JACC: ADVANCES VOL. 3, NO. 3, 2024

EDITORIAL COMMENT

Prognosis in Chronic Aortic Regurgitation

Does Pulmonary Hypertension Play a Role?*

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Contemporary studies have highlighted the importance of careful noninvasive assessment in patients with chronic aortic regurgitation (AR) by means of transthoracic or transesophageal echocardiogram and cardiac magnetic resonance.[1] Current guidelines rely primarily on symptom assessment, left ventricular (LV) ejection fraction (<55%), and LV end-systolic diameter (>50 mm or >25 mm/m^2) to inform clinicians on timing of aortic valve intervention.[2] However, recent literature suggests that outcomes may be improved with earlier surgery.[3] Additional noninvasive indices such as LV volumes may perform favorably when compared to traditional LV diameter measurement on echocardiography. These findings have garnered interest in evaluating other noninvasive assessments to determine prognostic impact in patients with significant AR and, more importantly, determining the appropriate timing of valvular intervention.[4]

Chronic AR results in increased LV wall tension, leading to LV remodeling and chamber dilatation with eccentric hypertrophy. These changes arise out of a need to avoid excessive increases in LV end-diastolic pressure and preserve cardiac output. However, this compensatory remodeling can lead to interstitial fibrosis and heart failure symptoms, which may not reverse following aortic valve replacement (AVR); thus, the timing of aortic valve surgery is paramount.[5] Pulmonary hypertension (PH) is particularly common in left-sided valvular disease and has been extensively studied in patients with mitral regurgitation or stenosis and aortic stenosis. In many instances, it is cited in current guidelines as a prognostic marker for tipping the scales toward intervention. The data surrounding PH in chronic AR is limited, and thus its prevalence, pathophysiology, prognostic significance, and role in informing the timing of valve replacement are uncertain.

In this issue of *JACC: Advances*, Anand et al[6] show that, in a retrospective single tertiary referral center cohort of 821 patients with moderate to severe AR, mild to moderate PH (right ventricular systolic pressure [RVSP] 41-59 mm Hg) and severe PH (RVSP >60 mm Hg) were present in 11% and 3% of patients, respectively. The presence of PH alone was associated with higher LV volumes and filling pressures, more symptoms, and increased mortality. When compared to patients with no PH, the HR for time to death was 1.59 (95% CI: 1.07-2.36, $P = 0.021$) for mild to moderate PH and 2.90 (95% CI: 1.63-5.15, $P < 0.001$) for severe PH. In patients with moderate-severe AR, AVR demonstrated a 36% relative risk reduction in death over a median follow-up of 7.3 years (HR: 0.64, 95% CI: 0.45-0.91), with increases in RVSP as low as 33 mm Hg being associated with mortality. However, among patients receiving AVR, survival did not appear to be influenced by the presence of PH (P for interaction = 0.23). Of the 57 patients with PH who underwent AVR, 61% had a significant decrease in their pulmonary pressures, as defined by a reduction in RVSP >8 mm Hg.

We commend the authors of this study, which provides important insights regarding the role of PH in patients with chronic AR. The observed 14% PH prevalence in this AR cohort is less than in patients with mitral insufficiency, in whom PH is considered a Class IIa recommendation for surgical repair.[1] This is not entirely surprising, as in chronic AR, PH develops downstream of LV remodeling and fibrosis and usually manifests once LV end diastolic pressure

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.100831

rises—a marker of decompensation. This is further confirmed by the fact that the authors found patients with PH to have more LV remodeling, higher E/e', and more indications for surgery. Importantly, PH was associated with reduced survival in univariable and multivariable analyses and was noted regardless of functional class, LV size and ejection fraction, or presence of conventional surgical indications such as LV ejection fraction <55%, end-systolic diameter >50 mm, or end-diastolic diameter >65 mm.

A recent publication by Ratwatte et al,[7] retrospectively examined the prevalence and prognostic implications of PH in >8,000 patients with at least moderate AR and preserved LV ejection fraction (>50%) over a median follow-up of 3.1 years. PH (RVSP >40 mm Hg) was observed in 44.4% of patients, and severe PH in 6.9%, which is higher than in the study by Anand et al. Potential reasons for this discrepancy include differences in the cohorts evaluated (younger and with fewer women in the latter) as well as inherent limitations of echocardiography in estimation of RVSP such as the need for an adequate tricuspid regurgitation signal.[8] In Ratwatte's cohort the risk of mortality increased in parallel with RVSP, becoming statistically significant at a threshold of RVSP >40 mm Hg. The HRs after adjusting for age and sex ranged between 1.5 and 3.3 for different degrees of PH severity, comparable to the findings by Anand et al. When excluding patients with significant LV dilatation (end systolic diameter >50 mm), reflecting a population who may not meet criteria for valvular intervention by current guidelines, the presence of at least mild PH was again associated with increased mortality, also in agreement with the present study.

Altogether, these findings support a deleterious influence of the presence of PH on outcomes in patients with chronic AR, particularly those with preserved LV ejection fraction and without significant LV dilatation, and underscore the importance of careful evaluation of pulmonary pressures during echocardiographic examinations. In addition, they raise the highly relevant question of whether practice guidelines should be revisited to include PH as a factor prompting surgical intervention. Anand et al did not observe an interaction between PH presence and the influence of AVR in survival. While the actual patient numbers in each group (without PH, mild-moderate PH, and severe PH) were likely too small for well-powered adjusted analyses, the findings support the authors' conclusion that, if otherwise indicated, surgery is not to be deferred because of pulmonary pressure elevations. Nonetheless, this study should not be interpreted as evidence that patients with PH but without other guideline criteria would benefit from early aortic valve intervention, an attractive and reasonable hypothesis that is however not supported by the aforementioned lack of an interaction between surgical outcomes and PH group and that will need testing in adequately powered, prospective studies. Anand et al observed significant early reductions in RVSP in 61% of patients undergoing AVR, and elevated filling pressures as determined by the E/e' ratio were the only factor associated with PH improvement in multivariable analysis. It will also be important to evaluate if long-term survival is impaired in those demonstrating persistent PH after AVR and whether monitoring E/e' may also play a role in determining the optimal timing for intervention.

In conclusion, this study together with the recent paper from Ratwatte et al, adds to the large body of evidence of a detrimental influence of PH on prognosis in left-sided valvular disease but in less well-studied AR. With recent data suggesting earlier thresholds for surgical referral than current guidelines state, noninvasive hemodynamic measures such as RVSP could play an important role in future clinical decision-making in chronic AR. Prospective, randomized studies aimed at utilizing PH in risk stratification and deciding surgical intervention will be useful in determining clinical utility moving forward.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS aortic regurgitation, pulmonary hypertension