Optimising the timing of aortic valve surgery: a multiparametric approach

Running title: Optimising the timing of aortic valve surgery

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Aortic regurgitation (AR) is the third most common valvular heart disease, after mitral regurgitation and aortic stenosis, occurring in up to 15% of adults.[1,2] Most commonly, AR occurs as a result of chronic degeneration, with the degree of regurgitation gradually worsening over time.[3,4] The gradual development of severe AR can present with heart failure symptoms, but this insidious process is commonly asymptomatic, and hence patients are often diagnosed at a later stage in the disease process. The timing of surgical intervention is of paramount importance. Premature valve replacement exposes patients to significant and unnecessary surgical risk; while delaying intervention carries the risk of irreversible myocardial damage.[5]

Current international guidelines place a heavy emphasis on the presence of symptoms to prompt surgical intervention in patients with severe AR.[3,4] However, with many patients not developing symptoms until late in the disease process, this potentially delays intervention and results in a critical time window being missed. In asymptomatic patients with severe AR the majority of class I indications for surgery are based on echocardiographic indices of left ventricular dilation and systolic function.[3,4]

There is a growing body of evidence to suggest that these current guidelines are too conservative, and prior to the development of left ventricular dilatation or left ventricular systolic dysfunction there is ongoing and irreversible myocardial damage, that is associated with worse outcomes.[6,7] Prior to the onset of overt heart failure, patients with severe AR may develop irreversible myocardial changes, which in turn may result in residual risk even after aortic valve replacement. The combination of excessive volume and pressure overload is initially accommodated for by eccentric hypertrophy, which preserves cardiac output.[5] Despite being asymptomatic, the increased left ventricular wall stress triggers cardiac fibroblasts to upregulate fibronectin synthesis, and change the myocardial collagen composition. The early fibrotic transformation of apoptotic myocardial cells is partially reversible, up until the development of diffuse fibrosis and scar tissue formation.[8] Therefore, before the development

of overt heart failure and echocardiographic structural changes, there is a time interval whereby surgical intervention is required to prevent irreversible cardiomyocyte damage.[5] Additional data are needed to assist the detection of early myocardial damage and challenge the current recommendations regarding the timing of surgical intervention.

Various clinical studies have demonstrated the utility of serum natriuretic peptides[9], speckle tracking[10,11], stress echocardiography,[12] and more recently cardiac magnetic resonance (CMR) derived AR quantification and myocardial tissue characterisation, in detecting myocardial damage and subclinical left ventricular systolic dysfunction.[13,14] Importantly, elevated natriuretic peptides, impaired global longitudinal strain and myocardial fibrosis, detected on late gadolinium enhancement imaging, are all associated with early adverse outcomes and an increased risk of mortality following aortic valve surgery.[9,10,15]

In the current issue of Circulation: Cardiovascular Imaging, Kockova et al[16] present data on a multiparametric scoring system that combined echocardiographic or CMR derived parameters and serum natriuretic peptides to detect early disease decompensation in patients with asymptomatic severe AR and preserved left ventricular systolic function. This prospective multi-centre study recruited 127 patients (age 45±14 years, 84% males) with asymptomatic severe AR and preserved left ventricular systolic function, all of whom underwent a comprehensive baseline assessment comprising of serum natriuretic peptides, transthoracic echocardiography and CMR. The study endpoint was the onset of indication for aortic valve surgery as per the current guidelines. The authors should be congratulated for conducting this study, with all challenges of using a multi-imaging approach to this population. This multiparametric strategy that combined a CMR derived measure of AR severity (either regurgitant volume or regurgitant fraction), a CMR derived measure of left ventricular remodelling (such as left ventricular end diastolic volume [LVEDV] index) and serum brain natriuretic peptide (BNP), demonstrated higher accuracy than any single parameter alone in

identifying patients with early disease decompensation. Furthermore, the performance of this proposed model remained robust in an external validation cohort. In the study by Kockova et al[16], indices of AR severity outperformed indices of left ventricular remodelling in predicting early disease progression; and CMR derived measures of AR severity outperformed all clinically relevant echocardiographic measures of AR severity. Additionally, this study demonstrated that the single most powerful predictors of disease progression were all indices of AR severity, rather than indices of left ventricular remodelling. At present, such measures are not featured in international guidelines regarding indications for surgical intervention,[3,4] but are potentially able to detect early decompensation even before the development of structural changes. The ability of AR regurgitant volume and regurgitant fraction to more accurately predict decompensation probably reflects a high incidence of early-stage AR disease in the study population. Even at this early-stage, patients had increased serum natriuretic peptides, impaired global longitudinal strain, and an increased prevalence of myocardial scar, detectible on late gadolinium enhancement imaging, all of which have been associated with adverse outcomes.[9,10,15] Myocardial damage was also confirmed histologically in a small cohort within the study who underwent a perioperative myocardial biopsy, which in turn demonstrated an increased extent of myocardial fibrosis.

There are a number of caveats to consider when drawing conclusions from these data. It is noteworthy that the majority of patients had a bicuspid aortic valve with an eccentric regurgitant jet, which may in part explain the reduced sensitivity of traditional echocardiographic indices of AR severity. Nonetheless, the accuracy and precision of CMR derived aortic flow measurements easily overcomes this common clinical conundrum, and undeniably outperforms all clinically relevant echocardiographic indices of severity. The overwhelming majority of patients in this study were male and the Authors have not reported the ethnicity data of the study population. It would be important to ensure these findings can

be replicated across a range of ethnicities and gender. Although use of CMR has undoubtedly increased the accuracy of identifying patients at risk of early decompensation, the authors quite rightly acknowledge that the wide application of CMR may not be possible in all healthcare settings, due to the significant specialist expertise and cost that would be required. This may represent a significant barrier in utilising CMR in all asymptomatic patients with severe AR and preserved left ventricular systolic function. Finally, the Authors do also acknowledge the presence of fibrosis on myocardial biopsies, but they fail to further explore the fundamental processes that characterize the reversible and irreversible myocardial changes in association with AR. The Authors focus on haemodynamic, functional and structural changes, but these processes have long been measurable with both CMR and echo, although with variable degree of accuracy and precision. Currently, CMR permits measurement of core myocardial pathways 1) fibrosis with the extracellular volume (ECV) measurement); 2) edema (T2 being the most specific marker); 3) myocyte response (derived from LV mass and ECV from the formula: LV mass x [1 - ECV]). These parameters would have added significant value in the reclassification of the stages with the addition of the core myocardial processes involved in the biology of myocardial remodelling in AR.

What is the importance of this study and how can we use these insights to improve patients' care? Optimizing the timing of surgical intervention is likely to lead to better outcomes. This study poses important questions regarding the current approach for timing of intervention and challenges the current recommended approach of focusing on echocardiographic measures of left ventricular remodelling and systolic function to determine the timing of surgical intervention, all of which have been demonstrated to be insensitive in identifying patients with an adverse clinical course. Indeed, several large studies have shown that asymptomatic patients with severe AR and a normal left ventricular ejection fraction have better pre- and post-operative outcomes if surgical intervention takes place below the currently recommended

thresholds, avoiding potential accrual or residual risk or limitation that persists post procedure.[17,18] The present study by Kockova et al[16], together with others, proposes an alternative approach to surgical intervention, with the aim of surgery taking place before irreversible myocardial damage has occurred. Future studies will be needed to comprehensively redefine the core processes involved (haemodynamic changes, structural and functional changes and myocardial consequences) and use these to reclassify disease stages. Optimal timing of intervention will require us to measure and identify these mechanisms underpinning that AR, their relative contributions in individuals, and choosing optimal timing of intervention accordingly. Use of multiparametric imaging to guide and support these developments will be key.

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