REVIEW

Pathophysiology and management of combined aortic and mitral regurgitation

Physiopathologie et prise en charge des insuffisances valvulaires aortiques et mitrales combinées

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Summary   The combination of aortic and mitral regurgitation is a typical example of a frequent yet understudied multiple valve disease scenario. The aetiology is often rheumatic or degenerative; less frequently it can be induced by drugs or radiation, or caused by infective endocarditis or congenital valvular lesions. Aortic regurgitation resulting in secondary mitral regurgitation is also not uncommon. There are limited data to guide the management of combined aortic and mitral regurgitation. Left ventricular dysfunction is frequent at initial presentation, and even more so postoperatively, suggesting that surgical management should not be delayed, particularly when symptoms occur or when there is evidence of even subtle left ventricular dysfunction. The decision to operate on one or both valves not only depends on the severity of each lesion, but also on several other factors, including age, co-morbidities and frailty, the increased operative risk of double valve surgery, the increased risk of long-term

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Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology; AR, aortic regurgitation; LV, left ventricle/ventricular; MR, mitral regurgitation.
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thrombotic and bleeding complications with multiple mechanical valves, the risk of leaving one valve unoperated and the probability of requiring redo surgery. The role of a multidisciplinary heart valve team is critical in this setting to optimize management and outcomes. The role of transcatheter approaches is currently limited, but technological advances will probably soon change the management paradigm.

MOTS CLÉS
Insuffisance aortique ;
Insuffisance mitrale ;
Cardiopathies valvulaires ;
Affections valvulaires multiples

Résumé   L'association d'une régurgitation valvulaire aortique à une régurgitation mitrale est un exemple typique d'affection plurivalvulaire, fréquente et cependant peu étudiée. Les étiologies rhumatismales et dégénératives sont les plus courantes ; l'endocardite infectieuse, les atteintes valvulaires médicamenteuses et radiques, ainsi que les valvulopathies congénitales devront aussi être recherchées. L'insuffisance aortique avec insuffisance mitrale secondaire est aussi une situation fréquente. La prise en charge des patients de ces patients n'a été que peu étudiée. La dysfonction systolique ventriculaire, fréquente lors du diagnostic, l'est encore plus en postopératoire, plaidant pour une prise en charge chirurgicale précoce, et ce, dès l'apparition de symptômes ou de signes › même discrets de dysfonction ventriculaire. La décision de traiter les deux valves d'emblée ou de n'en opérer qu'une dépendra non seulement de la sévérité de chacune des régurgitations, mais aussi de multiples facteurs, parmi lesquels l'âge, les comorbidités et la fragilité du patient, le risque opératoire et des risques hémorragiques et thrombotiques inhérents à la chirurgie bivalvulaire et le risque de laisser telle qu'elle une valve dysfonctionnelle et de devoir l'opérer ultérieurement. Une équipe multidisciplinaire spécialisée dans la prise en charge des affections valvulaires sera particulièrement bénéfique pour en optimiser le traitement et améliorer le pronostic du patient. Si la place dévolue au traitement percutané des affections bivalvulaires régurgitantes est actuellement limitée, il ne fait aucun doute que les progrès technologiques modifieront considérablement notre approche thérapeutique.

Background

The diagnosis of valvular heart disease has improved considerably over recent years, as has its management, but there are still limited data to guide clinical decision making in patients with multiple valve disease [1—3]. In this context, the combination of aortic regurgitation (AR) and mitral regurgitation (MR) is a typical example of a frequent yet understudied scenario [3]. The aim of this article is to provide a state-of-the-art review of the pathophysiology of this condition and management strategies, taking into account its various clinical presentations.

Aetiology and prevalence

With a reported prevalence in the CARDIA study of 0.5% in subjects aged 21 to 35 years, the combination of AR and MR is uncommon in young adults [4]. Among older patients with a mean age of 54 years from the Framingham cohort, the prevalence of regurgitation involving two valves was 10% for men and 8% for women, but more than mild MR and more than trace AR were infrequent [5]. However, Pai et al. reported that among patients with severe AR, up to one-quarter also had moderate-to-severe MR [6]. In a Swedish nationwide registry including all hospitals and specialized outpatient clinics, 10.7% of patients with AR had concomitant MR, and 8% of patients with a diagnosis of MR had concomitant AR [7]. Moreover, 22% of the patients with multiple valve disease had a combination of AR and MR, making this the third most frequent form of multiple and mixed valve disease [7].

In combined AR and MR, the two conditions may have a similar aetiology or, less frequently, be the result of two unrelated primary disease processes. In the EuroHeart Survey, rheumatic heart disease was the leading cause of multiple valve disease (51% of cases) (Fig. 1), and degenerative aetiologies were responsible for 41% of cases [8]. However, whereas the incidence of rheumatic heart disease has declined over the past few decades, the aging of the population of industrialized countries accounts for a shift towards degenerative aetiologies, without a global reduction in the overall prevalence of valvular heart disease [9].

All other aetiologies, including infective endocarditis, drugs, radiation and congenital valvular lesions, are much less frequent. Nonetheless, multiple valve disease is observed in more than 20% of patients with drug- or radiation-induced heart valve disease [10,11]. Multiple valve disease resulting from infective endocarditis carries an increased risk of heart failure [12].
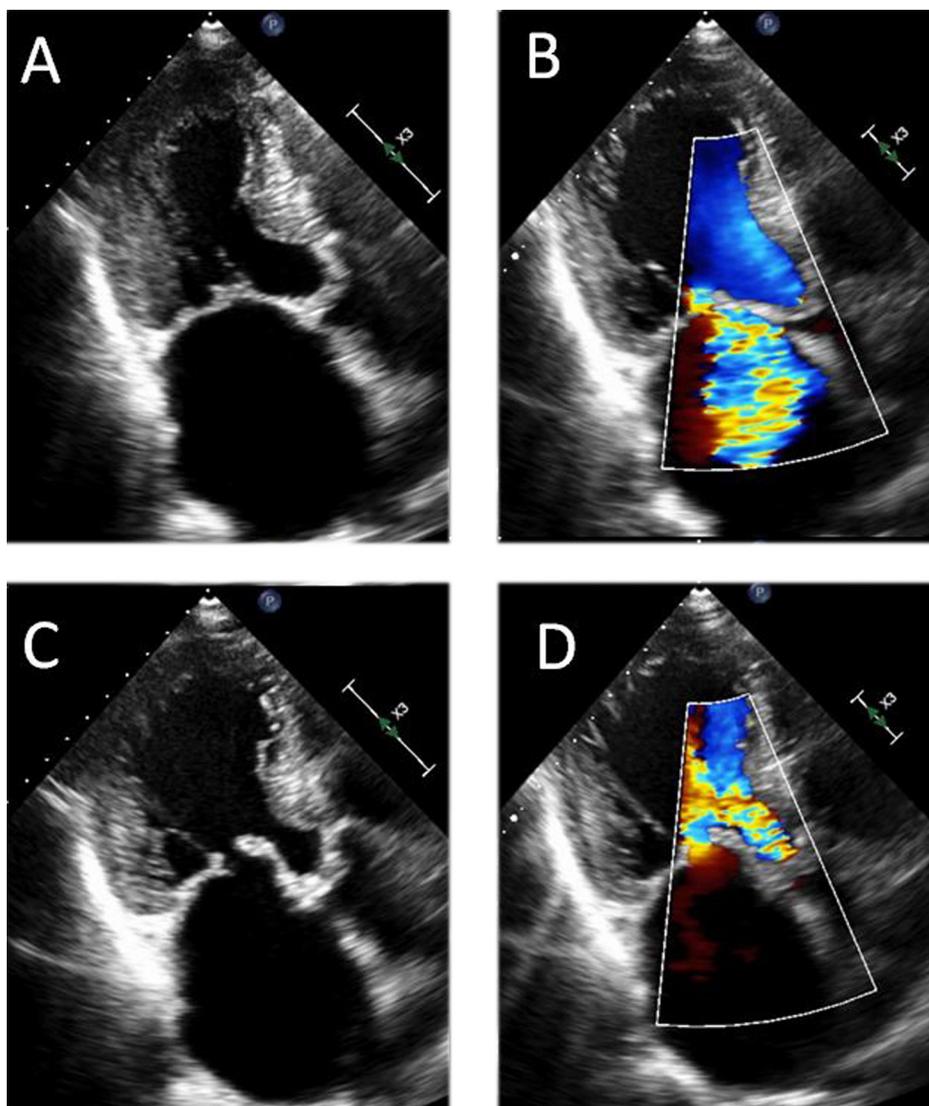
Figure 1. Combined rheumatic aortic and mitral regurgitation. A and B. Systolic still frames. C and D. Diastolic still frames.

Varying degrees of MR may result from remodelling, shape distortion and impaired function of the left ventricle (LV) associated with severe AR, thereby restricting mitral valve motion [13]. Secondary (functional) MR, in which the valve is structurally normal and the leaflet coaptation defect mainly results from ventricular and/or atrial remodelling, is common in patients with aortic valve disease; however, most studies included patients with aortic stenosis, and there are limited data focusing on patients with predominant AR [13,14]. In a series of 779 patients who had undergone aortic valve replacement, Lim et al. identified 155 patients (20%) with mild-to-moderate functional MR, but the number of patients with severe MR was not reported [14]. In a series of 816 patients with AR, Beaudoin et al. reported a 5.6% prevalence of moderate or severe secondary MR [13]. Interestingly, the authors attributed this low prevalence to a significant increase in mitral valve leaflet area compared with controls and with patients with functional MR of other aetiologies [13]. The mechanism of this valvular remodelling was unclear, but it was postulated that the increase in mitral valve leaflet area might be a compensatory mechanism, preventing the development of MR by helping to preserve a normal relationship to the area needed for closure in a dilated LV [13].

Pathophysiology

Both AR and MR increase left ventricular (LV) preload, whereas only AR has a significant effect on afterload, as a result of the impact of the increased total stroke volume ejected on systemic vascular resistance, and of the resulting systolic hypertension [15]. Therefore, severe LV dilatation may occur when AR and MR are present together. In addition, the resulting combination of volume and pressure load further increases wall thickness [16]. Thus, the resulting LV hypertrophy will usually be eccentric, with a wall thickness-to-cavity ratio typically < 0.45, and increased sphericity [17]. At the onset of symptoms, patients may have a reduced LV ejection fraction, which can be even worse than that associated with isolated AR or MR [17,18] (Fig. 2).
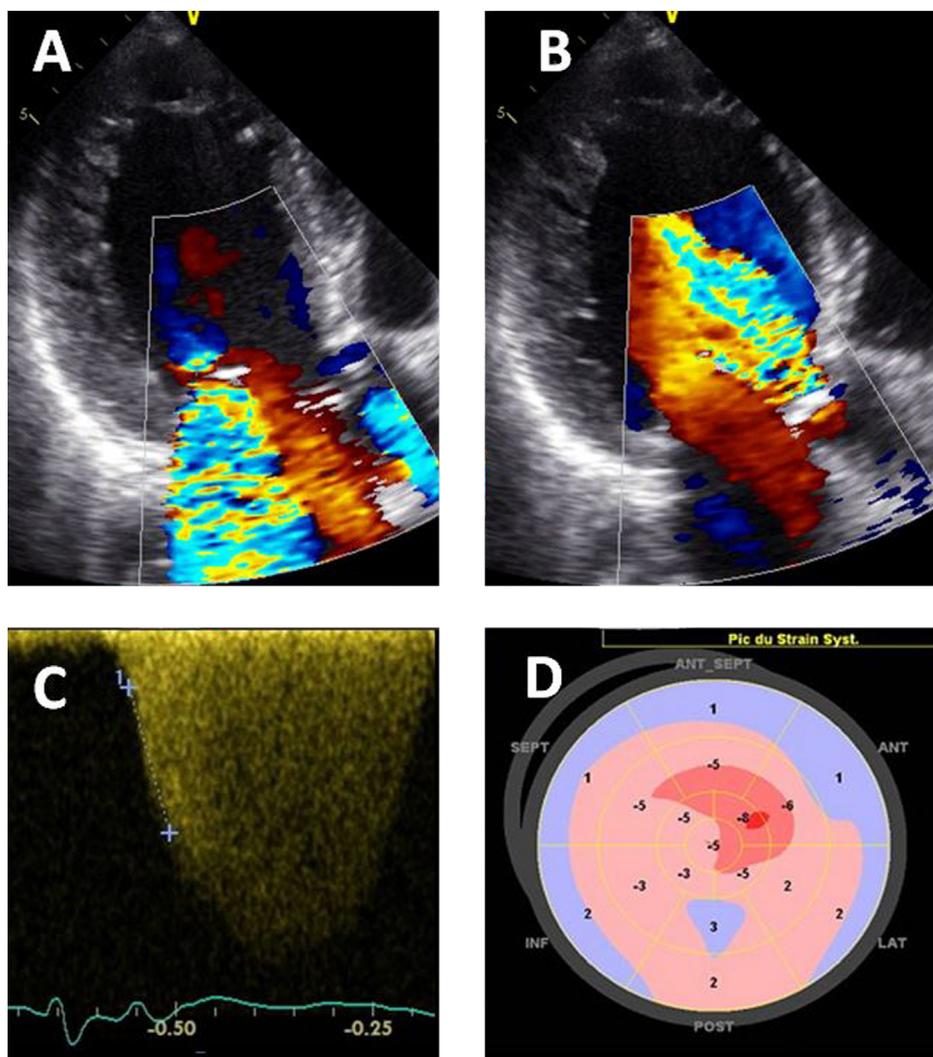
Figure 2. A. Severe mitral regurgitation. B. Severe aortic regurgitation. Left ventricular ejection fraction is 35% (not shown). C and D. Short dP/dt (618 ms; C) and marked reduction in global longitudinal strain (−6.4%; D) are consistent with severe left ventricular dysfunction.

When acute and severe AR develops in patients with pre-existing MR, the marked increase in LV end-diastolic pressure may be transmitted backwards, as premature mitral valve closure no longer limits the amount of flow into the left atrium and pulmonary veins (Fig. 3). The combination of AR and MR predisposes to atrial fibrillation and pulmonary hypertension. As a result of chronic volume and pressure overload, MR is an independent risk factor for reduced survival in patients with severe AR, with mortality increasing with each grade of MR severity [6].

Diagnosis

The proximal isovelocity surface area (PISA) method and the assessment of vena contracta for quantifying regurgitant lesions are lesser load-dependent methods that can be useful in this setting. By contrast, volumetric methods of assessing the severity of MR and AR can be challenging, because left-sided assessment of forward flow is invalid. However, the right ventricular outflow tract can be used as an alternative to assess the net forward flow [3,19]. The pressure half-time can be inaccurate in assessing the severity of AR, and the mitral-to-aortic velocity time integral ratio is inherently unreliable. Cardiac magnetic resonance imaging may be used to quantify regurgitant lesions, particularly when the echocardiographic image quality is inadequate or when echocardiography variables are discordant with clinical assessment [19,20]. However, volumetric methods can also be inaccurate in the presence of multiple regurgitant lesions, as these methods assume that only one valve is affected [21]. Cardiac magnetic resonance imaging may accurately quantify changes in ventricular volumes, mass and function and, hence, by assessing the global burden of the valve regurgitations, may contribute to determining the optimal timing for intervention [20].

No study has evaluated the value of global longitudinal strain in the specific setting of multiple valve disease. However, its role has been consistently highlighted in isolated AR and MR [22,23] and, consequently, it might be recommended for the detection of subclinical LV dysfunction.
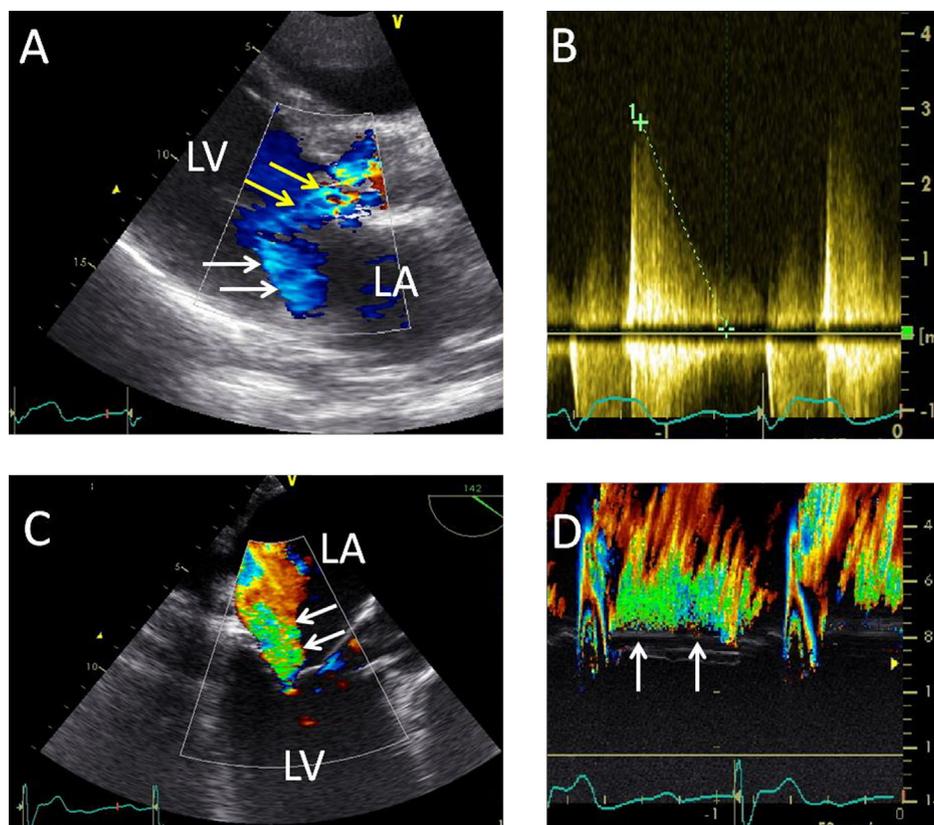
Figure 3. Acute aortic regurgitation (AR) as a result of infective endocarditis. A. Parasternal long-axis view showing concomitant AR (yellow arrows) and mitral regurgitation (MR) (white arrows) during end-diastole. B. The pressure half-time of the AR jet is 108 ms, consistent with severe AR. C and D. Colour Doppler and colour M-mode obtained in the 140° plane by transoesophageal echocardiography, confirming the occurrence of diastolic MR. Diastolic MR results from increased left ventricular diastolic pressure, and reflects premature mitral valve closure. LA: left atrium; LV: left ventricle.

Management

Most published results of double valve replacement for combined AR and MR come from studies focusing on young patients, predominantly with rheumatic heart disease aetiology [17,18,22,24]. Whether older patients with degenerative valve disease, and thus a longer history of valvular regurgitation and a lower life expectancy, would similarly benefit from extensive surgery is largely speculative. In general, the decision to operate on one or both valves depends on the severity of each lesion, but other factors should also be taken into account. The increased operative risk of double valve surgery [25,26] and the increased risk of long-term thrombotic and bleeding complications with multiple mechanical valves [27] should be balanced against the probability of requiring redo surgery and its inherent risk if only one valve is replaced. This decision must therefore take into account many factors, including patient age, co-morbidities and frailty [28]. In addition, expertise in cardiac imaging, cardiac surgery, haemodynamic management, geriatrics and anaesthesia, in the setting of a multidisciplinary heart valve team, is required to optimize management [28].

Effects of aortic valve replacement on the severity of MR

LV function, mass and volumes frequently improve following aortic valve replacement in patients undergoing surgery for severe AR, with a variable time-course response [29]. Thus, when concomitant functional MR is mild to moderate, aortic valve surgery for severe AR is expected to improve MR (Fig. 4). In a study by Lim et al., an improvement in MR severity was observed in 88% of patients, even without concomitant mitral valve annuloplasty, and was paralleled by a reduction in LV end-diastolic dimension [14]. However, whether correction of the volume overload by aortic valve replacement is sufficient to manage severe secondary MR has not yet been established.

Effects of double valve surgery on LV volume and function

As a result of specific loading conditions, LV function frequently decreases after mitral valve replacement for isolated MR, thereby precluding mitral valve surgery in patients with severe LV dysfunction. By contrast, LV function usually
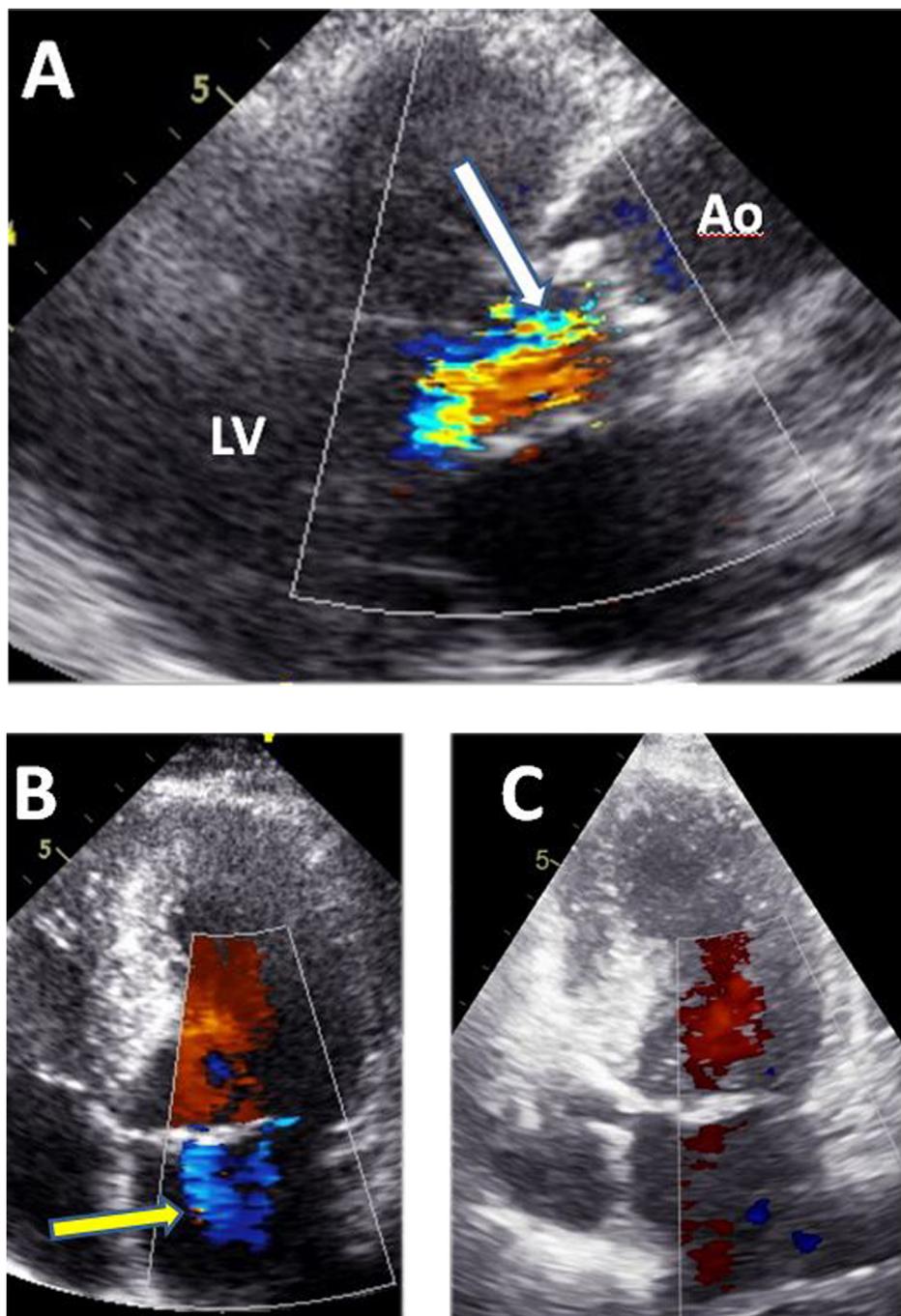
Figure 4. Severe aortic regurgitation. A. Using transoesophageal echocardiography, there is a large vena contracta, consistent with severe aortic regurgitation (white arrow). B. There is concomitant moderate secondary mitral regurgitation, as seen by transthoracic echocardiography (yellow arrow). C. Aortic valve replacement was performed; on the seventh postoperative day, only trace mitral regurgitation remained. Ao: ascending aorta; LV: left ventricle.

improves after aortic valve replacement for isolated AR, so the presence of even a severely depressed LV ejection fraction does not exclude aortic valve replacement. Whether double valve surgery for combined AR and MR improves or worsens LV performance is thus an important issue. Essop et al. compared the effects of double valve replacement for combined AR/MR with those of mitral valve replacement for isolated MR. A similar reduction in end-diastolic diameter was observed, but, 3 months after surgery, a larger

reduction in end-systolic diameter after double valve surgery was associated with a smaller deterioration in ejection fraction [30]. This observation suggests that levels of ejection fraction that preclude surgery for isolated MR might still be acceptable for double valve replacement for AR/MR [30]. However, discrepant results were reported by Gentles et al. [17]. In a child and young adult population, the development or persistence of postoperative LV dysfunction (defined as a Z-score < −2) occurred significantly
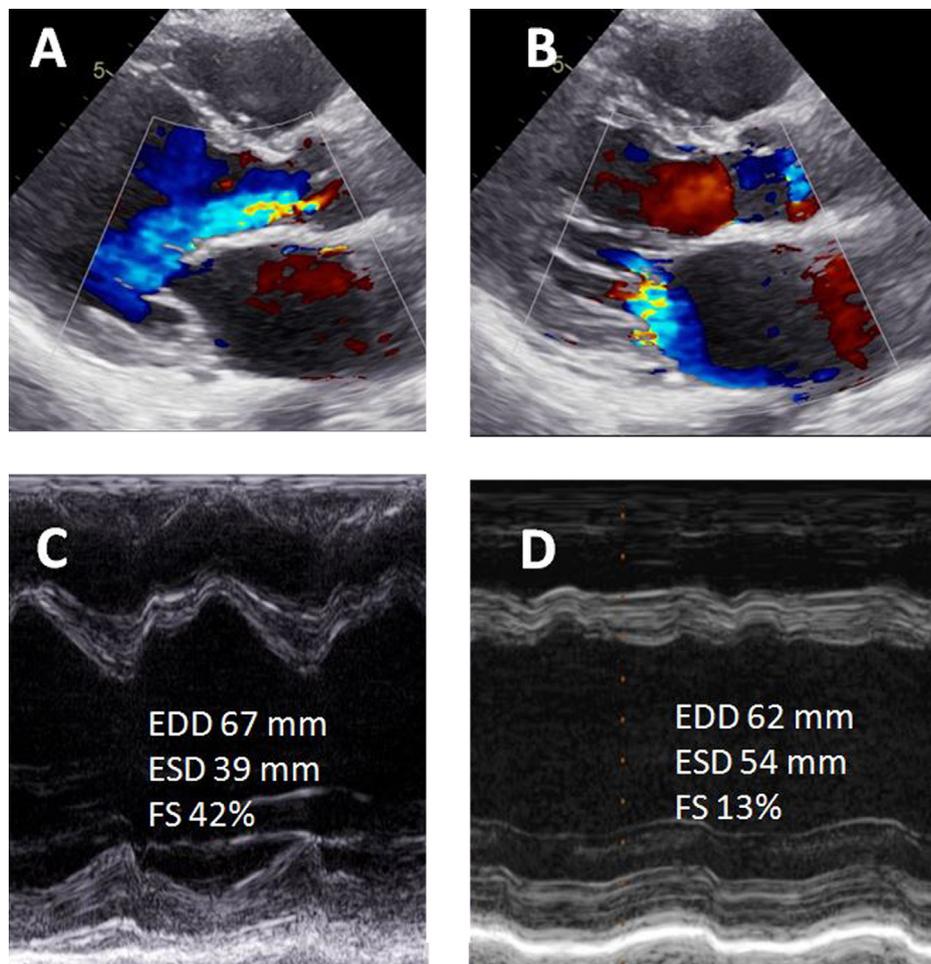
Figure 5.   A. and B. Diastolic and systolic parasternal long-axis views showing severe AR and moderate-to-severe MR, respectively. C and D. Despite being preserved before surgery (C), fractional shortening is markedly decreased following double valve replacement (D). EDD: end-diastolic diameter; ESD: end-systolic diameter; FS: fractional shortening.

more often after double valve surgery (84.4%) than after isolated aortic valve replacement for AR (35.7%) or isolated mitral valve replacement for MR (57.1%) [17] (Fig. 5). The better results from Essop et al. were attributed to a shorter duration of volume loading, thereby emphasizing the role of early surgical management [30]. Importantly, Skudicky et al. observed that, despite initial deterioration, LV ejection fraction tended to normalize 1 year after surgery [24]. Moreover, LV ejection fraction and end-systolic diameter were identified as independent predictive factors for postoperative systolic performance [24]. The probability of having an ejection fraction < 50% after a mean follow up of 40 months rose significantly when the preoperative ejection fraction was < 60%, and/or when the LV end-systolic diameter was > 40 mm [24]. There is currently no definite lower threshold that would contraindicate a double valve procedure, particularly if AR is predominant.

Surgery and prognosis

In a study dating back to the early 1990s, Niles et al. reported that patients with double valve replacement had significantly reduced postoperative survival, and more frequently reported persistent postoperative symptoms than patients who underwent surgery for single valve disease [18]. More recently, Pai et al. reported on a series of 191 patients with severe AR and concomitant grade 3—4+ MR. Among them, 65 patients underwent aortic valve replacement, and had significantly better survival than patients who did not have aortic valve replacement [6]. Importantly, among these patients, 39 had concomitant mitral valve surgery and 26 had only isolated aortic valve surgery. In this limited series, a survival benefit was observed only in the subgroup that had undergone mitral valve repair (17 patients). Similar benefits of mitral valve repair have been observed in retrospective series that included patients who had surgery for both AR and MR [31,32], but studies have also been published in which no benefit of mitral repair over replacement was shown [33,34]. Prospective data addressing this issue are currently lacking. Combined aortic and mitral valve repair has occasionally been attempted, yielding acceptable long-term survival rates, but with the drawback of limited durability, leading to a 10-year reoperation rate of 35% [35].
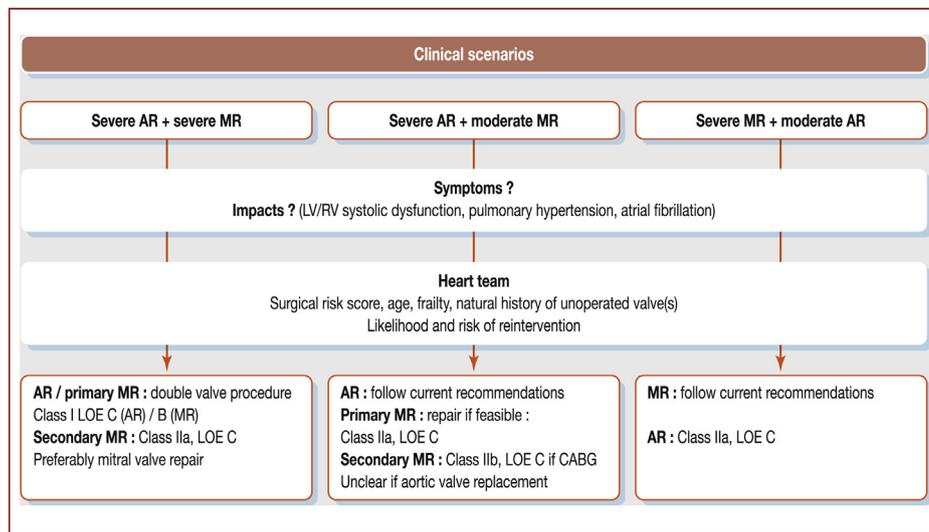
Figure 6.   Management strategy according to the severity of aortic regurgitation (AR) and of mitral regurgitation (MR), according to the American Heart Association/American College of Cardiology guidelines for the management of patients with valvular heart disease [2]. CABG: coronary artery bypass grafting; LOE: level of evidence; LV: left ventricular; RV: right ventricular.

Management according to lesion severity

Current literature lacks evidence-based management strategies, as emphasized by the C level of evidence supporting most recommendations in the current guidelines from Europe and the USA [1,2]. No medical treatment has proved beneficial for isolated or combined AR and MR. However, as is recommended in isolated AR, high blood pressure should be corrected using vasodilators, and diuretics may play an important role in reducing congestion and symptoms in patients with combined AR and MR for whom surgery is not feasible. Conventional heart failure treatments, including angiotensin-converting enzyme inhibitors, beta-blockers and mineralocorticoid receptors antagonists, should not be used in asymptomatic patients without LV dysfunction to avoid delay in symptom onset and, hence, in referral to surgery, but should be considered appropriate in patients not considered for surgery, or if symptoms and/or LV dysfunction persist or develop after surgery.

In clinical practice, the combination of AR and MR usually presents as one of the following scenarios: (1) the two regurgitations are severe; (2) AR is severe and MR is moderate; or (3) MR is severe and AR is moderate. Mild lesions need only watchful waiting. A management strategy adapted from current American Heart Association/American College of Cardiology (AHA/ACC) guidelines is presented in Fig. 6 [2].

Scenario 1: The two lesions are severe

In this setting, both lesions should be treated. Mitral valve repair or replacement in patients with chronic severe primary MR undergoing aortic valve replacement has received a Class I recommendation (level of evidence B), but has a Class IIa recommendation (level of evidence C) for secondary MR. Aortic valve replacement has a Class I recommendation (level of evidence C) for patients with severe AR while undergoing surgery for MR.

Scenario 2: AR is severe and MR is moderate

Severe AR should be managed according to current guidelines. However, whether moderate MR should be treated concomitantly remains controversial. Indeed, no survival benefit has been demonstrated after the surgical treatment of moderate secondary MR in prospective studies. Mitral valve repair in patients with moderate secondary MR undergoing coronary artery bypass surgery therefore has a Class IIb recommendation (level of evidence C) in current AHA/ACC guidelines. Moreover, the likelihood of MR improving following aortic valve replacement is high, making the need to treat MR in this setting even more questionable. Despite the lack of a randomized comparison between valve replacement and repair, it is widely accepted that, when feasible, valve repair is the preferred treatment for moderate primary MR. Therefore, concomitant mitral valve repair is considered reasonable in patients with chronic moderate primary MR undergoing cardiac surgery for other indications (Class IIa, level of evidence C).

Scenario 3: MR is severe and AR is moderate

Severe MR should be managed according to current guidelines. Correcting moderate AR at the time of mitral valve surgery is considered as reasonable in the AHA/ACC guidelines (Class IIa, level of evidence C), because of the likelihood of progressive worsening of AR over time.

Occasionally, two moderate lesions may have deleterious clinical repercussions, including symptoms, LV dilatation with or without dysfunction, reduction in net forward flow, increased natriuretic peptide concentrations and/or impaired exercise tolerance with maximal oxygen consumption (Fig. 7). To the best of our knowledge, no study has assessed the impact of combined moderate AR and moderate MR, and this scenario is not addressed in current guidelines. Nevertheless, such patients should undergo a thorough assessment of the global repercussions of the two regurgitant lesions. If the results are consistent with
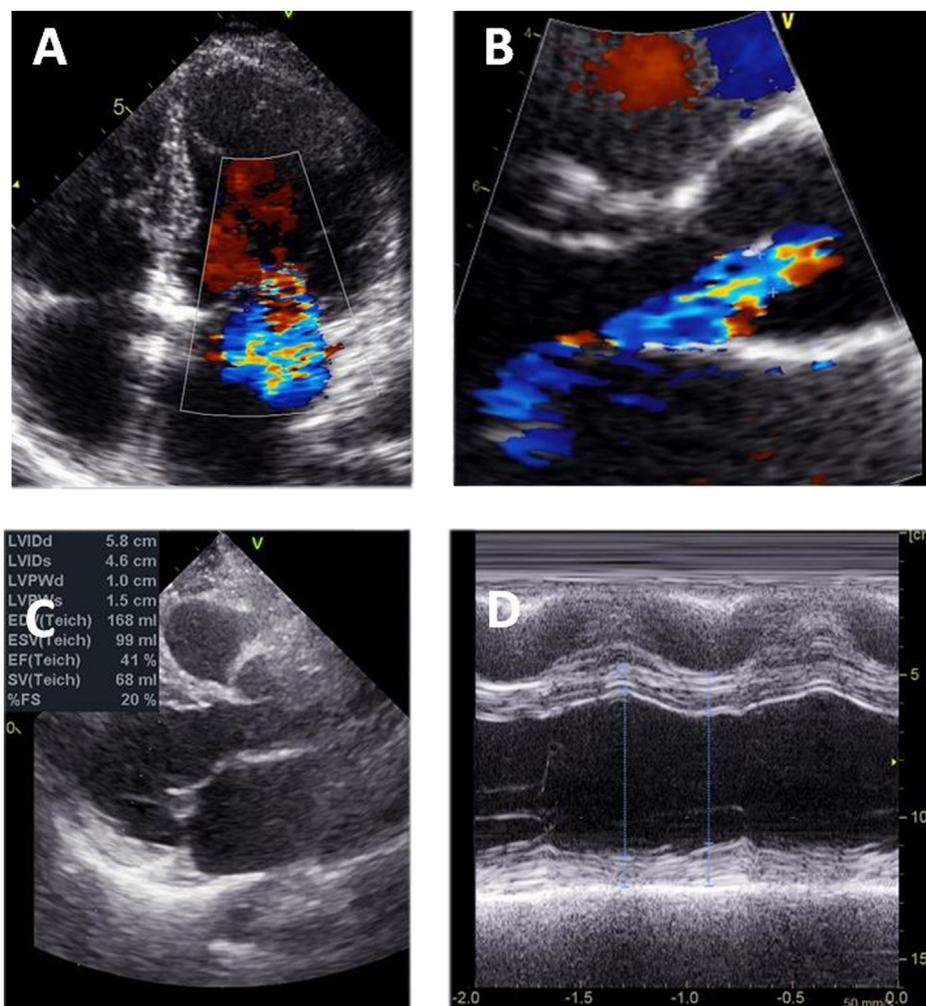
Figure 7. A and B. Rheumatic heart disease, including moderate mitral regurgitation (mitral effective regurgitant orifice 0.25 cm^2; A) and moderate aortic regurgitation (vena contracta 5 mm; B). C and D. Although each lesion is separately considered moderate, the left ventricle is mildly dilated (end-diastolic diameter 58 mm), consistent with a significant global impact of the two regurgitations.

a significant global haemodynamic impact, valve repair or replacement might be considered, but this strategy requires careful exclusion of confounding factors, including chronic lung disease and primary ventricular dysfunction.

The management of asymptomatic patients in the setting of combined AR and MR also lacks evidence-based support. If the two lesions are severe, the stricter thresholds of MR should be used to indicate surgery, including a LV end-systolic diameter ≥ 40 mm and/or a LV ejection fraction < 60% [1,24]. If MR or AR is predominant, the respective thresholds in current guidelines should be used [1,2], but even subtle evidence for LV dysfunction, including reduced global longitudinal strain, might be considered as an incentive for earlier surgery. As mentioned above, an assessment of the global repercussion should be strongly considered, including exercise testing to detect pseudoasymptomatic patients.

Role of transcatheter interventions

Percutaneous repair of MR has been shown to be safe and efficacious [36]. Although it has not yet become standard practice, there is recent evidence that transcatheter aortic valve replacement may be feasible in patients at high surgical risk with native valve AR [37]. However, the use of a fully transcatheter approach for the two conditions remains exceptional. In a recent literature review, Ando et al. identified 37 studies including 60 patients considered to be at high or inoperable surgical risk who had combined transcatheter aortic and mitral valve intervention. Among these, four patients (7%) had both AR and MR, three of whom had undergone at least one valve-in-valve procedure. Only one patient had a fully transcatheter approach performed on native valves [38,39].

Conclusions

There are limited data to guide the management of combined AR and MR. LV dysfunction is frequent at initial presentation and postoperative LV dysfunction is common, suggesting that surgical management should not be delayed, particularly when symptoms occur or when there is evidence of LV dysfunction. As with other combined valve disease

combinations, all decisions should be made by a multidisciplinary heart team in order to optimize patient outcomes. The role of transcatheter approaches is currently limited, but technological advances will probably soon change the management paradigm.

Disclosure of interest

The authors declare that they have no competing interest.

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