# Aortic Valve Surgery: Unveiling the Mystery of a Woman's Heart

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Several studies have reported a significant association between female gender and increased operative mortality following cardiac surgery including valve surgery.[1] However, it remains unclear whether or not female gender is really an independent risk factor or simply a marker for other factors. The article published by Caballero-Borrego et al in this issue of *Revista Española de Cardiología*[2] provides new insights in this regard. In this series of 577 patients with severe aortic stenosis (SAS) undergoing aortic valve replacement, the operative mortality was 2-fold higher in women (13%) than in men (7%). However, after adjustment for other potential confounders, including body surface area, female gender was no longer a significant predictor of mortality on multivariate analysis. Hence, in light of these findings, female gender does not appear to be an independent risk factor for operative mortality following aortic valve surgery. Nonetheless, it is important, from both scientific and clinical standpoints, to identify the factors that may be responsible for the increased perioperative morbidity and mortality that is typically observed in women. Identification of the causal factors, especially if they are modifiable, could indeed help to improve the outcome of aortic valve replacement in this specific population.

Some studies have demonstrated that, for the same degree of left ventricular (LV) pressure overload, i.e. the same levels of transvalvular pressure gradients in the case of aortic stenosis, women tend to have more pronounced concentric LV remodelling and hypertrophy compared to men.[3] In this regard, it has been reported that severe LV concentric remodelling is associated with increased risk of operative mortality following aortic valve replacement.[4] The specific hormonal, metabolic, and physiological status associated with female gender can modulate the LV compensatory response to pressure overload. The exaggerated concentric remodelling may, in turn, accelerate impairment of coronary microcirculation and development of LV diastolic dysfunction. Moreover, a recent study from our group has reported that patients with a small concentric remodelled ventricle often have reduced stroke volume and thereby low transvalvular gradient despite the presence of SAS and preserved LV ejection fraction.[5] Interestingly, this "paradoxical low flow, low gradient SAS" was more frequent in women and it was associated with worse outcome, especially when treated medically.[5,6]

Another intriguing result of the study of Caballero-Borrego et al[2] is that women were older and had higher transvalvular gradients and higher prevalence of heart failure at the time of referral to surgery compared to men. This raises the possibility that women are referred to surgery at a later stage of disease compared to men, which may then contribute to increase their operative risk. There are several hypotheses that may be proposed to explain the delayed referral to surgery in women: *a)* women develop symptoms at a higher degree of stenosis severity, *b)* they are more tolerant to symptoms than men, *c)* they adapt their level of physical activity to avoid symptoms, *d)* they are less prone to rapidly report the symptoms to their treating physician, and *e)* the physicians tend to underestimate or neglect the symptoms related to SAS, to a larger extent in women than in men. We reported that the presence of paradoxical, low flow, low gradient, SAS despite preserved LV ejection fraction may lead to an underestimation of disease severity and symptoms and thereby to an under-utilization of aortic valve replacement.[5] Given that, as mentioned above, this pattern is more frequent in women, it may thus contribute to the delayed referral to surgery in these patients. Recent studies have also demonstrated that the degree of valve stenosis, per se, is an independent

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predictor of early and late mortality following valve replacement, even after adjustment for symptoms, LV hypertrophy, and LV ejection fraction etc.[7,8] Indeed, a very severe stenosis as defined by an aortic valve area <0.6 $cm^2$ was independently associated with increased postoperative mortality. This finding is consistent with the concept that a long-standing, severe pressure overload may cause alterations in myocardial perfusion, ultra-structure, and function,[9] which may ultimately become irreversible even if the pressure overload is relieved by valve replacement. The currently used indices of LV function, such as LV ejection fraction have a low negative predictive value for the detection of myocardial systolic dysfunction in presence of LV concentric remodelling. Hence, LV dysfunction may develop insidiously in the asymptomatic patient with SAS, and especially in women with pronounced LV concentric remodelling. In this context, Doppler-echocardiographic evaluation of myocardial strain by speckle tracking analysis may help to reveal sub-clinical alteration of myocardial contractility. Serial follow-up of the plasma levels of natriuretic peptides also provides a simple and low-cost method for the early detection of excessive myocardial stretch and ensuing myocardial decompensation.[10] Exercise testing may also be helpful to unmask symptoms and, if combined with echocardiography, to assess myocardial contractile reserve.[11] All these complementary diagnostic tools enable more precise assessment of disease severity and thus a more enlightened decision with regards to the optimal timing for surgery in women with SAS.

Women also often have smaller height and body surface area, larger body mass index, and narrower aortic root compared to men. These factors may render the operation technically more complex, which may, in turn, prolong the aortic cross-clamp time and compromise myocardial protection. Although not analyzed in the study of Caballero-Borrego et al,[2] prosthesis-patient mismatch is another operative factor that may have accounted for the increased operative mortality observed in women. Prosthesis-patient mismatch occurs when the effective orifice area of a normally functioning prosthesis is too small in relation to patient's body surface area. Its main hemodynamic consequence is the persistence of abnormally high transprosthetic gradients. This "sequela" is more frequent in women because they often have a small calcified aortic root, thereby limiting the implantation of prostheses with larger effective orifice areas. Several studies have reported that prosthesis-patient mismatch is an independent risk factor for operative mortality.[12,13] And importantly, as opposed to most other risk factors for operative mortality, mismatch can be avoided or its severity reduced with the use of prospective strategy at the time of operation.[14]

In conclusion, women with SAS undergoing aortic valve replacement have significantly higher operative mortality compared to men. However, adjustment for other confounders reveals that female gender is not an independent risk factor for mortality. Moreover, this factor is obviously not modifiable. So, future studies should focus on the identification of the preoperative and operative factors that are responsible for the increased operative mortality in this population. Pending the results of these studies, a closer and more comprehensive follow-up is recommended in women with SAS in order to optimize the timing of surgery and thus potentially the outcome of these patients. In this regard, particular attention should be paid at the time of echocardiographic exam to appropriately identify the presence of a paradoxical low flow, low gradient SAS pattern, which is frequent in women and may contribute to the underestimation of disease severity. Myocardial strain analysis, plasma natriuretic peptides and exercise testing may also be useful for risk stratification and clinical decision making in women with findings of SAS and no apparent symptoms or LV dysfunction. Finally, if surgery is contemplated in women with SAS, it is important to pay attention to the prevention of prosthesis-patient mismatch given that this risk factor is more likely to occur in this population.

As very well said in the movie "Titanic": "a woman's heart is a deep ocean of mystery" and we certainly need many more studies, such as the one of Caballero-Borrego et al, to unveil this mystery.

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