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EDITORIAL

Sacubitril/Valsartan to Reduce Secondary Mitral Regurgitation

Refinement of Guideline-Directed Medical Therapy?

Article, see p 1354

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Secondary mitral regurgitation (MR) is the result of intrinsic dysfunction of the failing left ventricle (LV) in the absence of organic mitral valve dysfunction. The mitral valve apparatus depends on the intricate and balanced function of all individual components (mitral annulus, leaflets, chordea tendineae, papillary muscles, and LV wall) to prevent backward flow during systole or obstruction to flow during diastole.[1] This delicate mitral valve function is maintained by a balance between tethering forces and closing forces (Figure A, Left). However, in secondary MR, the failing LV disturbs this balance by increasing tethering forces and reducing closing forces (Figure A, Right). This also results in an increased static and pulsatile load on the left atrium and the pulmonary circulation. In addition, the regurgitant volume reduces the effective LV stroke volume.[2]

Although secondary MR is associated with a poor outcome, it is questionable whether direct reduction of the degree of MR through surgical or interventional procedures is capable of partially reversing the underlying disease of the LV. In contrast, the current backbone of established therapies for secondary MR aim at improving the misbalance between tethering and closing forces by treating the underlying sick LV itself.[3] Indeed, adequate decongestion and optimal doses of guideline-directed medical therapy, including angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid receptor blockers, all induce LV reverse remodeling, which is associated with a decrease in LV volumes and sphericity, coinciding with a reduction in MR.[4] Conversely, cardiac resynchronization therapy in selected patients with reduced LV ejection fraction (LVEF) and electromechanical dyssynchrony reduces secondary MR by synchronizing and improving LV regional and global contraction, often inducing significant reverse remodeling that lessens the tethering forces and improves closing forces.[5] It is important to note that this does not only beneficially reduce the degree of MR, but also improves the downstream alterations of pulmonary hypertension and poor right ventricular-arterial coupling that characterize severe secondary MR in patients with heart failure.[5]

More recently, sacubitril/valsartan has been shown to reduce the rate of heart failure hospitalization and cardiovascular mortality in the PARADIGM-HF trial (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) in selected symptomatic patients with heart failure with reduced LVEF (HFrEF) <35%.[6] Sacubitril/valsartan not only inhibits the renin-angiotensin-aldosterone pathway, but also increases the natriuretic peptide

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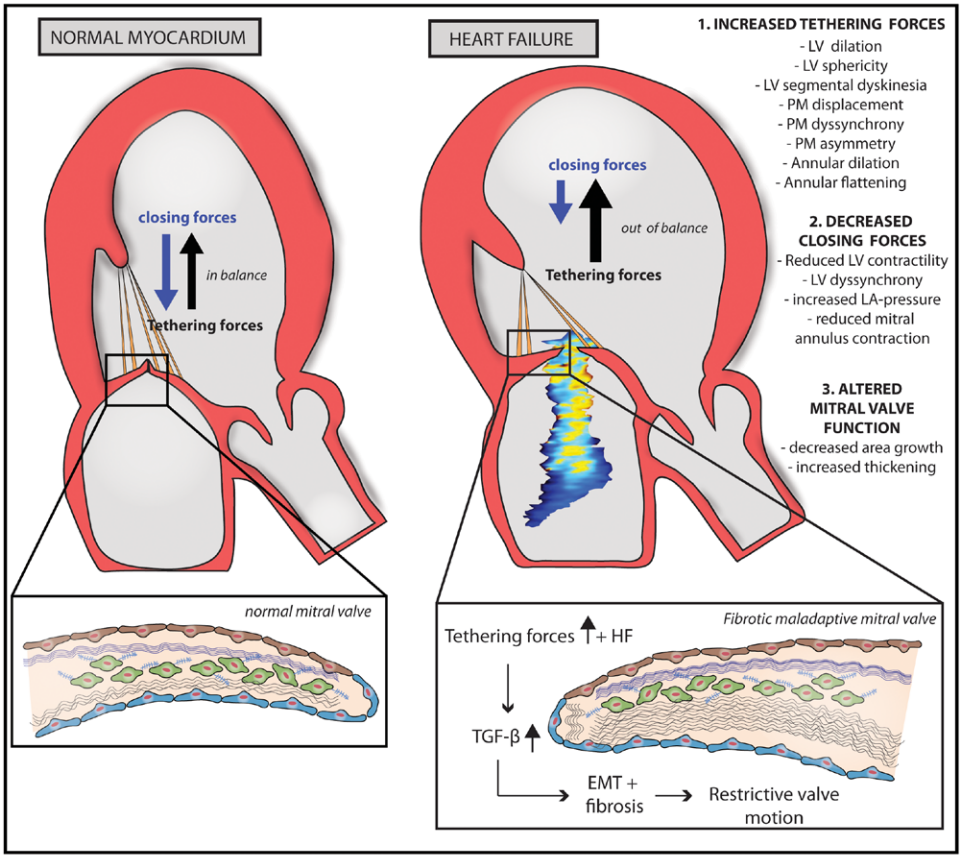
A Pathophysiologic basis of secondary MR



B Comparison of included patients in COAPT, MITRA-FR and PRIME-study

	COAPT	MITRA-FR	PRIME
Number of patients	614	304	118
Age , years	72.3 ± 11.2	70.4 ± 10.0	62.6 ± 11.2
Ischemic etiology HF	61%	59%	36%
NYHA-class II/III/IV in %	39% / 52% / 9%	33% / 59% / 8%	88% / 12% / 0%
Baseline ACE-I/ARB/(ARNI)° Baseline Beta-blocker Baseline MRA Baseline loop diuretic	67% 90% 50% 89%	83% 89% 55% 99%	100% 88% 43% 88%
LVEF, %	31 ± 9	33 ± 7	34 ± 7
LVEDVi (ml/m²)	101 ± 34	135 ± 35	116 ± 39
Mean EROA, cm²	0.41 ± 0.15	0.31 ± 0.10	0.20 ± 0.10
EROA < 0.40 cm²	59%	84%	94%
EROA > 0.40 cm²	41%	16%	6%
Follow-up duration trial	2y*	1y	1y
Primary endpoint	Recurrent HF	HF or death	Change in EROA
Annualized mortality rate	19%	23%	0.8%

Figure. Overview of therapeutic targets in secondary MR.
A, Depiction of the pathophysiologic basis for secondary MR. **B**, Overview of randomized controlled trials with the MitraClip system for secondary MR. °Patients in the PRIME study (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) only received ACE-I or ARB at baseline, no ARNI. *Planned follow-up in COAPT extended until 5 years. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor-neprilysin inhibitor; EMT, endothelial-to-mesenchymal transition; EROA, effective regurgitant orifice area; HF, heart failure; LA, left atrium; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PM, papillary muscle; and TGF-β,tissue growth factor-beta.

pathway, thereby significantly influencing the neurohormonal portrait of the patient with HFrEF. A small observational study indicated incremental LV reverse remodeling after switching from ACE-I or ARB to sacubitril/valsartan in eligible patients with HFrEF.[7] However, whether sacubitril/valsartan reduces the grade of

secondary MR remains largely unknown, especially because no echocardiographic data were collected in the PARADIGM-HF trial.[6]

In this issue of *Circulation*, Kang and colleagues[8] now address this gap in knowledge. The authors prospectively included symptomatic patients with heart failure with a baseline LVEF between 25% and 50%, despite optimal medical therapy with an ACE-I/ARB and β-blocker and significant secondary MR, defined as an effective regurgitant orifice area (EROA) >0.1 cm^2. This definition is questionable, because severe secondary MR is typically defined as EROA ≥0.2 cm^2 or regurgitant volume >30 mL (in European guidelines). Although great discussion exists about which cutoff best describes severe secondary MR, the grade of MR should also be interpreted in light of the extent of LV dilation.[2] In addition, patients were not eligible for cardiac resynchronization therapy or revascularization, thereby identifying a patient population without well-established additional interventions capable of reducing the grade of MR while improving outcome. After withdrawal of the ACE-I/ARB, patients were randomly assigned to maximal tolerable dose of either valsartan or sacubitril/valsartan, which allowed them to specifically investigate the additional effect of sacubitril. It is important to note that both treatment groups received similar uptitration of the ARB component during the study, reaching almost 80% of the target dose at 12 months, which is remarkably high. This in conjunction with the low mortality rate during follow-up perhaps indicates that this patient population was not very sick, which is also illustrated by the large amount of patients with a nonischemic cardiomyopathy and functioning in New York Heart Association class II. This, in addition to the lower EROA, is important to bear in mind when comparing this study with recent studies assessing the effect of MitraClip for secondary severe MR (see Figure B).[9,10] The primary end point of the study was the change in EROA from baseline to 12-month follow-up. The authors should be congratulated with this well-conducted multicenter, randomized, controlled trial. Not only was the therapy assignment blinded, but all echocardiographic analyses were performed in a central core laboratory. In addition, the proximal isovelocity surface area radius was calculated as an average from an early, mid, and late systolic frame. This is important because the severity of secondary MR is dynamic throughout the cardiac cycle.[11] Indeed, measuring the proximal isovelocity surface area radius in early systole overestimates MR severity, whereas measuring it in a midsystolic frame underestimates severity. It is interesting to note that, after 12 months, the EROA was significantly more reduced in patients treated with maximal tolerable doses of sacubitril/valsartan in comparison with valsartan (absolute EROA reduction –0.058 cm^2 versus –0.018 cm^2; relative reduction 30% versus 9%). Similarly, sacubitril/valsartan was also more efficient in reducing the regurgitant volume, and in inducing additional reverse remodeling at follow-up, as well.

Despite the elegant demonstration of an improvement in the severity of MR with sacubitril/valsartan, further understanding about the mechanisms responsible for this improvement is desirable. Perhaps these results should be interpreted in the general context of the pharmacological profile of sacubitril/valsartan and the misbalance between tethering forces and closing forces in secondary MR (Figure A).[1] First, through increased natriuretic peptide activity, sacubitril reduces both the afterload and preload, which are both hemodynamic determinants of MR severity. Second, the more pronounced reduction in LV end-diastolic volume (and perhaps also LV sphericity) in the sacubitril/valsartan group should also lead to a more pronounced reduction in tethering forces. However, Kang and colleagues do not show a more pronounced reduction in incomplete leaflet closure area (tenting area), which would have been expected if a reduction in tethering was an important driving mechanism behind the reduction in EROA. Third, greater improvement in closing forces could also explain the more pronounced reduction in EROA in the sacubitril/valsartan. This is likely both the result of a chronic reduction in left atrial pressures (illustrated by the lower left atrial volume) and an improvement in LV contractility. Although the authors did not measure direct markers of LV contractility (eg, dP/dt), we have previously found an improvement in metrics of systolic function following initiation of sacubitril/valsartan.[7] Fourth, it is often underrecognized that the mitral valve leaflets are not just innocent bystanders. They undergo leaflet growth to improve leaflet coaptation as a response to tethering. Indeed, insufficient leaflet adaptation contributes to MR severity in secondary MR.[12] More recently, it has been recognized that tethering forces also induce increased fibrotic leaflet thickening driven by tissue growth factor beta overexpression.[13] This maladaptive process restricts leaflet motion and hampers adequate leaflet coaptation. It is interesting to note that losartan has been shown to suppress tissue growth factor beta overexpression, thereby reducing fibrotic leaflet thickening.[13] It is more interesting that proteomics studies suggest that a combination of an ARB with sacubitril results in a more pronounced synergistic inhibition of tissue growth factor beta.[14] Therefore, additional studies assessing the impact of sacubitril/valsartan on leaflet adaptation would be interesting. In conclusion, this trial suggests that sacubitril/valsartan should become an integrated part of the guideline-directed medical therapy for secondary MR. Although the PARADIGM-HF study only included patients who have HFrEF with an LVEF <35%, the current study does suggest a role for sacubitril/valsartan for patients with heart failure

with an LVEF between 25% and 50% and moderate to moderate-severe MR. Perhaps it is important to recognize that LVEF is a less precise marker of LV function in the presence of severe MR, because the regurgitant volume diminishes the LV end-systolic volume, thereby increasing LVEF.

It is interesting to note that the recent COAPT trial (Cardiovascular Outcomes Assessment of MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) demonstrated, as a first, that direct targeting of the regurgitant volume with MitraClip in carefully selected patients who have HFrEF with severe secondary MR reduces heart failure hospitalizations.[10] It is important to note that, although the patients needed to be treated by experienced heart failure specialists before referral, only 62% of patients in the control group were treated with ACE-I/angiotensin-receptor-neprilysin inhibitor/ARB at baseline. However, the discordant results with the MITRA-FR trial (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation), which included patients with less severe secondary MR but more advanced LV dilation, perhaps indicate that patient selection (severe MR without advanced LV dilation) is important (see Figure B).[9] Indeed, once the LV has remodeled significantly, it is well established that the presence of severe MR loses its prognostic relation with poor outcome.[15] As such, percutaneous interventions targeting secondary MR in that setting might be futile in reverting the progressed disease, thereby underscoring the importance of adequate follow-up of patients under uptitration of guideline-directed medical therapy and assessment of eligibility for additional percutaneous interventions. Clearly, further analysis of the COAPT and MITRA-FR trials and the finalization of the RESHAPE-HF2 trial (A Clinical Evaluation of the Safety and Effectivieness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation; NCT02444338) will help to understand the precise place of percutaneous techniques to reduce the degree of MR and improve clinical outcome. However, for now, it is clear that, before contemplating these percutaneous interventions, guideline-directed medical therapy should always be optimized first. This intrinsically includes the prescription of the class I lifesaving therapy sacubitril/valsartan.

ARTICLE INFORMATION

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