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EDITORIAL COMMENT

Aortic Regurgitation

The Value of Clinical Signs*

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Surgery for all types of valve disease is most clearly indicated for symptoms or for adverse left ventricular (LV) remodeling or systolic dysfunction (1,2). However, for aortic stenosis, a blunted blood pressure rise on exercise (1,2) or a raised plasma B-type natriuretic peptide level (1) are already recognized as Class II indications for surgery. In this issue of the *Journal*, Yang et al. (3) provide preliminary evidence that physiological measures could similarly become indicators for earlier surgery in chronic severe aortic regurgitation (AR).

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Yang et al. (3) looked at diastolic blood pressure (DBP) and resting heart rate (RHR) in a retrospective descriptive study of 820 patients with moderate-severe or severe AR. Patients with other types of valve disease or coexistent significant structural cardiac pathology were excluded, but those with coronary artery disease or symptoms were included. The mean age was 59 ± 17 years and 82% were men, which is in line with other studies of AR (4,5). The primary outcome was all-cause death during medical therapy. Secondary endpoints were aortic valve replacement (AVR) and the composite of AVR plus all-cause death.

During a follow-up of 5.5 ± 3.5 years, AVR was performed in 400 patients and death occurred in 104 under medical management and 49 after valve surgery. Patients with DBP <70 mm Hg and RHR >60 beats/min were more likely to have severe AR and symptoms and to undergo AVR. However, DBP and RHR were independently related to all-cause death after adjusting for guideline indications for surgery (symptoms, LV ejection fraction, indexed LV end-systolic diameter), age, sex, grade of AR, comorbidities including hypertension, and also medication (except for diuretic agents). There was a direct linear relationship between all-cause death and RHR >60 beats/min. For DBP, there was a J-shaped relationship, with risk rising below a DBP 70 mm Hg to a peak at 55 mm Hg and rising again above a DBP 85 mm Hg. Both DBP and RHR were also independently related to the secondary endpoints of AVR and the composite of AVR and all-cause death. After aortic valve replacement, RHR, but not DBP, continued to be related to all-cause death and was also associated with reduced reverse remodeling.

How can these observations be explained? The authors suggest that low DBP is a physiological response to severe AR and increased aortic stiffness, a known independent adverse cardiovascular risk factor (6). However, DBP was not predictive of outcome after AVR and was similar in patients with and without hypertension. These observations suggest that severe AR, rather than increased aortic stiffness, was the main cause of a low DBP. A low DBP increases the risk of death as a result of reduced coronary perfusion pressure and is most important prognostically in people age >60 years or with coronary disease (7). The risk of death above a DBP 85 mm Hg was most likely due to the exacerbating effect of systemic hypertension.

The heart rate in chronic severe AR is usually low and it is likely that the high RHR in this study was a sign of early hemodynamic decompensation. A high RHR remained a marker of death after AVR and was also associated with reduced reverse remodeling, both consistent with persistent LV dysfunction. The primary outcome was all-cause and not cardiac death, and it is possible that confounding comorbidities also affected the results. One example might be anemia as a result of a gastrointestinal malignancy causing a high RHR. Unfortunately, these uncertainties are inevitable in a retrospective design.

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It would be interesting to assess the effect of exercise echocardiography on blood pressure and heart rate in the patients in this study. Patients with a higher RHR might have reduced contractile reserve on exercise (8). We already know that a fall in stroke volume occurs in apparently asymptomatic patients with severe aortic stenosis in whom symptoms are revealed on exercise, but it rises in those who remain symptom-free (9). The fall in stroke volume is accompanied by a rise in heart rate in early exercise (10). It is possible that a similar observation would be seen in AR and might be prognostically useful.

How should we use these observations? Recent studies suggest that surgery should be considered earlier than current guidelines recommend (1,2), above an indexed LV systolic diameter 20 mm/m^2 or below an LV ejection fraction 55% (4,5,11). However, these may be normal or close to normal levels, as is already true of current recommendations for repair of mitral valve prolapse (1,2). The operative risk for AVR is low, but, unlike for mitral repair, the patient then has a life-long exposure to the possible complications of a replaced valve. Therefore, better ways of refining risk are needed. A progressive rise in LV diameter or fall in ejection fraction on serial echocardiograms are probably more important than absolute thresholds. Other methods of refining risk include exercise testing (1,2) to reveal occult symptoms, global longitudinal strain (12), or beta-type natriuretic peptide levels (13) as markers of early LV decompensation or regurgitant fraction on cardiac magnetic resonance imaging (14). Future work should explore the interactions between DBP or RHR and imaging and blood biomarkers ideally using machine learning in large datasets. This work could then inform a randomized controlled trial of early surgery which, as yet, has not been done for any of the guidelines (1,2) or newly suggested thresholds (4,5,11) for surgery.

However, as the authors suggest, a DBP <70 mm Hg or RHR >60 beats/min can already provide a red flag to alert the clinician to the need for greater vigilance. This includes taking note of even nonspecific symptoms, considering an exercise test, and rechecking serial echocardiograms for adverse changes. The authors suggest that they can also be triggers for referring to a heart valve team, but we believe that all patients with severe and even moderate AR should already be seen by cardiologists with specialist valve competencies (15) ideally in a specialist valve clinic (16). This study is useful in our time of ever-increasing diagnostic sophistication for highlighting the importance of simple physiological markers on the routine clinical examination, which can readily be obtained by all clinicians.

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