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Editorial

# Bicuspid Aortic Valve Syndrome requires new diagnostic tools to better stratify patients

## El syndrome valvular aortico bicuspide require nuevas herramientas para la mejor estratificacion diagnostica de estos pacientes

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There is controversy in the literature about indications for aortic arch replacement in patients with bicuspid aortic valve (BAV), and in this issue Berbel and colleagues' intention is to analyze a cohort of patients from their centre and describe the prevalence of aortic arch dilatation.[1] They reviewed 161 patients with BAV and aortic aneurysms who presented for elective surgery, with mean follow-up duration of 32 months. Dilatation of the aortic arch (defined as diameter ≥40 mm and/or aortic size index (ASI) ≥2.1 cm/m$^2$) was observed in 44 patients (27.3%) by diameter or 52 (32.3%) by ASI. Only 18 patients underwent arch replacement during the index procedure. Arch replacement was undertaken at the discretion of the operating surgeon based on diagnostic imaging and their analysis of the need to intervene.

The level of detail provided in this paper is a significant strength, and differentiates it from previous publications. The authors provide a comprehensive description of four things: the dimensions of each segment of the aorta; the nature of the valvular dysfunction; the pattern of aortic dilatation, grouped into five distinct patterns; and the Sievers classification of the morphology of the BAV. In their statistical analysis, the authors examined the possible associations between the presence, absence and progression of aortic arch dilatation with factors such as age, sex, presence of bovine arch, pattern of dilatation, and morphologies of BAV. They found that age, Sievers BAV classification Type 1 R-N and lateral bicuspid valve opening were predictive of aneurysmal growth. More importantly, the authors observed that dilatation of the arch after surgery was extremely slow, at a rate of 0.3 mm/year. Only two patients in the series required re-intervention for aortic complications, and none were for the arch. Survival at 5 years was 95%, without any aortic-related mortality.

This series is quite comparable to a similar work by Park and colleagues,[2] who described the natural history of the aortic arch in patients with BAV. They examined a cohort of 422 BAV patients undergoing repair or replacement of the ascending aorta, but without intervention on the arch. Patients were followed for median 4.2 years. Once again, none of the patients required reoperation for arch dilatation, and no progressive dilatation of the arch was observed.

Since the inception of aortic replacement procedures, the indications for surgery have primarily been based upon either aortic measurements, or catastrophic presentations. Patients have the aorta repaired or replaced because it has grown past a guideline-driven threshold of diameter, or because they have presented to the emergency department with symptoms of aortic dissection or rupture. In the latter case, aortic surgery is a life-saving measure, but in the former, clinicians are relying upon potentially unreliable numbers. Current guidelines indicate that the ascending aorta or arch should be replaced if the diameter is more than 5.5 cm.[3] However, studies have shown that as many as 60% of patients presenting with aortic dissection or rupture, the very complication that elective arch replacement intends to prevent, have aortic dimensions that were below the guidelines' threshold for elective intervention.[4] We also know that many patients live a full and uneventful life with mildly dilated aortas that may never cause clinical symptoms or complications.

The decision to pursue elective surgery on a patient with an enlarged ascending aorta or arch involves balancing the potential risks of the procedure against the future risk of an aortic dissection or rupture. The current guidelines have analyzed these risks, and determined that the threshold for intervention is an aortic diameter of ≥5.5 cm for an isolated aortic procedure. It must be noted, though, that the guidelines are based on published reports from high-volume centres with highly-skilled operators. Lower-volume centres and less-experienced surgeons may have a higher rate of perioperative complications that should not be underestimated. In spite of this, the indications for aortic surgery continue to broaden as the perioperative risks have continued to decline. There may be a temptation to view aortic replacements during concomitant cardiac surgery as a prophylactic measure, but studies have clearly demonstrated that patients with dilated aortas who have previously undergone aortic valve replacement rarely experience significant growth in their aortas, both ascending and arch.[2,5]

There is a clear need for a biological tool that will help us both screen and longitudinally follow the activity of the aortic wall at a cellular level. Changes in the structure of the aortic wall, including activation of valvular interstitial cells and presence of oxidative damage, are common to all aortic pathologies, and provide a potential avenue for a biological reclassification of different types of patients with BAV and trileaflet aortic valves (TAV). Several groups, including ours, have identified biomarkers and are working to develop serological tools that may help us understand what is happening within the aortic wall. Our group found that soluble receptor for advanced glycation end product (sRAGE), a serological biomarker, was associated with aortic wall instability in both BAV and TAV patients.[6] sRAGE was detected in the blood, and was strongly correlated with tissue biomarkers that were elevated in

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patients with histologically abnormal aortas. Tissue biomarkers are diagnostically limited as they cannot be measured except on explanted tissue, so the correlation of the tissue biomarker with sRAGE was necessary. This work, and the work of other groups, represents an important step away from the previous generation of research focused solely on genetic tools; most patients with aortic wall instability do not have a genetic syndrome such as Marfan or Loeys-Dietz. The most efficient approach appears to be a proteomic one. This will allow us to initially evaluate individual patients, and then follow the changes in biomarker levels longitudinally in conjunction with yearly diagnostic imaging.

In summary, the article by Berbel and colleagues concurs with the existing literature, and states that in patients with BAV undergoing surgery for either the valve or an aortic aneurysm, the arch should not be replaced unless it specifically and independently meets criteria for intervention. The data clearly show that at 32 months of follow-up, not a single patient in Berbel's cohort required reoperation for the arch, which is identical to the results observed by Park and colleagues. The data simply do not support the increased risk of morbidity and mortality associated with arch replacement in most hands. As perioperative morbidity and mortality rates continue to decline, we must resist the temptation to prophylactically replace segments of the aorta, such as the aortic arch, simply because we can. Now, it is incumbent on clinicians and scientists to pursue a dynamic, biological approach to aortopathies that incorporates the cellular and molecular changes that alter the very structure of the aortic wall.

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