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REVIEW ARTICLE

Mitral regurgitation in heart failure with preserved ejection fraction: The interplay of valve, ventricle, and atrium

Sebastiaan Dhont[1,2,3], Gitte van den Acker[4], Tim van Loon[4], Frederik H. Verbrugge[5,6], Jan Verwerft[1,7], Sébastien Deferm[2,8], Timothy W. Churchill[9], Wilfried Mullens[1,2,3], Joost Lumens[4†], and Philippe B. Bertrand[1,2,3*†]

[1]Faculty of Medicine and Life Sciences, LCRC, Hasselt University, Diepenbeek, Belgium; [2]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [3]Department of Future Health, Ziekenhuis Oost-Limburg, Genk, Belgium; [4]Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands; [5]Center for Cardiovascular Diseases, University Hospital Brussels, Jette, Belgium; [6]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium; [7]Department of Cardiology, Jessa Hospital, Hasselt, Belgium; [8]Department of Cardiology, Inselspital Bern, Bern, Switzerland; and [9]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA

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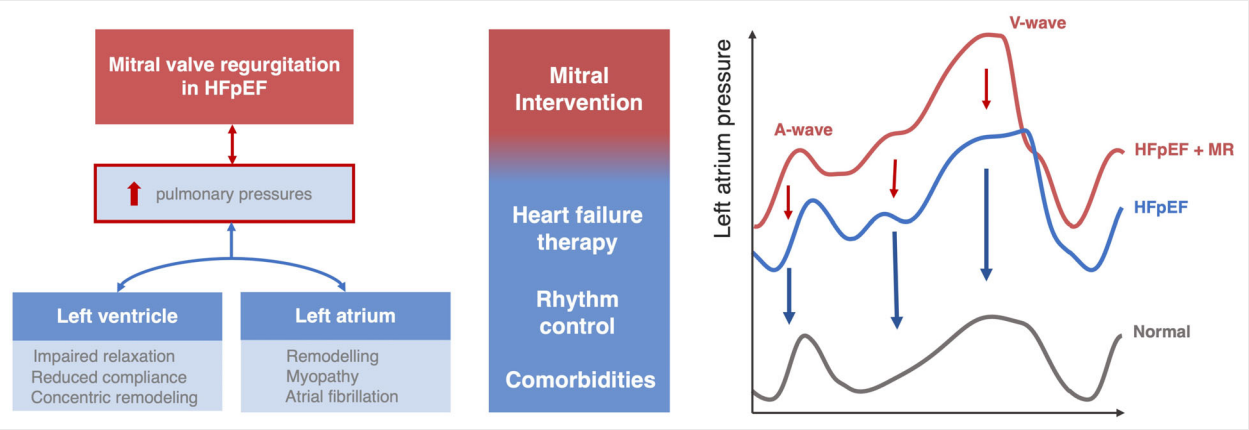
Mitral regurgitation (MR) is highly prevalent among patients with heart failure and preserved ejection fraction (HFpEF). Despite this combination being closely associated with unfavourable outcomes, it remains relatively understudied. This is partly due to the inherent heterogeneity of patients with HFpEF. To address this gap, dissecting HFpEF into mechanism-based phenotypes may offer a promising avenue for advancing our comprehension of these complex intertwined conditions. This review employs the validated CircAdapt model to explore the haemodynamic implications of moderate to severe MR across a well-defined spectrum of myocardial disease, characterized by impaired relaxation and reduced myocardial compliance. Both heart failure and mitral valve disease share overlapping symptomatology, primarily attributed to elevated pulmonary pressures. The intricate mechanisms contributing to these elevated pressures are multifaceted, potentially influenced by diastolic dysfunction, left atrial myopathy, and MR. Accurate evaluation of the haemodynamic and clinical impact of MR necessitates a comprehensive approach, taking into account the characteristics of both the left atrium and left ventricle, as well as their intricate interactions, which may currently be underemphasized in diagnostic practice. This holistic assessment is imperative for enhancing our understanding and refining therapeutic strategies within this patient cohort.

*Corresponding author. Ziekenhuis Oost-Limburg, Synaps Park 1, 3600 Genk, Belgium. Tel: +32 473824294, Email: philippe.bertrand@zol.be

†Contributed equally as co-senior authors.

Graphical Abstract



The interplay of MR and HFpEF: understanding increased pulmonary pressures and strategies for management. HFpEF, heart failure with preserved ejection fraction; MR, mitral valve regurgitation.

Keywords Heart failure with preserved ejection fraction • Mitral regurgitation • Diastolic dysfunction • Pressure–volume loops

Introduction

Heart failure with preserved ejection fraction (HFpEF) comprises at least 50% of all heart failure patients and is projected to impose an escalating burden on our healthcare in the near future.[1–3] Mitral regurgitation (MR) is frequently encountered in patients with HFpEF, largely attributed to atrial enlargement (called atrial functional MR [AFMR]) and age-related structural valve degeneration.[4,5] This is substantiated by data from the European Society of Cardiology Heart Failure Long-Term registry[5] and the study by Bartko *et al.*[6] The former registry documents that 19.5% of patients with HFpEF ($n = 1462$) experience moderate or severe MR, while Bartko *et al.*'s cohort study ($n = 7362$) reports a varied prevalence, with severe MR in 5% of patients with HFpEF, moderate in 61%, and mild or none in 34%. Unlike functional MR in heart failure with reduced ejection fraction (HFrEF), the role of MR in HFpEF remains underexplored.[7] Although even mild MR in HFpEF is closely linked with unfavourable outcomes, it remains unclear whether MR is causally contributing or merely a marker of atrioventricular disease severity.[4,8–11]

Exertional dyspnoea is the predominant symptom observed in both patients with HFpEF and patients with significant MR, which is assumed to arise from elevated pulmonary pressures leading to pulmonary oedema and eventually to right ventricular failure.[12,13] The challenge lies in discerning the exact underlying mechanisms responsible for these increased upstream pressures, potentially influenced by left ventricular (LV) diastolic dysfunction, left atrial (LA) myopathy, and/or the mitral regurgitant flow. The identification and treatment of the culprit lesion(s) are crucial for effective clinical management and prognosis. *Figure 1* illustrates the clinical scenario of a patient with HFpEF and MR, as increasingly encountered in daily clinical practice. One challenge is that LV diastolic dysfunction and a diseased left atrium by itself can result in prominent v-waves due to abnormal atrioventricular coupling.[14] On the other hand, in the setting of a less compliant left atrium, even mild to moderate MR can have significant haemodynamic implications.[15,16]

To enhance the therapeutic strategies for MR in HFpEF, it is essential to gain a more comprehensive understanding of the haemodynamic impact, the underlying pathophysiological mechanisms, and the intricate interplay between the valve and myocardium. The growing importance of this issue is underscored by the extensive range of percutaneous interventions currently available, expanding treatment eligibility to include frail patients with HFpEF, who frequently have numerous comorbidities, for interventions aimed at reducing MR. Consequently, it is crucial to rigorously select those patients who are most likely to derive significant benefit from these costly therapeutic procedures. This review aims to critically explore the haemodynamic consequences of MR in HFpEF by reviewing existing literature and employing a validated computer haemodynamic simulation environment.

Stratifying heart failure with preserved ejection fraction into haemodynamic phenotypes

Patients with HFpEF typically exhibit varying degrees of atrioventricular disease with diastolic dysfunction and elevated

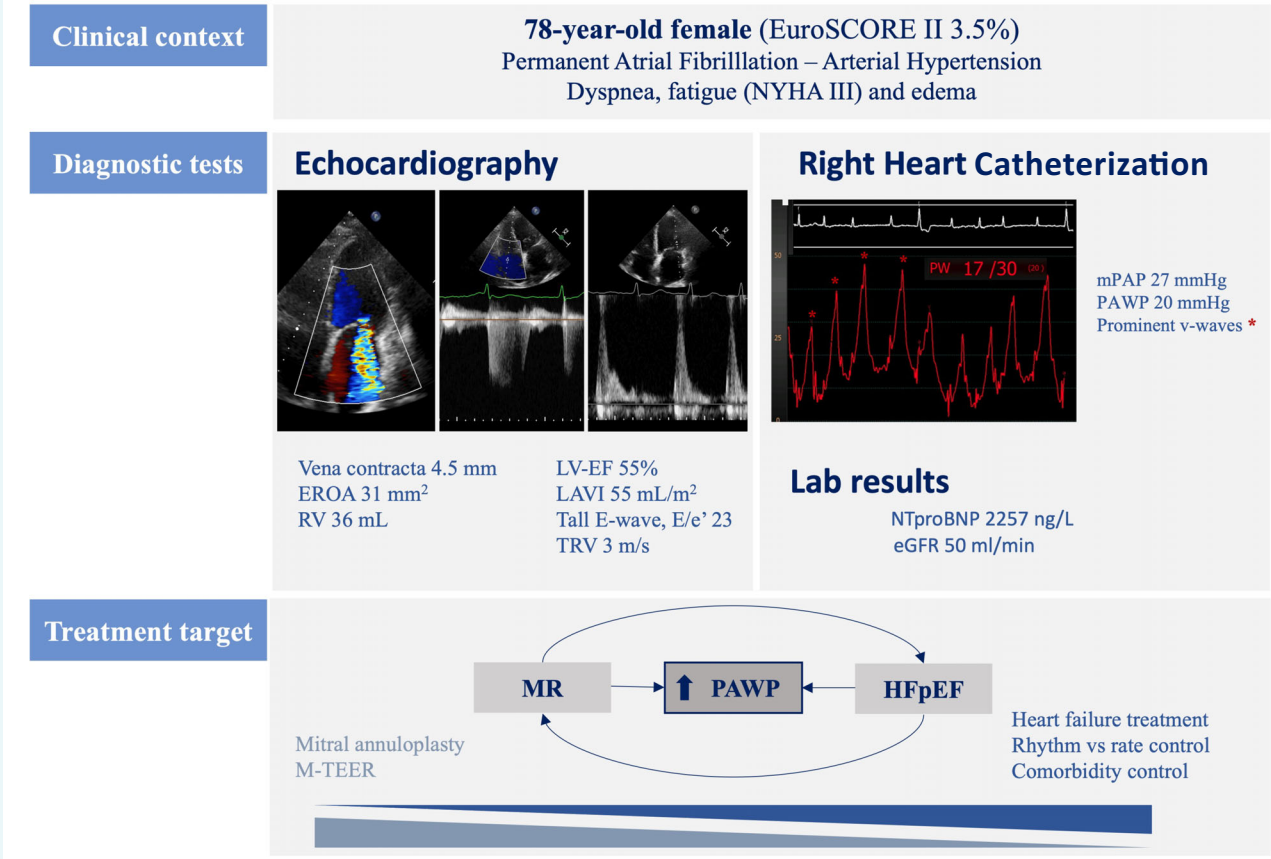


Figure 1 Evaluating the clinical challenges of treating the mitral valve in symptomatic heart failure with preserved ejection fraction (HFpEF) with moderate to severe mitral regurgitation (MR). EROA, effective regurgitant area; eGFR, estimated glomerular filtration rate; LAVI, left atrial volume index; LV-EF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; M-TEER, mitral transcatheter edge-to-edge repair; NTproBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAWP, pulmonary arterial wedge pressure; RV, regurgitant volume; TRV, tricuspid regurgitant jet velocity.

filling pressures as central components. To better comprehend the haemodynamic impact of MR, we further categorize HFpEF as predominant atrial, ventricular, or a mixed phenotype as shown in *Figure 2*. For instance, what appears to be moderately volumetric MR may exhibit significant haemodynamic severity when occurring alongside a non-compliant left atrium. This can exacerbate LA hypertension and its downstream adverse effects.[11] Conversely, addressing moderate or severe MR in patients with prominent stiffening of the left ventricle and diastolic dysfunction may not substantially affect left-sided filling pressures, offering limited symptomatic and prognostic benefits. This complex diagnostic scenario requires an integrated systems physiology approach that elucidates the functional interplay between the diseased valve and its surrounding environment.

For the purpose of this review, we utilized the validated CircAdapt model to explore haemodynamics in patients with HFpEF. Briefly, the CircAdapt model of the human cardiovascular system offers a digital platform for well-controlled quantitative analyses of cardiac haemodynamics for a diverse range of boundary conditions.[17–20] *Figure 3* illustrates normal atrial and ventricular pressure–volume loops, as simulated by the default CircAdapt model. In the following paragraphs, we will use this platform to explore haemodynamic consequences of moderate to severe MR (effective regurgitant orifice area [EROA] of 30 mm^2) across a comprehensive and well-defined spectrum of myocardial diseases. This spectrum includes conditions characterized by impaired relaxation and reduced myocardial compliance in both atrial and ventricular myocardium. Consequently, HFpEF is defined here from a haemodynamic perspective as increased myocardial stiffness, rather than as a clinical syndrome.

Mitral regurgitation in normal setting

Regurgitant mitral flow interrupts the normal isovolumetric contraction of the ventricle, resulting in a decrease in LV volume during systolic pressure build-up (*Figure 4*). During the subsequent ejection phase, which is often prolonged in patients with MR, the overall LV afterload is diminished given the low pressure LA backflow, also contributing to a decrease of end-systolic volume (ESV). In patients with severe MR undergoing percutaneous mitral

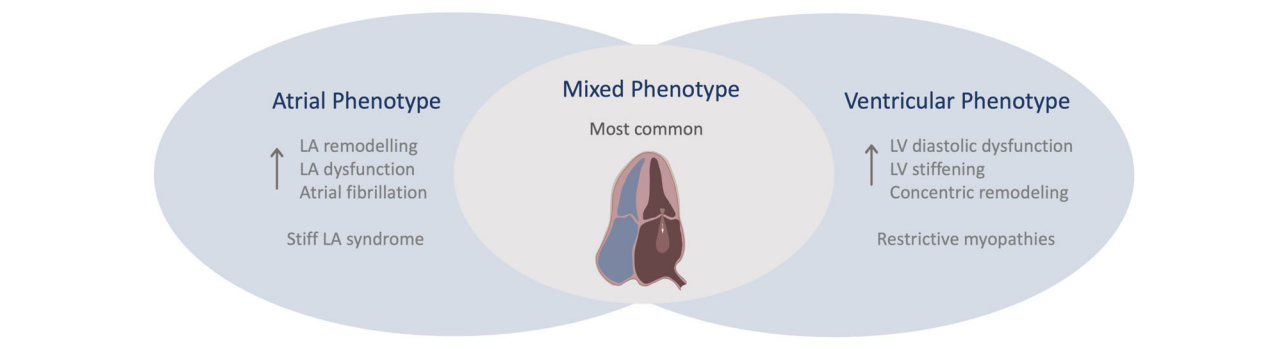


Figure 2 Stratifying heart failure with preserved ejection fraction into haemodynamic predominant phenotypes. LA, left atrial; L, left ventricular.

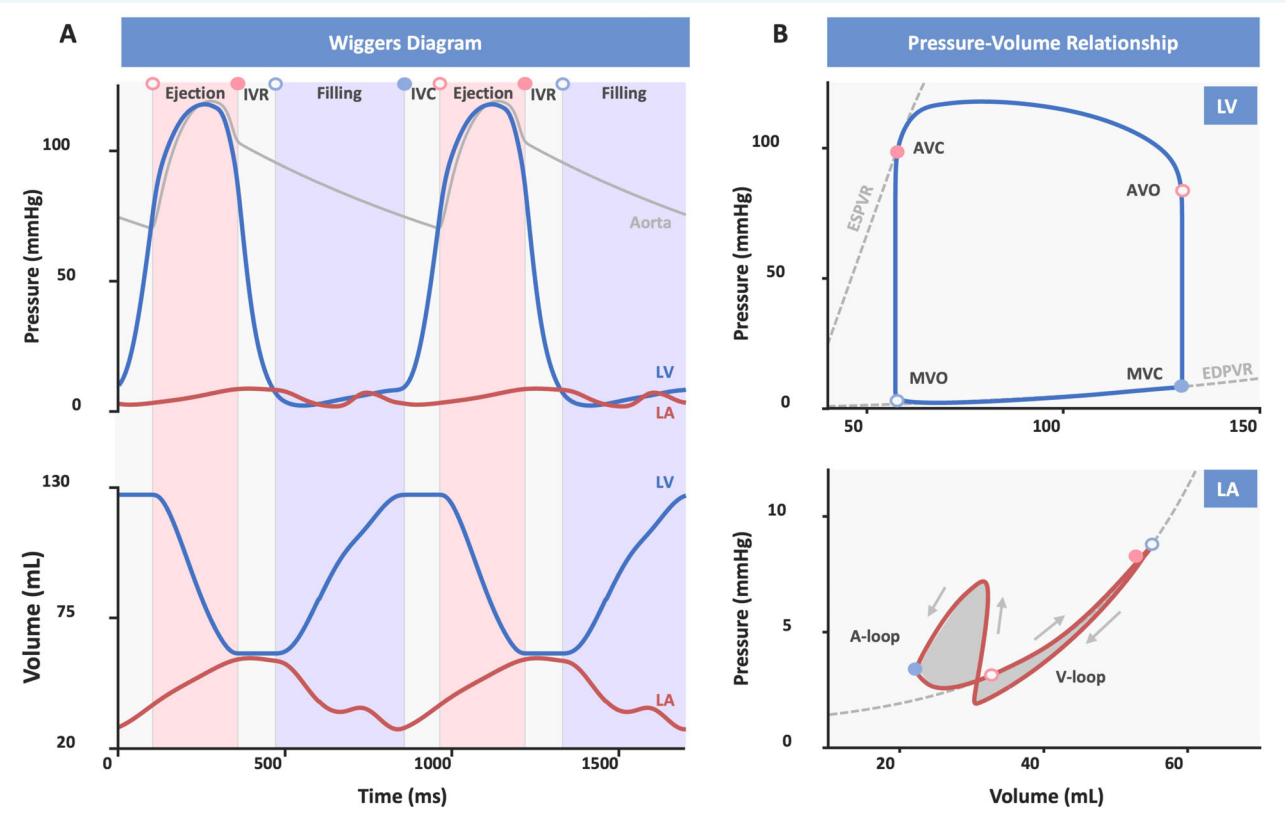


Figure 3 Normal left ventricular and left atrial pressure–volume loops using the CircAdapt model. (*A*) Wiggers diagram with pressure and volume tracing as a function of time during the cardiac cycle. (B) Left ventricular (top) and left atrial (bottom) pressure–volume loop. A-loop, atrial loop; AVC, aortic valve closure; AVO, aortic valve opening; EDPVR, end-diastolic pressure volume relationship; ESPVR, end-systolic pressure volume relationship; IVC, isovolumetric contraction; IVR, isovolumetric relaxation; LA, left atrium; LV, left ventricle; MVC, mitral valve closure; MVO, mitral valve opening; V-loop, ventricular loop.

transcatheter edge-to-edge repair (M-TEER), haemodynamic assessment before and after the procedure indeed demonstrated a significant increase in ESV by a mean of 11 ml ($p = 0.006$) immediately after M-TEER.[21] Moreover, an increase in ESV, as clinically monitored by the end-systolic diameter (≥40 mm) serves as an important prognostic marker and a compelling indication of deteriorating coping mechanisms, necessitating intervention.[22]

During the filling phase, the endless loop of volume overload leads to an augmentation in LV end-diastolic volume, which is initially well tolerated in a compliant left ventricle given the non-linear end-diastolic pressure–volume relationship (EDPVR). As per the Frank–Starling mechanism, the elevated preload plays a pivotal role in global LV performance.[23] The net effect of these changes is an increased width and corresponding area of

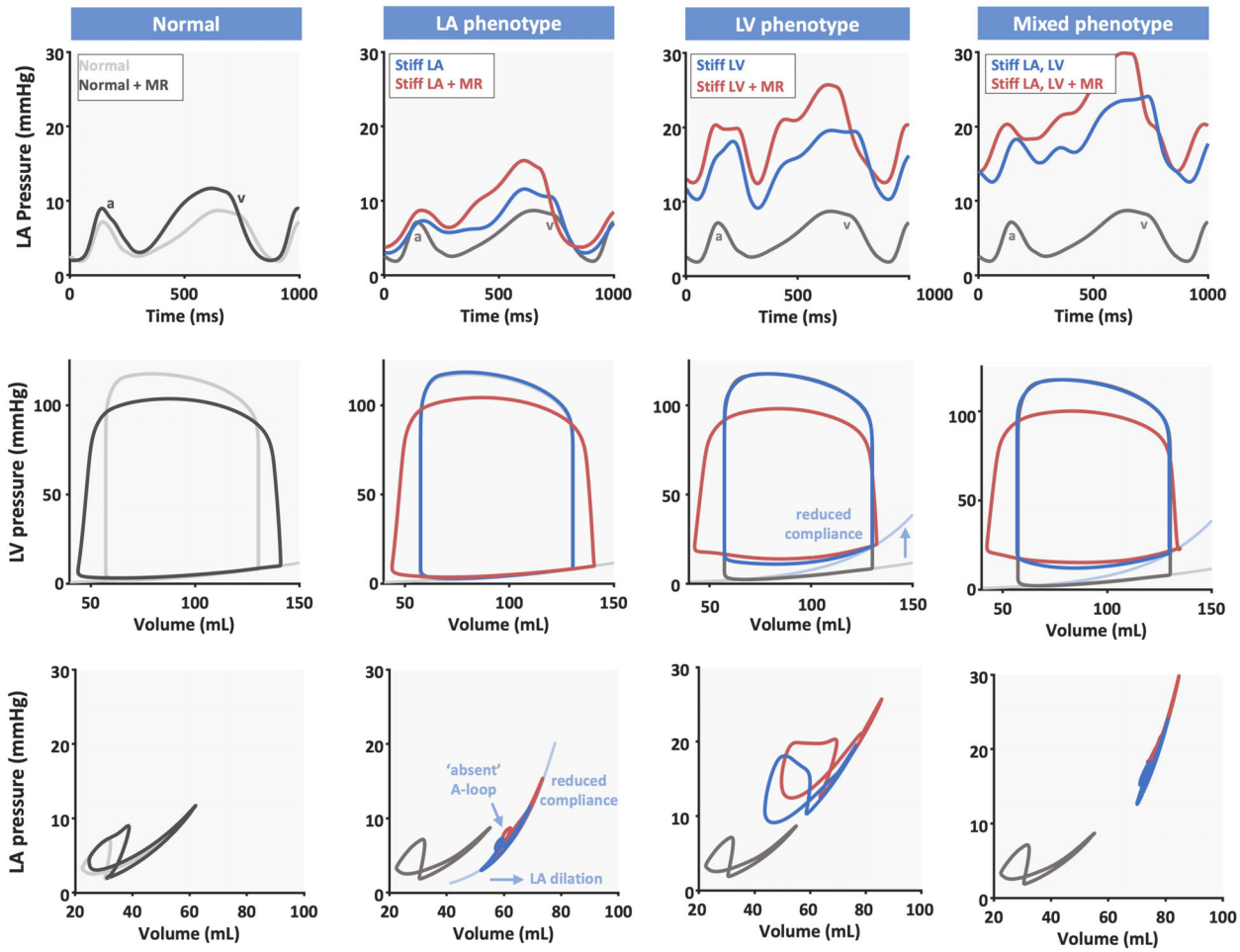


Figure 4 Comparison of left ventricular and left atrial pressure–volume loops and tracings in normal hearts, left atrial and left ventricular phenotypes without and with mitral regurgitation (MR). A-loop, atrial loop; LA, left atrium; V-loop, ventricular loop.

the pressure–volume loop, augmenting total stroke volume and (misleading) supranormal LV ejection fraction. Gaemperli *et al.*[21] observed an immediate reduction in ejection fraction from 55% to 42% following M-TEER. This reduction was attributed to a substantial 21% increase in afterload. Despite this, cardiac output increased by 0.9 L/min, and load-independent parameters of LV contractility, such as end-systolic pressure–volume relationship, were not significantly affected.

In the setting of a compliant left atrium and left ventricle, the v-wave induced by a moderate MR jet is restricted in its impact on pulmonary artery wedge pressure (PAWP), owing to the proficient LA buffer and the effective volume handling capabilities of the left ventricle. Furthermore, after MR reduction (as depicted in *Figure 3*), the limited v-wave completely vanishes. In the study by Gaemperli *et al.*,[21] where 48% had degenerative MR and the mean ejection fraction was 50%, a mean reduction of the v-wave by 7 mmHg (from 22 to 14 mmHg, $p = 0.001$) was reported immediately after M-TEER.

Thus, within a well-functioning surrounding environment, moderate to severe MR can be adequately accommodated through LA and LV adaptation.

Mitral regurgitation in heart failure with preserved ejection fraction with predominant ventricular phenotype

In patients with impaired LV compliance, as commonly observed in HFpEF, the EDPVR displays an upward and leftward shift.[24,25] As a consequence, even minor alterations in volume overload, such as the presence of moderate MR, can elicit substantial pressure fluctuations as illustrated in the simulation environment when predominant LV stiffness is modelled (*Figure 4*).[2,17,24,26] The significant rise in end-diastolic pressure (EDP) imparts resistance to ventricular filling and is subsequently transmitted to the left atrium, which now operates at a higher pressure setpoint.

This phenomenon is prominently illustrated in the LA pressure–volume loop, wherein a global rightward shift is evident

while adhering to the intrinsic (non-linear) EDPVR curve. Furthermore, the biphasic pattern, reflective of the combined influences from atrial and ventricular contractions, remains well-preserved. These increased pressure levels superimpose over the MR jet, serving as a crucial factor in long-term LA remodelling. Nonetheless, owing to the left atrium's sustained functional capacity, it still effectively buffers the moderate MR.

While the v-wave becomes more prominent, the overall influence on pulmonary pressures remains restricted in comparison to simulated HFpEF patients without MR. Indeed, the haemodynamic HFpEF study by Tamargo *et al.*[11] showed that the v-wave amplitude at rest was higher in a HFpEF cohort with versus without mild to moderate MR (25 ± 10 vs. 19 ± 8 mmHg) while the difference in mean wedge pressure was rather small (17 ± 6 vs. 15 ± 5 mmHg). This understanding holds the potential to facilitate therapeutic management, as while the superimposed MR jet can exacerbate the v-wave amplitude, it does not overwhelm the left atrium's buffering capacity. The primary concern in these patients remains the elevated EDP.

Mitral regurgitation in heart failure with preserved ejection fraction with predominant atrial phenotype

Isolated atrial myopathies, encompassing predominant atrial amyloidosis, autosomal-recessive atrial cardiomyopathies, as well as atrial fibrillation (AF) and ablation-induced atrial scar, have been recognized as aetiological factors contributing to HFpEF, ultimately culminating in the manifestation of severe atrial standstill and stiff LA syndrome.[27] In the simulated LA pressure–volume loop (*Figure 4*), these observations manifest as a pronounced steepening of EDPVR and a notable reduction in atrial contribution or A-loop, consequently leading to the loss of its characteristic biphasic pattern as evidenced in HFpEF dogs with predominant atrial HFpEF.[28]

The presence of additional MR in this poorly functioning left atrium induces a rightward shift and further accentuates the influence of the left ventricle.[29–34] However, it is noteworthy that the upward shift (pressure increase) is of a mild to moderate degree, primarily due to the efficient diastolic transfer of volume and pressure to the compliant left ventricle. In a study conducted by Inciardi *et al.*,[34] it was demonstrated that the connection between EROA and pulmonary pressures in heart failure patients (mean ejection fraction of 52%) was significantly influenced by LA function, as evaluated through non-invasive strain imaging (p-value for interaction < 0.001). In patients with a normal peak atrial longitudinal strain exceeding 30%, there was no correlation between an increase in EROA and pulmonary pressures. Conversely, in patients with lower peak atrial longitudinal strain, a progressive rise in EROA showed a significant correlation with increased pulmonary pressures.[34]

The invasive v-wave assessment proves to be neither sensitive nor specific, rendering it an imprecise measure for assessing MR severity in patients with HFpEF and atrial dysfunction.[14,35] The poorly compliant left atrium alone can induce a v-wave during ventricular contraction, which becomes evidently more pronounced with the superimposition of MR (*Figure 3*). In the study of Tamargo *et al.*,[11] the presence of mild to moderate MR tended to associate with adverse outcome (log-rank $p = 0.08$), but this appeared to be largely due to the coexistence of LA dysfunction (log-rank $p = 0.0001$) stressing the importance of considering the left atrium when evaluating MR.

Mitral regurgitation in heart failure with preserved ejection fraction with mixed phenotype

The majority of HFpEF patients exhibit involvement of both the atrial and ventricular compartments as remodelling occurs as a continuous and interconnected process, thereby making it challenging to ascertain the individual impact of each component. Advancements in imaging techniques and a growing focus on adopting a multimodality approach hold promise in enhancing this integrative approach.

The simulated LA pressure tracing in the combined phenotype (*Figure 4*) presents intriguing features. In comparison to the normal condition, the left atrium functions at an elevated pressure setpoint due to heightened LV end-diastolic pressure. Moreover, the intrinsic functions of the left atrium are compromised, evident from the impaired waveforms including the disappearance of the A-loop with minimal atrial contribution. Notably, the v-wave remains prominent, even in the absence of moderate MR.

This highlights the clinical conundrum that merely addressing the regurgitant jet will not lead to normalization of LA pressures, which has become a noteworthy concept in routine clinical practice due to the increasing utilization of percutaneous interventions within HFpEF. Although successful reduction in MR has been documented in observational studies of mitral interventions, the primary therapeutic objective remains the reduction of LA pressure to enhance both symptoms and outcomes. In addition, it is important to mention that the association between LA pressure, PAWP, symptomatic presentation and exercise capacity may not be linear.[36] The pathophysiology in this context is significantly influenced by factors including pulmonary vasculature dynamics and the ability of the right ventricle to adapt to heightened pressures.

Management of mitral regurgitation in patients with heart failure with preserved ejection fraction

Building upon the pathophysiological insights discussed earlier and illustrated in *Figure 4*, we strongly advocate for a thorough assessment and treatment of the underlying HFpEF before considering these patients for mitral valve intervention (*Figure 5*). This approach parallels the perspective in HFrEF, where functional MR is recognized as secondary to underlying ventricular disease, demanding a dedicated heart failure treatment. Interestingly, current clinical practice guidelines for valve disease do not discriminate between ventricular and atrial functional MR.[37]

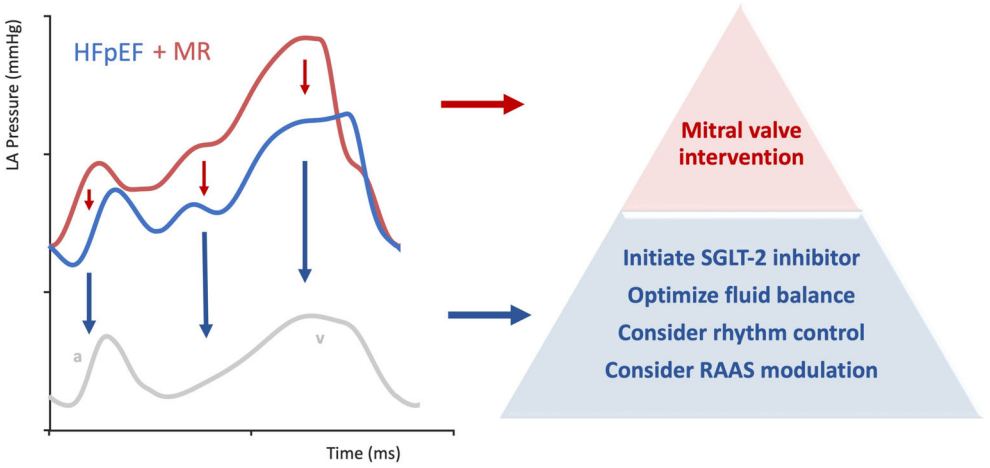


Figure 5 Proposed treatment strategy of mitral regurgitation (MR) in heart failure with preserved ejection fraction (HFpEF). LA, left atrium; SGLT-2, sodium–glucose cotransporter 2; RAAS, renin–angiotensin–aldosterone system.

Pharmacological approach

An optimal fluid balance is of paramount importance as diuretics can rapidly alter pulmonary congestion in HFpEF by mitigating the steep rise in pressures in the higher EDPVR range.[38] Additionally, diuretics may augment the closing forces on the mitral valve by reducing LA pressure more than LV pressure.[39] During decongestion in HFpEF, Ennezat *et al.*[40] found that there was an average decrease of mitral regurgitant volume and EROA of 11 ml and 8 mm^2, respectively. An analysis of the BIOSTAT-CHF registry showed that adhering to guideline-recommended medical therapy for HFrEF in patients with HFpEF was associated with an increased likelihood of improving MR.[41] Positive LA remodelling has been reported in HFpEF patients, mice and rats treated with angiotensin-converting enzyme inhibitors or the angiotensin receptor–neprilysin inhibitor sacubitril/valsartan.[33,42] Furthermore, angiotensin II receptor blockers have been proposed to modulate mitral valve leaflet remodelling.[43] Lastly, sodium–glucose cotransporter 2 inhibitors (SGLT2i) have shown to be effective in HFpEF.[44] Patients with severe valvular heart disease were however excluded and mechanism-based insights are eagerly awaited.[45,46] Recently presented data suggest a clear haemodynamic benefit of SGLT2i in HFpEF, with 24 weeks of dapagliflozin associated with a reduction in the PAWP of 3.5 mmHg at rest and 5.7 mmHg during exercise.[47] Furthermore, dapagliflozin administration in stable outsetting patients with chronic heart failure results in global reverse remodelling of cardiac structure, including reductions in LA volumes regardless of ejection fraction.[48]

Rhythm control

Given the high prevalence of AFMR amongst HFpEF patients, early AF-directed treatment is expected to improve MR over time. The retrospective data of Gertz *et al.*[49,50] suggest that reducing the burden of AF decreases the severity of MR. Compared with patients with recurrent AF, there was a greater reduction in LA volume and mitral annular diameter. Sinus rhythm restoration allows gradual recovery of annular dynamics, may improve diastolic and LA function and is linked with improved outcome in HFpEF.[51–53] Newer techniques, especially pulsed field ablation, seem to result in less scar formation and may conceptually cause less detrimental impact on LA function, although long-term data are still pending.[54,55] The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) paves the way for rhythm control in the early stages of AF.[56] Approximately 44% of both arms of the study (rhythm control vs. usual care) had valvular heart disease, although the details of this are not further specified. Additionally, the initiation of guideline-directed medical therapy serves to mitigate the likelihood of (recurrent) AF.[57]

Intervention

Percutaneous valve interventions have opened therapy options for frail HFpEF patients. Much research effort has focused on patient selection, although the indication in HFpEF is still an unexplored territory. One can hypothesize that LV unloading, the increase in forward cardiac output and decrease in pulmonary pressures can outweighs the potentially negative LV afterload increase by eliminating the backward LA flow.[21] Based on retrospective data, M-TEER (MitraClip, Abbott Vascular, Santa Clara, CA, USA) has been shown to significantly reduce MR grade regardless of LV filling pressure and LV ejection fraction.[9,58,59] In small series, a significant increase in LA function and decrease in LA volume were seen in HFpEF patients with initially severe MR.[60–62] Interestingly, severely elevated LA pressures at baseline are associated with worse long-term survival regardless of MR aetiology or the degree of post-procedural MR reduction, which may represent underlying atrioventricular disease explaining at least part of the increased pressures.[63] Recent data raise the question of whether percutaneous interventions might be effective in HFpEF with moderate or

severe MR in order to restore the bidirectional relationship of LA remodelling and low-grade MR.[11] Of note, despite the appropriate initiation of pharmacological management, the patient illustrated in *Figure 1* continued to exhibit prominent symptoms. Subsequently, the M-TEER procedure was performed, successfully mitigating regurgitation. However, it yielded only marginal enhancements in pulmonary pressure and symptomatology. Further investigation into a more integrative diagnostic approach may necessitate a reconsideration of our clinical strategy, although definitive answers remain elusive.

Future perspectives

Despite the intertwined nature of HFpEF and MR, their relationship remains underexplored. MR is determined by dynamic interactions between closing and tethering forces on the mitral valve and can thus vary over time and during exercise. Approximately one-third of AFMR cases intensify during handgrip exercise, yet the prognostic and therapeutic implications of this phenomenon are unclear and warrant additional investigation.[64]

The therapeutic approach is currently hypothetical and based on pathophysiology. There is a deficiency in prospective randomized trials, encompassing valve procedures, rhythm control, and potential pharmacological interventions. The ongoing PRAISE-MR trial (NCT05991284), which tests sacubitril/valsartan in AFMR, may provide further insights.

Conclusion

Mitral regurgitation is highly prevalent in patients with HFpEF. Determining thresholds when MR is an active contributor to symptoms instead of an innocent bystander is of particular interest given the evolving management options. Although the left atrium is the first chamber to receive the volume excess, current guidelines focus on the impact on LV function to indicate treatment intervention. As a call to action, there is a compelling need for a more integrated diagnostic approach that considers the functional status of the ventricle, atrium, and valve. Comprehensive understanding and quantification of these entities require knowledge of their functional interactions. As HFpEF is an often an 'umbrella' diagnosis, dissecting it into mechanism-based subtypes could move the field forward.

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References

1. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure – abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953–1959. https://doi.org/10.1056/NEJMoa032566
2. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, *et al.* Heart failure with preserved ejection fraction: Recent concepts in diagnosis, mechanisms and management. *Heart* 2022;**108**:1342–1350. https://doi.org/10.1136/heartjnl-2021-319605
3. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res* 2019;**124**:1598–1617. https://doi.org/10.1161/CIRCRESAHA.119.313572
4. Kajimoto K, Sato N, Takano T; investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Functional mitral regurgitation at discharge and outcomes in patients hospitalized for acute decompensated heart failure with a preserved or reduced ejection fraction. *Eur J Heart Fail* 2016;**18**:1051–1059. https://doi.org/10.1002/ejhf.562
5. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, *et al.* Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585. https://doi.org/10.1002/ejhf.813
6. Bartko PE, Heitzinger G, Pavo N, Heitzinger M, Spinka G, Prausmüller S, *et al.* Burden, treatment use, and outcome of secondary mitral regurgitation across the spectrum of heart failure: Observational cohort study. *BMJ* 2021;**373**:n1421. https://doi.org/10.1136/BMJ.N1421
7. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, *et al.* Atrial functional mitral regurgitation: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:2465–2476. https://doi.org/10.1016/j.jacc.2019.02.061
8. Coats AJS, Anker SD, Baumbach A, Alfieri O, von Bardeleben R, Bauersachs J, *et al.* The management of secondary mitral regurgitation in patients with heart failure: A joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur Heart J* 2021;**42**:1254–1269. https://doi.org/10.1093/eurheartj/ehab086
9. Gröger M, Scheffler JK, Schösser F, Schneider LM, Rottbauer W, Markovic S, *et al.* Percutaneous edge-to-edge mitral valve repair for mitral regurgitation improves heart failure symptoms in heart failure with preserved ejection fraction patients. *ESC Heart Fail* 2021;**8**:5010–5021. https://doi.org/10.1002/ehf2.13561
10. Lancellotti P, Gérard PL, Piérard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. *Eur Heart J* 2005;**26**:1528–1532. https://doi.org/10.1093/eurheartj/ehi189
11. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, *et al.* Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:489–498. https://doi.org/10.1002/ejhf.1699
12. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: A review. *JAMA* 2023;**329**:827–838. https://doi.org/10.1001/jama.2023.2020
13. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered hemodynamics and end-organ damage in heart failure: Impact on the lung and kidney. *Circulation* 2020;**142**:998–1012. https://doi.org/10.1161/CIRCULATIONAHA.119.045409
14. Pichard AD, Diaz R, Marchant E, Casanegra P. Large V waves in the pulmonary capillary wedge pressure tracing without mitral regurgitation: The influence of the pressure/volume relationship on the V wave size. *Clin Cardiol* 1983;**6**:534–541. https://doi.org/10.1002/clc.4960061104
15. Reddy YNV, Murgo JP, Nishimura RA. Complexity of defining severe 'stenosis' from mitral annular calcification. *Circulation* 2019;**140**:523–525. https://doi.org/10.1161/CIRCULATIONAHA.119.040095
16. Dziadzko V, Dziadzko M, Medina-Inojosa JR, Benfari G, Michelena HI, Crestanello JA, *et al.* Causes and mechanisms of isolated mitral regurgitation in the community: Clinical context and outcome. *Eur Heart J* 2019;**40**:2194–2202. https://doi.org/10.1093/eurheartj/ehz314
17. van Loon T, Knackstedt C, Cornelussen R, Reesink KD, Brunner La Rocca HP, Delhaas T, *et al.* Increased myocardial stiffness more than impaired relaxation function limits cardiac performance during exercise in heart failure with preserved ejection fraction: A virtual patient study. *Eur Heart J Digit Health* 2020;**1**:40–50. https://doi.org/10.1093/ehjdh/ztaa009
18. Lumens J, Delhaas T, Kirn B, Arts T. Three-wall segment (TriSeg) model describing mechanics and hemodynamics of ventricular interaction. *Ann Biomed Eng* 2009;**37**:2234–2255. https://doi.org/10.1007/s10439-009-9774-2
19. Arts T, Delhaas T, Bovendeerd P, Verbeek X, Prinzen FW. Adaptation to mechanical load determines shape and properties of heart and circulation: The CircAdapt model. *Am J Physiol Heart Circ Physiol* 2005;**288**:H1943–H1954. https://doi.org/10.1152/AJPHEART.00444.2004
20. Kirkels FP, van Osta N, Rootwelt-Norberg C, Chivulescu M, van Loon T, Aabel EW, *et al.* Monitoring of myocardial involvement in early arrhythmogenic right ventricular cardiomyopathy across the age spectrum. *J Am Coll Cardiol* 2023;**82**:785–797. https://doi.org/10.1016/j.jacc.2023.05.065
21. Gaemperli O, Biaggi P, Gugelmann R, Osranek M, Schreuder JJ, Bühler I, *et al.* Real-time left ventricular pressure-volume loops during percutaneous mitral valve repair with the MitraClip system. *Circulation* 2013;**127**:1018–1027. https://doi.org/10.1161/CIRCULATIONAHA.112.135061

22. Bonow RO, O'Gara PT, Adams DH, Badhwar V, Bavaria JE, Elmariah S, *et al.* 2020 Focused update of the 2017 ACC Expert Consensus Decision Pathway on the management of mitral regurgitation: A report of the American College of Cardiology Solution set Oversight Committee. *J Am Coll Cardiol* 2020;**75**:2236–2270. https://doi.org/10.1016/j.jacc.2020.02.005
23. Gaasch WH, Meyer TE. Left ventricular response to mitral regurgitation. *Circulation* 2008;**118**:2298–2303. https://doi.org/10.1161/CIRCULATIONAHA.107.755942
24. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: A guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;**289**:H501–H512. https://doi.org/10.1152/AJPHEART.00138.2005
25. Weiss JL, Frederiksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *J Clin Investig* 1976;**58**:751–760. https://doi.org/10.1172/JCI108522
26. Smiseth OA, Morris DA, Cardim N, Cikes M, Delgado V, Donal E, *et al.* Multimodality imaging in patients with heart failure and preserved ejection fraction: An expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2022;**23**:e34–e61. https://doi.org/10.1093/ehjci/jeab154
27. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, *et al.* EHRA/HRS/APHRS/SOLAECE Expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–1490. https://doi.org/10.1093/europace/euw161
28. Zakeri R, Moulay G, Chai Q, Ogut O, Hussain S, Takahama H, *et al.* Left atrial remodeling and atrioventricular coupling in a canine model of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2016;**9**:e003238. https://doi.org/10.1161/CIRCHEARTFAILURE.115.003238
29. Sugimoto T, Bandera F, Generati G, Alfonzetti E, Barletta M, Losito M, *et al.* Left atrial dynamics during exercise in mitral regurgitation of primary and secondary origin: Pathophysiological insights by exercise echocardiography combined with gas exchange analysis. *JACC Cardiovasc Imaging* 2020;**13**:25–40. https://doi.org/10.1016/j.jcmg.2018.12.031
30. Kouris NT, Kostakou PM, Tryfou ES, Olympios CD. Incidence and causal association of functional atrial mitral regurgitation in HFpEF. *Hellenic J Cardiol* 2023;**69**:51–56. https://doi.org/10.1016/J.HJC.2022.09.013
31. Bisbal F, Baranchuk A, Braunwald E, Bayés de Luna A, Bayés-Genís A. Atrial failure as a clinical entity: JACC review topic of the week. *J Am Coll Cardiol* 2020;**75**:222–232. https://doi.org/10.1016/j.jacc.2019.11.013
32. Obokata M, Negishi K, Kurosawa K, Tateno R, Tange S, Arai M, *et al.* Left atrial strain provides incremental value for embolism risk stratification over CHA_2DS_2-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr* 2014;**27**:709–716.e4. https://doi.org/10.1016/J.ECHO.2014.03.010
33. Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: Structure, function, and significance. *Circ Heart Fail* 2014;**7**:1042–1049. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001276
34. Inciardi RM, Rossi A, Bergamini C, Benfari G, Maffeis C, Greco C, *et al.* Mitral regurgitation, left atrial structural and functional remodelling and the effect on pulmonary haemodynamics. *Eur J Heart Fail* 2020;**22**:499–506. https://doi.org/10.1002/ejhf.1677
35. Maeder MT, Nägele R, Rohner P, Weilenmann D. Pulmonary hypertension in stiff left atrial syndrome: Pathogenesis and treatment in one. *ESC Heart Fail* 2018;**5**:189–192. https://doi.org/10.1002/ehf2.12234
36. Sarma S, MacNamara JP, Balmain BN, Hearon CM Jr, Wakeham DJ, Tomlinson AR, *et al.* Challenging the hemodynamic hypothesis in heart failure with preserved ejection fraction: Is exercise capacity limited by elevated pulmonary capillary wedge pressure? *Circulation* 2023;**147**:378–387. https://doi.org/10.1161/CIRCULATIONAHA.122.061828
37. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.*; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632. https://doi.org/10.1093/eurheartj/ehab395
38. Hsu S, Fang JC, Borlaug BA. Hemodynamics for the heart failure clinician: A state-of-the-art review. *J Card Fail* 2022;**28**:133–148. https://doi.org/10.1016/j.cardfail.2021.07.012
39. Bertrand PB, Schwammenthal E, Levine RA, Vandervoort PM. Exercise dynamics in secondary mitral regurgitation: Pathophysiology and therapeutic implications. *Circulation* 2017;**135**:297–314. https://doi.org/10.1161/CIRCULATIONAHA.116.025260
40. Ennezat PV, Maréchaux S, Bouabdallaoui N, le Jemtel TH. Dynamic nature of pulmonary artery systolic pressure in decompensated heart failure with preserved ejection fraction: Role of functional mitral regurgitation. *J Card Fail* 2013;**19**:746–752. https://doi.org/10.1016/j.cardfail.2013.09.006
41. Pagnesi M, Adamo M, Sama IE, Anker SD, Cleland JG, Dickstein K, *et al.* Clinical impact of changes in mitral regurgitation severity after medical therapy optimization in heart failure. *Clin Res Cardiol* 2022;**111**:912–923. https://doi.org/10.1007/s00392-022-01991-7
42. Tantisuwat L, Saengklub N, Boonpala P, Kumphune S, Panyasing Y, Kalandakanond-Thongsong S, *et al.* Sacubitril/valsartan mitigates cardiac remodeling, systolic dysfunction, and preserves mitochondrial quality in a rat model of mitral regurgitation. *Sci Rep* 2023;**13**:11472. https://doi.org/10.1038/s41598-023-38694-6
43. Kagiyama N, Mondillo S, Yoshida K, Mandoli GE, Cameli M. Subtypes of atrial functional mitral regurgitation: Imaging insights into their mechanisms and therapeutic implications. *JACC Cardiovasc Imaging* 2020;**13**:820–835. https://doi.org/10.1016/j.jcmg.2019.01.040
44. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2024;**26**:5–17. https://doi.org/10.1002/ejhf.3024
45. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, *et al.*; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–1461. https://doi.org/10.1056/NEJMoa2107038
46. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, *et al.*; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**:1089–1098. https://doi.org/10.1056/NEJMoa2206286
47. Borlaug BA, Reddy YNV, Braun A, Sorimachi H, Omar M, Popovic D, *et al.* Cardiac and metabolic effects of dapagliflozin in heart failure with preserved ejection fraction: The CAMEO-DAPA trial. *Circulation* 2023;**148**:834–844. https://doi.org/10.1161/CIRCULATIONAHA.123.065134
48. Pascual-Figal DA, Zamorano JL, Domingo M, Morillas H, Nuñez J, Cobo Marcos M, *et al.*; DAPA-MODA Study Investigators. Impact of dapagliflozin on cardiac remodelling in patients with chronic heart failure: The DAPA-MODA study. *Eur J Heart Fail* 2023;**25**:1352–1360. https://doi.org/10.1002/ejhf.2884
49. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE, *et al.* Evidence of atrial functional mitral regurgitation due to atrial fibrillation: Reversal with arrhythmia control. *J Am Coll Cardiol* 2011;**58**:1474–1481. https://doi.org/10.1016/j.jacc.2011.06.032
50. Hoit BD. Atrial functional mitral regurgitation: The left atrium gets its due respect. *J Am Coll Cardiol* 2011;**58**:1482–1484. https://doi.org/10.1016/j.jacc.2011.06.033
51. Deferm S, Bertrand PB, Verhaert D, Verbrugge FH, Dauw J, Thoelen K, *et al.* Mitral annular dynamics in AF versus sinus rhythm: Novel insights into the mechanism of AFMR. *JACC Cardiovasc Imaging* 2022;**15**:1–13. https://doi.org/10.1016/j.jcmg.2021.05.019
52. Packer DL, Piccini JP, Monahan KH, al-Khalidi HR, Silverstein AP, Noseworthy PA, *et al.*; CABANA Investigators. Ablation versus drug therapy for atrial fibrillation in heart failure. *Circulation* 2021;**143**:1377–1390. https://doi.org/10.1161/CIRCULATIONAHA.120.050991
53. Machino-Ohtsuka T, Seo Y, Ishizu T, Sugano A, Atsumi A, Yamamoto M, *et al.* Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2013;**62**:1857–1865. https://doi.org/10.1016/j.jacc.2013.07.020
54. Mathuria N. Pulsed-field ablation for atrial fibrillation: The future is now? *JACC Clin Electrophysiol* 2021;**7**:628–629. https://doi.org/10.1016/j.jacep.2021.03.007
55. Karanasos A, Tyrovolas K, Tsiachris D, Efremidis M, Kordalis A, Karmpalioti M, *et al.* Left atrial function post radiofrequency and cryoballoon ablation assessed by volume-pressure loops. *Front Cardiovasc Med* 2022;**9**:830055. https://doi.org/10.3389/fcvm.2022.830055
56. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, *et al.*; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–1316. https://doi.org/10.1056/NEJMoa2019422
57. Abu-Qaoud MR, Kumar A, Tarun T, Abraham S, Ahmad J, Khadke S, *et al.* Impact of SGLT2 inhibitors on atrial fibrillation recurrence after catheter ablation in patients with type-2-diabetes. *JACC Clin Electrophysiol* 2023;**9**:2109–2118. https://doi.org/10.1016/j.jacep.2023.06.008
58. Claeys MJ, Debonnaire P, Bracke V, Bilotta G, Shkarpa N, Vanderheyden M, *et al.* Clinical and hemodynamic effects of percutaneous edge-to-edge mitral valve repair in atrial versus ventricular functional mitral regurgitation. *Am J Cardiol* 2021;**161**:70–75. https://doi.org/10.1016/j.amjcard.2021.08.062

59. Orban M, Rottbauer W, Williams M, Mahoney P, von Bardeleben RS, Price MJ, *et al.* Transcatheter edge-to-edge repair for secondary mitral regurgitation with third-generation devices in heart failure patients – results from the Global EXPAND Post-Market study. *Eur J Heart Fail* 2023;**25**:411–421. https://doi.org/10.1002/ejhf.2770
60. Biersmith M, Orsinelli DA, Harfi TT, Lilly S, Boudoulas KD. Effect of mitral valve transcatheter edge-to-edge repair on indices of left atrial performance in chronic mitral regurgitation. *Echocardiography* 2022;**39**:1420–1425. https://doi.org/10.1111/ECHO.15470
61. Iliadis C, Kalbacher D, Lurz P, Petrescu AM, Orban M, Puscas T, *et al.* Left atrial volume index and outcome after transcatheter edge-to-edge valve repair for secondary mitral regurgitation. *Eur J Heart Fail* 2022;**24**:1282–1292. https://doi.org/10.1002/ejhf.2565
62. Popolo Rubbio A, Testa L, Grasso C, Sisinni A, Tusa M, Agricola E, *et al.* Transcatheter edge-to-edge mitral valve repair in atrial functional mitral regurgitation: Insights from the multi-center MITRA-TUNE registry. *Int J Cardiol* 2022;**349**:39–45. https://doi.org/10.1016/j.ijcard.2021.11.027
63. el Shaer A, Mahayni A, Simard T, Eleid M, Guerrero M, Rihal CS, *et al.* Baseline left atrial pressure predicts mortality following transcatheter edge-to-edge mitral valve repair. *JACC Cardiovasc interv* 2021;**14**:2306–2308. https://doi.org/10.1016/j.jcin.2021.07.057
64. Spieker M, Sidabras J, Lagarden H, Christian L, Angendohr S, Zweck E, *et al.* Prevalence and prognostic impact of dynamic atrial functional mitral regurgitation assessed by isometric handgrip exercise. *Eur Heart J Cardiovasc Imaging*. https://doi.org/10.1093/EHJCI/JEAD336 Published online ahead of print 08/12/23.