-month, and 12-month time point, respectively (Fig. 1). Similar to the pial-collateral dependent cohort, patients who were lost to follow up at the earlier time points were included in their respective time group if they followed up at later time points.

The patients' average MAPs were then determined at each time point. The outcome measure was a meaningful drop in MAP, defined as a drop of 10 mm Hg from the patient's MAP immediately before intervention or as the cessation/decrease in at least one antihypertensive medication. For further discussion regarding why 10 mm Hg MAP difference was used, see this group's pilot study.[8]

After accounting for patients lost to follow up, 47 patients had been previously seen by primary or subspecialty care allowing them to serve as their own controls and thus, this study was a nonrandomized, within-subject design. This allowed patients to serve as their own controls for personal and lifestyle factors not otherwise affected by CAS.[8]

Statistical Analysis

Statistical analysis was performed using R software version 3.5.3 (https://www.r-project.org). Due to the low number of patients in each group, a Fisher Exact Test was used to compare each set of nominal data. Multivariate logistic regression was used to assess for possible confounding variables (presence of

an incomplete COW, hypertension, hyperlipidemia, diabetes mellitus, gender, history of TIA or stroke, age, and increases in blood pressure medication). For all statistical tests, a $p < 0.05$ was considered statistically significant.

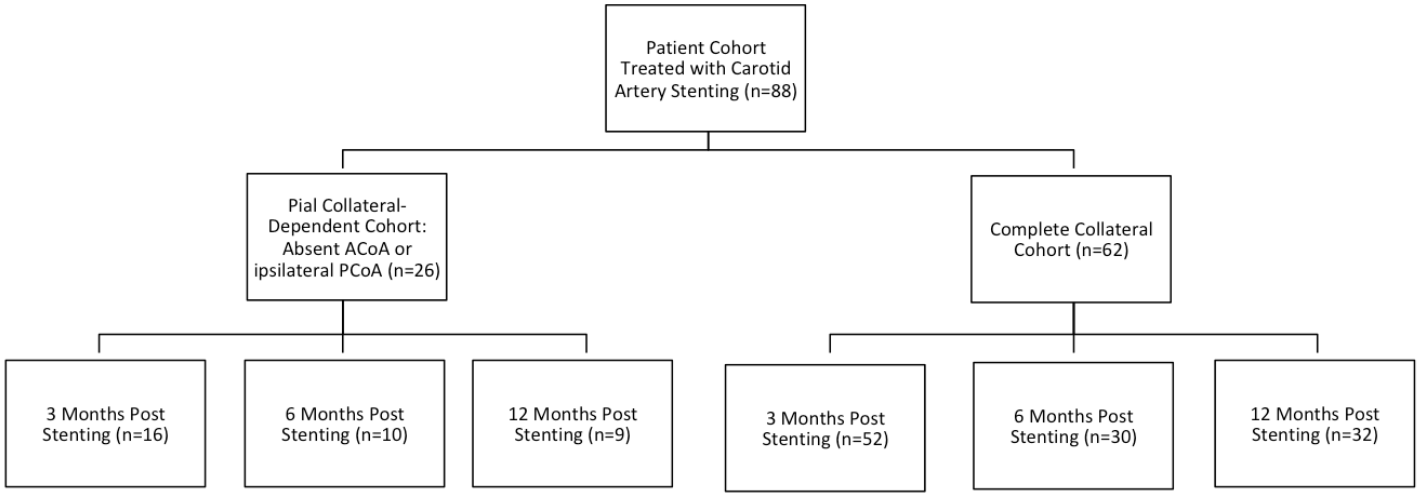

Figure 1. Organizational schema of patients (pts). The difference in the number of patients between the cohorts and follow up periods is due to lack of patient follow up.

Results

Across cohorts, there were 70.6% male patients, 48.5% of patients were over the age of 70, and 63.2% had a history of a TIA or stroke. The majority of patients had previous diagnoses of comorbid conditions such as HTN (75%), HLD (55.9%), and DM (63.2%).

As found in the previous pilot study, patients in the pial-collateral dependent circulation cohort were more likely to have a meaningful drop in blood pressure than those in the collateral circulation cohort 3 months after carotid stenting. Fourteen of the 16 patients (87.5%) in the pial collateral cohort had this outcome, while only 22/52 (42.3%) patients in the complete collateral cohort had the primary outcome ($p<0.0016$ by analysis with Fisher Exact Test). Multivariable logistic regression at 3 months revealed that the pial collateral-dependent cohort remained an independent predictor of a meaningful drop in BP.

At 6 months post stenting, 6/10 (60%) of patients in the pial collateral dependent cohort had a meaningful drop in BP, while 10/30 (33.3%) of patients in the complete collateral cohort had the outcome. At 12 months post stenting 5/9 (55.6%) of patients in the pial collateral dependent cohort had a meaningful drop in BP, while 13/32 (40.6%) in the complete collateral cohort did. In the more longitudinal follow up periods, 6 and 12 months, Fisher Exact Tests did not result in significant differences between the cohorts ($p=0.1529$, $p=0.417$, respectively).

Discussion

While various studies have shown a link between carotid atherosclerosis and hypertension, the pathophysiology in this association is unknown. [3-5, 7] As with this current study, the previous pilot study by this same group found that patients dependent on the small caliber pial collaterals to maintain

adequate cerebral perfusion were more likely to demonstrate a meaningful drop in their MAP at 3 months when compared to patients relying on a complete COW. This group previously hypothesized that as dictated by Poiseuille's law of fluid dynamics, patients reliant on their smaller caliber, higher resistance pial collaterals would require a larger MAP to maintain constant cerebral blood flow.

While the effect on blood pressure after carotid stenting or endarterectomy caused by carotid sinus baroreceptors stimulation is well documented,[9, 10] it seemed that this anatomical difference in patients might have explained the effect on blood pressure. Although there was a significant difference between the patients reliant on their pial collaterals and those reliant on a complete COW 3 months after stenting ($p<0.0016$), this relationship was not seen in more longitudinal follow up periods. At 6 and 12 months post stenting, there was no significant difference between the two cohorts ($p=0.1529$, $p=0.417$, respectively).

Although there is a transient effect on blood pressure in patients that rely on their pial collaterals for cerebral perfusion, there is no significant longitudinal effect. Despite the clear limitations in this retrospective, low powered study, it seems as if the effect that carotid artery stenting has on blood pressure is transient. Moreover, while the concept that lower caliber vessels have inherently more resistance, as stated by Poiseuille's Law, there are many assumptions in this law that would be violated in the human cardiovascular system.

Firstly, Poiseuille's Law assumes that flow in a pipe is laminar with constant velocity. This is clearly not completely true in human vessels, especially in older patients with atherosclerotic arterial disease. Since the heart beats periodically, there is also fluid acceleration. Furthermore, blood vessels are not of a constant diameter, dilating and constricting in response to stimuli. While Poiseuille's Law could be used as a model for the human vessels, it would not be fully accurate.

Moreover, the mechanical properties of pial collateral arterioles in patients with hypertension may react differently from those in patients without hypertension. Chan et al. found that the pial collateral vessels in mice with hypertension were more vasoconstricted than those in normotensive mice. This likely potentiates the effect of cerebral blood flow through the pial collaterals in aged and hypertensive mice, the populations that showed this vasoconstriction in the study. [11] As most of the patients in this study were hypertensive or older than 70 years of age, this could potentially explain why a higher MAP would be necessary to maintain cerebral perfusion. However, it is uncertain whether these vasoconstrictive properties lead to systemic hypertension or if the hypertension causes the constriction followed by worsening hypertension and whether CAS could break this potential cycle.

The hypothesis that patients reliant on their pial collaterals would have a longitudinal response in their blood pressure would best be tested with a significantly larger sample size. The sample size of this study is an evident limitation, with upwards of 60% of the original patient population lost to follow up. It would also be important to compare patients with and without systemic hypertension, which may prove difficult given the population that is most commonly affected by carotid artery stenosis.

Conclusion

This study finds that while there seems to be a sustained drop in blood pressure after carotid artery stenting that appears to be dependent on the anatomical differences in cerebral vasculature and is likely not related to carotid sinus effects, the longitudinal effect of stenting on blood pressure is uncertain and likely not related to anatomical variation. Based on this limited, retrospective study with a small sample size, carotid artery stenting would not likely have a longitudinal affect on patients' systemic hypertension. Further evaluation with a larger cohort and comparing hypertensive and normotensive patients to account for possible mechanical differences in the pial collaterals would be most prudent.

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