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Mind the Brain: Stroke Risk in Young Adults With Coarctation of the Aorta

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Before the advent of surgery to repair coarctation of the aorta (CoA), this diagnosis carried a rather grim prognosis. Many affected infants died in the first year of life. Of those surviving infancy, the life expectancy was greatly diminished. From 1956 to 1970 Maurice Campbell attempted to document the natural history of common congenital heart defects, including CoA.

Maurice Campbell attempted to document the natural history of common congenital heart defects, including CoA. Using necropsy reports and follow-up observations of patient cohorts, he estimated that "the median age of death for subjects with coarctation is 31 years, instead of 72.5 years as normally." He further estimated that 91.5% of patients with CoA would die by the age of 60 years.[1] Through pioneering efforts, care has advanced remarkably. Full-term infants diagnosed and surgically repaired in the first year of life have a 98% chance of being alive and well 5 years later.[2] A study of 254 survivors of CoA surgical repair between 1948 and 1976 found that 81% were alive ≥50 years after their surgery,[3] and the outlook in the modern medical era is even more encouraging.

As with many congenital heart defects, we are only just beginning to understand the phenotypic and genetic heterogeneity of this complex condition, and the developmental mechanisms are still being defined. Response to CoA therapy is also variable. Approximately 4% of patients with surgically repaired CoA, 5% of those status post–stent therapy, and 15% following balloon dilation develop aneurysms associated with the site of intervention.[4] Many reports detail the occurrence of hypertension after successful repair of aortic obstruction and how the risk increases with age. More recently, we also have learned that even patients with repaired CoA have a 10% risk of developing intracranial aneurysms and are at increased risk of stroke.[5] The article by Pickard et al in this issue of the *Journal of the American Heart Association* (*JAHA*) now informs us that ischemic and hemorrhagic strokes occur at a much earlier age than in the general population and are not solely related to persistent hypertension.[6]

Early Risk of Stroke in Patients With CoA

Stroke is among the 10 leading causes of death in all adult age groups, but the incidence of stroke increases dramatically with age.[7] Even more important is the substantial neurologic morbidity that frequently accompanies a stroke. This study found that stroke occurred at a significantly earlier age in individuals with a history of CoA. In fact, 75% of strokes occurred in those <64 years and, thus, in patients who are likely still active in the workforce. The striking findings about the age at which stroke occurs in this population raise several important questions that must be addressed to develop preventive strategies to reduce neurologic morbidity in this population.

The earlier onset of stroke in this population begs the question of cause. Presumably, hypertension would be a primary risk factor. Although hypertension was present within the majority of all patients with stroke, patients with coarctation may be hypertensive at earlier ages and for longer periods of time. Alternatively, arteriopathies attributable to atherosclerosis or other underlying vascular abnormalities may play a role in stroke pathogenesis. Typically, strokes are classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria: small vessel, large vessel, cardioembolism, other, or unknown.[8] Future studies classifying ischemic stroke according to TOAST criteria will be helpful in determining which mechanisms are most responsible in patients with CoA.

The authors also found an increased proportion of subarachnoid hemorrhage (SAH) among patients with stroke with CoA. The median age of 23 years at which SAH occurred

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was even younger than that at which ischemic stroke occurred in such patients, and an astounding 35 years younger than in those without CoA. Intracranial aneurysms account for the vast majority of SAHs and have known associations with CoA.[9] Indeed, in this study, there was an increased frequency of unruptured aneurysms in patients with CoA who presented with stroke (4% versus 2%). Given the high mortality rates of up to 51% associated with SAH,[10] this study highlights the importance of considering intracranial aneurysms in patients with CoA.

Two hypothesized mechanisms have been proposed to explain the development of intracranial aneurysms in patients with CoA: (1) developmental abnormalities of the arterial wall and (2) pathologic changes as a result of mechanical forces attributable to hypertension.[11] The former hypothesis could mean that these aneurysms are different in nature and, thus, may have implications in terms of rupture risk and treatment, whereas the latter hypothesis would suggest that they occur because of the earlier development of risk factors, such as hypertension. One recent study found no intracranial aneurysms in a group of patients who all underwent CoA repair early in life and had magnetic resonance angiographic screening for intracranial aneurysms in adolescence.[12] Although such findings call the developmental hypothesis into question, it remains a possibility given that in the present study there were no significant differences between the groups in terms of other modifiable risk factors.

Implications for Screening and Treatment

Every well-executed epidemiologic study leaves us wanting to know more. Further registry and retrospective studies with relevant imaging data can answer some questions posed herein. Often, such questions are best answered by prospective controlled studies, but these may not be feasible. The age at repair, type of repair (surgical versus transcatheter), degree of residual obstruction, and aortic arch morphological features (gothic versus rounded) would all need to be controlled for in a small population who would need to be followed up and tested over decades. Absent prospective trials, should clinicians act on the conclusions of this report? The answer is probably yes, although we will not know for many years whether the proposed steps have any impact.

Assuming that stroke risk factors common in the general population will also increase the risk of stroke in patients with CoA, clinicians should counsel their patients with CoA accordingly. We should strongly emphasize the avoidance of tobacco products, benefits of exercise, weight control, and nonatherogenic diets. In patients with diabetes mellitus, stricter glucose control might be advocated. Given the prominence of SAH and intracranial aneurysms in the population with CoA,[5,6] these patients should be screened for intracranial aneurysms. A reasonable approach would be to perform cerebrovascular imaging along with aortic arch imaging, after adolescence and then every 10 years, depending on the specific clinical situation. The optimal study to use is controversial, but computed tomographic angiography may be more sensitive than magnetic resonance angiography.[13]

Perhaps most important, we must vigorously diagnose and treat systemic hypertension. Office blood pressure measurement is easy to perform and repeat on an annual basis, but alone may not be adequate to identify all of our at-risk patients. To better expose at-risk individuals, exercise testing with blood pressure measurement can be helpful. There can be a poor correlation between maximal exercise blood pressure and future cardiovascular events, although submaximal and/or after exercise blood pressures do presage cardiovascular morbidity.[14,15] A recent study of >60 000 patients without CoA confirms what hypertension researchers have reported for years: ambulatory blood pressure monitoring is a better predictor of hypertension-related morbidity than in-office blood pressure readings alone. Furthermore, the study demonstrated that patients with "masked" hypertension (those with a nonhypertensive office blood pressure but abnormal ambulatory recording) were at the greatest risk.[16] Ambulatory blood pressure monitoring is a seriously underused health resource in the United States. This is not for a lack of technology or reliability, but because medical insurance typically does not pay for ambulatory blood pressure monitoring; when insurance does cover the cost, evidence of white coat hypertension must be documented.[17,18] Yet, the patients we must identify are those who have acceptable office blood pressures, but are hypertensive with ambulatory blood pressure monitoring. The routine use of ambulatory blood pressure monitoring would allow us to better stratify risk of stroke and cardiovascular disease in patients with CoA.

The best management strategy for hypertensive patients with CoA falls outside the scope of this editorial. First, the adequacy of the repair must be established. The presence of upper extremity hypertension or a hypertensive response to exercise alone does not necessarily indicate the need for further aortic intervention. A combination of careful replicated arm and leg blood pressure measurements and aortic arch imaging by magnetic resonance imaging or computed tomographic scanning (computed tomographic scanning needed for patients with aortic stents in place) is required. Medical therapy relies on β blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers and should be tailored to the individual patient.

Summary

Success always presents new challenges. With the strides we have made in the survival of patients with CoA, we must now

address the possible morbidities our patients may face as they move into their mid to late adult years. Epidemiological studies, like that of Pickard et al,[6] will be instrumental in focusing on issues that require our further attention to continue extending the remarkable achievements already accomplished in the world of congenital heart disease.

Disclosures

None.

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