Aortic Coarctation and Coronary Artery Disease

The XY Factor

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Aortic coarctation (CoA) is a congenital defect involving a constriction of the aortic arch, usually occurring near the site of insertion of the ductus arteriosus. Surgical and endovascular repair techniques and success rates, measured by short-term survival, elimination of the gradient across the stricture, and normalization of systemic blood pressure, improved steadily over the last half of the 20th century. Despite apparently successful correction of the obstruction, however, individuals with a history of CoA demonstrate excess morbidity and premature mortality associated with hypertension (HTN), cerebrovascular accident, coronary artery disease, and aortic dissection/rupture.1–3 These adverse outcomes are to some extent independent of the severity of the original obstruction, type of treatment, restenosis, or presence of prosthetic grafts.2,4 Whereas blood pressure usually normalizes for a time after successful repair, ≈one third of CoA patients develop HTN by adolescence5 and ≈90% by middle age.2 The pathogenesis of the later onset HTN remains poorly understood.6 Normotensive children and young adults who had undergone successful CoA repair were found to have persistent endothelial dysfunction7 and impaired arterial reactivity,8 suggesting that intrinsic vascular abnormalities might contribute to the risk for premature coronary artery disease (CAD), independent HTN.

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In this issue of Circulation, a well-designed cross-sectional study from McGill University specifically addresses the CAD risk in CoA.9 Roifman et al9 identified 756 individuals diagnosed with CoA and 6471 with ventriculoseptal defect between the years 1983 and 2005 from Quebec’s Congenital Heart Disease Database. They compared the rate of cardiovascular diagnoses in age-matched CoA and ventriculoseptal defect cohorts (median age 30 years). The CoA group had significantly greater rates of HTN (45% versus 16%), CHF (15% versus 7%), and stroke (5.5% versus 2.6%; P<0.0001 for all). CoA patients also had higher CAD (4.9% versus 3.5%), but this was not statistically significant after adjusting for the greater prevalence of CAD risk factors HTN, hyperlipidemia, and male sex in the CoA group. The authors conclude that CoA is not an independent risk factor for CAD. The relatively high rate of CAD in the ventriculoseptal defect group is unexpected and does not appear in previous reports.3 The current study is important because of its large sample size, appropriate contemporaneous control group, and sophisticated statistical design. Its observations are also more recent and likely more reflective of current medical practice than earlier studies. It is thus very striking that the prevalence of cardiovascular comorbidities remains so high, despite the advances in surgical and medical interventions relevant to this disorder. The major point emphasized by Roifman et al9 is the need for targeting treatment of traditional cardiovascular risk factors such as HTN and dyslipidemia in patients with CoA to prevent the late complications associated with the diagnosis.

No one would argue with this recommendation, but is not entirely clear that standard risk factor treatment is effective in reducing the occurrence of CAD and stroke in CoA. The 4.9% prevalence of CAD observed in this cross-sectional analysis focused on the year 2005 is very similar to historical observations of 5.1%, reviewed by Verheugt et al.3 The 5.5% prevalence of cerebrovascular disease reported in the current study is actually greater than earlier estimates.3 Reports of excess coronary and cerebrovascular disease in CoA patients date from the 1970s, and if standard medical treatment and follow-up were effective in these patients, we should have seen reduced prevalence of CAD and CVA by the year 2005.

Unfortunately, Roifman et al9 do not have information on the treatment of cardiovascular risk factors in their Quebec study cohort. They extracted diagnoses such as HTN and hyperlipidemia from medical records and used these variables to analyze CAD risk in the cohort. However, the designation of HTN in the medical record is usually linked to prescription of anti-HTN medications, and it seems likely that many, if not most, CoA patients enrolled in the Quebec health care system are receiving standard care. In support of this view, Tzemos et al10 reported that young adults with bicuspid aortic valve (BAV) followed in Ontario over the same period were receiving medical treatment for HTN and dyslipidemia. It is thus unproven at this point in time that conventional treatment prevents coronary and cerebrovascular disease in CoA patients. I do not doubt the authors’ experience that treatment in expert hands can be effective, but prospective studies documenting successful medical treatment protocols are essential going forward. Additional limitations of this study, duly noted by the authors, include lack of information about primary treatment of the CoA, such as age or type of repair, the occurrence of restenosis, or the presence of associated defects such as BAV.

Progress in elucidating the genetic origins of CoA and related cardiovascular developmental defects is key to iden-
tifying individuals at greatest risk for complications and developing more effective interventions to improve their long-term prognosis. In recent years, studies of families with congenital heart malformations have shown clustering of mechanistically and apparently genetically related left ventricular outflow tract (LVOT) defects, including BAV, CoA, and left heart hypoplasia.\textsuperscript{11–15} It is unlikely that a single major locus will be found to cause all these LVOT defects, and we may expect to learn of a host of genes implicated in cardiovascular development as the pace of genetic discovery escalates over the next decade. A salient factor in the inheritance of CoA and BAV that has received remarkably little study is the increased risk conferred by male sex. It is indispensible that LVOT defects are significantly more common in males versus females by a ratio of at least 2:1. Probably not coincidentally, girls and women with a single X chromosome (Turner syndrome, TS) demonstrate a distinct profile of LVOT anomalies; the live-born prevalence of hypoplastic left heart is estimated at 10\%, aortic coarctation at 12\%, and BAV at 30\%.\textsuperscript{16} Similar to CoA patients, adults with TS experience excess morbidity and premature mortality resulting from complications of congenital heart disease, HTN, and premature cerebrovascular and CAD.\textsuperscript{17} We have shown that the cardiovascular phenotype is found in Turner individuals lacking only the short arm of the X or Y chromosome,\textsuperscript{18} suggesting that loci important for LVOT development are present on Xp and Yp. These observations led to our hypothesis that 2 copies of a gene present on both sex chromosome short arms are essential for normal cardiovascular development.\textsuperscript{19} The candidate gene would escape X inactivation in females and be expressed from X and Y chromosomes in males. The Y allele is predicted to be more prone to disruption than the X allele as a consequence of Y chromosome mutability.

The short arms of human sex chromosomes contain contiguous strips of homologous genes that engage in autosomal-like recombination during meiosis, hence termed a “pseudo-autosomal” region (PAR1). Haploinsufficiency for the PAR1 gene SHOX causes the short stature characteristic of TS,\textsuperscript{20} and it is possible that haploinsufficiency for other as yet unknown genes in the region causes the LVOT defects characteristic of TS. This proposition is supported by fact that murine species that have lost PAR1 genes from the sex chromosomes tolerate X monosomy very well without cardiovascular issues, whereas domestic species with highly conserved PAR1 on X and Y chromosomes do exhibit the TS phenotype, including CoA.\textsuperscript{21} A PAR1 gene defect would demonstrate an apparent autosomal inheritance pattern, consistent with LVOT pedigree studies. Finally, PAR1 localization of an LVOT related gene(s) may explain the greater prevalence of these defects among males, because the meiotic recombination rate for this region is 7-fold greater in males than females,\textsuperscript{22} increasing risk for Yp gene disruption. The extremely high recombination rate of PAR1 with significant discordance between males and females has presented major statistical challenges for genetic mapping in this region. Thus, until recently, PAR1 has been a genetic blind spot for positional cloning, linkage analyses, and genome-wide association studies. It is anticipated that future studies including more accurate and extensive coverage of this region may identify PAR1 genes related to congenital heart disease.

Alternatively, the cardiovascular phenotype in TS could be attributable to haploinsufficiency for Xp:Yp homologous gene(s) outside of PAR1.\textsuperscript{23} A very recent study reported functional null mutations in the Y-chromosome allele of transducin $\beta$-like protein 1 (TBLIY) in 2/83 study subjects with nonsyndromic CoA.\textsuperscript{24} This gene is located in a Yp region very prone to rearrangements, and variation in this specific locus correlates with atherogenic lipid profiles in men of different ethnic groups.\textsuperscript{25} Interestingly, Roifman et al\textsuperscript{9} report in the current study a significantly higher prevalence of hyperlipidemia in CoA versus ventriculo septal defect patients. These recent developments indicate that further studies focused on the sex chromosome short arms could be very productive in illuminating the genetic underpinnings of the male predisposition to both CoA and CAD.

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### Disclosures

None.

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