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New nosologies: atriogenic valvular regurgitation

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Functional mitral regurgitation and functional tricuspid regurgitation occur due to cardiac remodelling in the presence of macroscopically normal valve apparatus. Two main mechanisms are involved: a ventricular phenotype (when ventricular remodelling and dysfunction are predominant) and an atrial phenotype (when annulus dilatation and atrial remodelling are predominant). Both phenotypes are frequent in patients with heart failure and are associated with a significant increase in morbidity and mortality, representing a relevant therapeutic target. This work focuses on the epidemiology, pathophysiology, prognosis, and therapy of atrial functional regurgitation.

Introduction

Functional mitral regurgitation (FMR) and functional tricuspid regurgitation (FTR) occur due to cardiac remodelling in the presence of macroscopically normal valve apparatus.

Two distinct phenotypes can be identified: a ventricular form, mainly related to alterations in the geometric relationships between the valve and the ventricle, and an atrial form, mainly related to annular dilatation, impaired contraction, and atrial remodelling.

Both phenotypes pose a clinical challenge due to their increased prevalence, the physiopathological complexity that distinguishes them, and their prognostic and therapeutic implications. This work focuses on atrial functional regurgitation, both atrial FMR (aFMR) and atrial FTR (aFTR).

Epidemiology

FMR affects up to 30% of patients with HF, and it is more common in subjects with HF with reduced ejection fraction (≤40%) (HFrEF), followed by those with HF with mildly reduced ejection fraction (41–49%) (HFmrEF) and preserved ejection fraction (≥50%) (HFpEF).

Prospective registry data indicate that the prevalence of moderate-to-severe FMR is ∼35% in patients with HFrEF, 30% in those with HFmrEF, and ∼20% in those with HFpEF.[1]

However, no studies are specifically designed to analyse the prevalence of FMR phenotypes (ventricular vs. atrial) across various HF categories. It is reasonable to assume that in patients with HFrEF, ventricular mechanisms are predominant, while in HFmrEF and HFpEF, ventricular mechanisms become progressively less relevant in favour of atrial mechanisms.[2] Data from prospective registries indicate a uniform distribution of FTR across HF, with an overall prevalence estimated to be around 20%. The challenging quantification of FTR may limit the accuracy of available studies.

Pathophysiology and prognosis

Historically, the isolated dilation of the mitral and tricuspid annulus has been considered the primary aetiopathogenetic mechanism for aFMR and aFTR. Recent evidence has expanded this perspective, highlighting a more complex role of the atrium and the annular dynamics. The mitral and tricuspid annulus functions in a complex and dynamic manner throughout the cardiac cycle; during systole, the area decreases by ∼25% due to ventricular contraction. The annulus, therefore, promotes the coaptation of the valve leaflets, contributing to the continence of the valve.

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A study by Dziadzko *et al.*[3] investigated the aetiologies of isolated MR in the general population, highlighting a significant increase in the prevalence of aFMR with advancing age.[3] Patients with aFMR also exhibit a greater prevalence of atrial fibrillation (AF) and hypertension compared with those with a ventricular phenotype. Such observations are expected because AF is generally related to annular dilation and atrial remodelling. AF also leads to a change in the dynamics of the annulus. The reduction in the mitral and tricuspid annular area is markedly decreased because of the impaired contraction of the annulus, contributing to the development of valvular regurgitation.[4,5]

However, aFMR and aFTR can also occur in the presence of sinus rhythm, especially in patients with HFpEF. In HFpEF, diastolic dysfunction and increased atrial filling pressures cause annular dilation and atrial remodelling.[4,5] Another relevant aspect, besides the volumetric remodelling of the atrium, is represented by the structural alterations (fibrosis) induced by both AF and HFpEF. Therefore, a vicious circle is established, in which AF and HFpEF act as causal and maintaining mechanisms for aFMR and aFTR.[5,6] Both conditions are associated with a poor prognosis. Studies have shown that aFMR is associated with a significant increase in mortality compared with the general population, although it presents a more favourable prognosis than the ventricular phenotype. AMR is associated with an increased risk of developing HF compared with patients with organic mitral regurgitation. Similarly, a significant association between FTR and increased mortality has been documented in HFrEF and HFpEF. However, the prognosis is more favourable for aFTR than the ventricular phenotype.[6]

Therapeutic approaches

Atrial FMR

Optimized medical therapy is the first and essential step in treating FMR in all its phenotypes.[7] However, current recommendations for managing valvular heart disease do not differentiate pharmacological and non-pharmacological therapeutic indications, depending on the specific phenotype of FMR (ventricular vs. atrial). In the case of HFpEF, the only medications endorsed in Class I by current guidelines are sodium–glucose cotransporter 2 (SGLT2) inhibitors. The role of glucagon-like peptide 1 (GLP-1) receptor agonists, finerenone, glucose-dependent insulinotropic peptide, and GLP-1 receptor co-agonists in HFpEF requires additional investigations.

Loop diuretics are recommended to reduce the symptoms and signs of congestion after using the above-mentioned drugs. In HFpEF, the treatment of risk factors and comorbidities (hypertension, diabetes) is also essential. Strategies for rhythm and rate control are also highly relevant in patients with AF, since restoring sinus rhythm has been proved to correlate with a significant improvement in the severity of valvular regurgitation.[8]

In cases of severe symptomatic aFMR that persists despite the previously mentioned treatments, options include valve repair or replacement, using either a surgical or transcatheter approach. While surgery for the ventricular phenotype of FMR has not demonstrated benefits in randomized clinical trials, surgical annuloplasty has shown good results in patients with aFMR based on physiopathological reasons and results from controlled series.[9] However, advanced age and comorbidities are often present in these patients, increasing the surgical risk significantly and encouraging the adoption of transcatheter treatment options. Available transcatheter therapies consist of repair strategies that promote leaflet coaptation or annuloplasty and valve replacement strategies. Repair strategies are the most commonly used, mainly through transcatheter edge-to-edge repair (TEER). A study conducted by Gertz *et al.*[10] examined patients from the COAPT trial [Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure (HF) Patients with FMR] who had a previous history of AF, assuming a mixed aetiology (atrial and ventricular) of FMR in these subjects.[10] Patients with a history of AF showed more dilated atria, increased left ventricular ejection fraction values, reduced ventricular volumes, and similar severity of MR when compared with patients without a history of AF. Patients with a history of AF exhibited a poorer prognosis yet still gained advantages from TEER using the MitraClip device (Abbott). Similarly, Tanaka *et al.*[11] investigated the efficacy of TEER in 118 patients with aFMR.[11] TEER was demonstrated to be a safe and effective strategy with a significant reduction in the degree of MR that remained stable in the follow-up at 3 months and 1 year. Multivariate analysis showed that severe left atrial dilation and a low leaflet-annulus index are associated with an increased risk of residual MR $\geq$ 2+ after TEER. Therefore, accurate patient selection for TEER is crucial, as it is for patients with ventricular phenotype.

The results of the MATTERHORN trial (Transcatheter vs. Surgical Mitral Valve Repair in Patients with Heart Failure and Secondary Mitral Regurgitation) were recently published. They showed the non-inferiority of TEER compared with surgery in terms of efficacy in patients with HF and severe FMR, along with a superior safety profile. The results were similar in patients with the atrial and ventricular phenotype of MR.[12]

Finally, transcatheter annuloplasty interventions (e.g. Cardioband, Carillon) are promising, though they are not yet fully established in clinical practice.

Atrial FTR

There are no specific recommendations for optimizing medical therapy for FTR.[8] Diuretics help reduce symptoms and clinical signs of congestion. This case confirms the indication for using SGLT2 inhibitors in patients with HFpEF as prognosis-modifying drugs. Rhythm and rate control strategies in patients with AF are also essential options.

According to the current guidelines for FTR, Class I surgery is advised exclusively for patients undergoing left-sided valve intervention. In these patients, surgical treatment of TR should also be considered in cases of non-severe TR when there is significant annular dilation.[8] The type of surgical approach strictly depends on the aetiology of FTR. When the primary aetiopathogenetic mechanism is annular dilation, surgical annuloplasty is the preferable approach. In clinical practice, however, isolated tricuspid valve surgery, especially valve replacement, continues to be rarely used due to the perioperative mortality.[13] As a result, there has been a growing scientific interest in transcatheter treatments for the repair (TEER, annuloplasty) or replacement (heterotopic or orthotopic) of the tricuspid valve. The international TriValve registry,

which represents the largest cohort of patients with severe symptomatic TR undergoing percutaneous treatment, has shown that transcatheter treatment is associated with an increase in survival and a reduction in hospitalizations compared with optimized medical therapy alone.[14] A significant finding is that most of the patients included in the registry (>90%) had a functional aetiology; among these, many had aFTR associated with HFpEF. Subsequently, the results of the TRILUMINATE trial (Trial to Evaluate Treatment with Abbott Transcatheter Clip Repair System in Patients with Moderate or Greater Tricuspid Regurgitation) and the 3-year follow-up confirmed a significant improvement in the degree of valvular regurgitation, functional capacity, and quality of life in patients with severe TR treated with TEER with the TriClip device (Abbott). However, no significant mortality benefit was observed compared with optimized medical therapy.[15]

Among the transcatheter options, annuloplasty and TEER are preferable when annular dilation is the primary aetiopathogenetic mechanism. In contrast, transcatheter valve replacement appears to be a promising alternative in patients with advanced cardiac remodelling and significant coaptation gaps. Recently, the EVOQUE tricuspid valve replacement system (Edwards) obtained approval from the Food and Drug Administration following the positive results at 6 months after the TRISCEND II trial (Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy Using a Novel Device) in patients with severe TR. However, some critical aspects remain unresolved, such as severe right ventricular dysfunction, the potential future need for the implantation of electronic devices, and the presence of a small or excessively wide annulus unsuitable for the available prosthesis sizes.

Conclusions

AFM and aFTR are two clinical conditions that are receiving increasing attention due to their increased prevalence in patients with HF, particularly in HFpEF, and their significant impact on prognosis. The distinction between atrial and ventricular phenotypes is crucial for personalized management, as the different aetiopathogenesis requires diversified therapeutic strategies. Optimized medical therapy, including diuretics to reduce symptoms and signs of congestion and SGLT2 inhibitors as prognosis modifiers in patients with HFpEF, together with rhythm and rate control strategies in patients with AF, represent the first and essential steps in the therapeutic algorithm. However, in patients who remain symptomatic, surgical and transcatheter valve repair and replacement techniques should be considered as valid options. Given that most of these patients have high surgical risk due to their advanced age and multiple comorbidities, transcatheter techniques offer a valid treatment option, with their efficacy and safety supported by registries and clinical trials. Dedicated studies are needed to identify optimal patient selection and investigate long-term data.

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Data availability

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Disclaimer

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