Current Hypertension Reports (2019) 21: 20
https://doi.org/10.1007/s11906-019-0928-9

HYPERTENSION AND THE HEART (BHARATHI UPADHYA, SECTION EDITOR)

The Role of Arterial Hypertension in Mitral Valve Regurgitation

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Published online: 28 February 2019

Abstract

Purpose of Review To review medical literature for evidence of association between hypertension and mitral regurgitation (MR) and summarize potential favorable effects of antihypertensive drugs on MR natural history and treatment.

Recent Findings Hypertension and MR are common diseases affecting a large proportion of the general population. Contemporary evidence suggests that hypertension may worsen the progression and prognosis of MR through augmented mechanical stress and increased regurgitation volume. Renin-angiotensin axis inhibitors, beta-blockers, and vasodilators have been tested in order to prevent or decrease primary or secondary MR.

Summary Although antihypertensive agents may improve hemodynamic parameters and left ventricular remodeling in primary MR, there is no strong evidence of benefit on clinical outcomes. On the other hand, a beneficial effect of these drugs on secondary MR is better established. Moreover, there are no studies evaluating a possible benefit of lower blood pressure targets in MR. Randomized controlled trials are warranted to elucidate the precise role of antihypertensive therapy on treatment of MR.

Keywords Mitral valve · Mitral regurgitation · Mitral calcification · Hypertension · Antihypertensive treatment

Introduction

Valvular heart diseases are among the most predictable causes of heart failure (HF) and are present in a relatively large proportion of the population [1]. Mitral regurgitation (MR) is the most common valve disease [2]. Currently, the repair or replacement of the damaged valve is considered the only effective treatment for this valvulopathy [3••, 4••]. In contrast, there is no consensus regarding the medical therapy that may alter the natural history of the disease or delay the need for interventional treatment [3••, 4••, 5••]. Hypertension is a major risk factor for cardiovascular disease [6] and, similarly to MR, is common in the general population with the prevalence of both conditions being increasing with age [1, 2, 7••, 8–10]. The high co-prevalence of hypertension and MR, especially in older populations [2, 9, 11•, 12, 13], along with relevant mechanistic data [14], indicate that there may be an association between these two disorders. Whether this association is causal, and hypertension represents a true risk factor for the incidence and progression of MR is not clear. Moreover, evidence about a favorable impact of blood pressure (BP) lowering and antihypertensive agents in general on MR is scarce and conflicting. This review investigates the association between hypertension and MR as well as the possible benefits of tailored antihypertensive treatment on the natural history of mitral valve disease.

Methods and Materials

A systematic review of the literature for all relevant articles was performed until March 2018 using MEDLINE and COCHRANE LIBRARY. Articles were limited to those

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This article is part of the Topical Collection on *Hypertension and the Heart*

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published in the English language. A manual search for references from reports of human studies or review articles was performed to identify additional relevant evidence. Our search included studies about both primary and secondary MR in patients with a native mitral valve. Animal studies and studies that enrolled non-adults (< 18 years old) or patients with a prosthetic valve were excluded. Table 1 summarizes the main findings from studies that investigated the effect of different classes of antihypertensive agents on MR [15–52•].

Results

MR and Hypertension: Pathophysiology

From a pathophysiological point of view, hypertension is closely, though indirectly, related to secondary mitral regurgitation (i.e., MR with structurally normal valve leaflets and chordae tendineae). Hypertension is a major risk factor for coronary artery disease (CAD), myocardial infarction (MI), and heart failure with either reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), all of which can result in secondary MR [4••, 53••, 54]. Secondary (or functional) MR is typically attributed to mitral annulus dilation due to dilation of the left ventricle (LV) and papillary muscle dysfunction due to ischemia, segmental myocardial dysfunction, or adverse LV remodeling [53••, 55•]. An underrecognized mechanism also believed to participate in pathogenesis of secondary MR in both HFrEF and HFpEF is increased left atrial (LA) pressure and LA enlargement that promote mitral valve tenting (impaired coaptation of leaflets during systole) and mitral annulus dilation [4••, 55•]. Indeed, LA size and echocardiographic indices serving as surrogates of LA pressure have been associated with presence and severity of secondary MR, mitral annulus size, and mitral valve tenting area [56, 57, 58•, 59•]. As hypertension frequently causes LA dilation [54], these considerations strengthen the pathophysiological link between hypertension and secondary MR, especially in patients with HFpEF, a condition closely associated with hypertension [54, 60, 61]. In addition, presence of atrial fibrillation (AF) may contribute to MR worsening, as it causes LA enlargement and consequently mitral annulus dilation [4••, 55•], whereas restoration of sinus rhythm in AF patients has been associated with MR improvement [54, 58•]. Hypertension is considered a possible risk factor for AF [62] and the assumed role of AF in MR progression might suggest another link between hypertension and MR.

Regarding primary MR, its association with hypertension seems more complex and less certain. The mitral valve is exposed to remarkable mechanical stress during systole, especially at the phase of isovolumetric contraction, when left ventricular pressure rapidly increases. Higher BP values obviously cause an elevation in systolic LV pressure, simultaneously increase the gradient between left ventricle and left atrium and also predispose to higher LA diastolic pressures. As a consequence, long-standing hypertension increases the overall hemodynamic load imposed on the mitral valve, which may promote its degeneration or accelerate structural damage at an intrinsically abnormal valve resulting in valvular regurgitation [53••, 63]. Moreover, increased BP exerts a deleterious hemodynamic effect on an insufficient mitral valve. In 1996, Levine et al., based on the Torricelli principle and the Gorlin equation [64], proposed that the mitral regurgitation volume (MRV) can be calculated by the following equation: $MRV = MROA \times C \times Ts \times \sqrt{(LVsm - LAsm)}$, where MROA is the mitral regurgitant orifice area, C is a constant, Ts is the duration of systole, LVsm is the left ventricular systolic mean pressure, and LAsm is the left atrial systolic mean pressure [LVsm-LAsm = mean pressure gradient (MPG)] [14]. In case of coexisting hypertension, LVsm is augmented due to elevated afterload and MRV increases, therefore MR worsens. Indeed, a significant increase in regurgitant flow and regurgitant orifice occurs in MR patients, when BP is raised with non-inotropic agents [65]. A possible causal association between hypertension and MR is further strengthened by data suggesting that valve calcification, a common cause of mitral valve degeneration and insufficiency, shares common mechanisms and risk factors with atherosclerosis, or even may actually be a form of atherosclerosis, for which hypertension is a major risk factor [66]. Therefore, treatment of hypertension may prevent progression or even development of MR. This concept does not provide novel information, since it is well-known that hypertension should definitely be treated in all individuals [6]. Nevertheless, it confers an additional motivation for optimal BP control and raises the question whether more aggressive antihypertensive therapy with lower BP targets would have a favorable impact on the natural history of this valvulopathy.

MR and Hypertension: Prevalence

Mitral regurgitation and arterial hypertension are both common conditions with high prevalence in the general population. It is estimated that approximately 30% of adults worldwide are hypertensives, a proportion that increases steadily with age, with 75% of people aged 70 years and older having elevated BP levels [7••, 8]. Mitral regurgitation is the most common valvulopathy. Around 90% of individuals of a cohort of the Framingham Heart Study ($n = 2881$) had a detectable MR with the large majority of cases being classified as "mild MR" (approximately 20%) or "trace" (approximately 70%). Rates of "moderate" or "severe" MR were much lower in the same study (up to 2%) [2]. Similar results were reported in a cohort of 3486 subjects in the Strong Heart Study [9]. The prevalence and severity of mitral regurgitation seem to be age-dependent [2, 9, 10].

Table 1 Summary of studies assessing the effect of different classes of antihypertensive drugs on primary and secondary mitral regurgitation

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
ACEIs/ARBs							
Heck et al. 1985 [15]	Open-label	3–5 months	10	Chronic MR	Captopril 25 mg × 3 (no control)	Change in myocardium physiology	Reduction in RF*.
Wisenbaugh et al. 1994 [16]	RCT	6 months	32	Asymptomatic or mildly symptomatic severe MR	Captopril 25 mg × 3 vs placebo	Change in myocardium physiology	No significant difference in LVEDV, LVESV, LVEF.
Schon et al. 1994 [17]	Open-label	1 year	12	Moderate to severe MR	Quinapril 10–20 mg (no control)	Change in myocardium physiology, functional status	Reduction in RVol: −42%, $p = 0.0001$; LVEDV: 146 ± 26 to 109 ± 24 mL/m^2, $p = 0.0001$; LVESV: 63 ± 43 to 47 ± 29 mL/m^2, $p = 0.002$; septal wall thickness: 11.8 ± 0.7 to 10.8 ± 0.8 mm, $p = 0.0006$; LV mass: −15%, $p = 0.0004$. Significant improvement in NYHA class (by nearly 1 class).
Høst et al. 1997 [18]	Open-label	4 weeks	14	Mild to severe MR due to MVP	Ramipril 10 mg (no control)	Change in myocardium physiology	Reduction in RVol: −14%, $p < 0.05$. No significant change in LV volumes and mass.
Marcotte et al. 1997 [19]; Wong et al. 2006 [20]	RCT	1 year	23	Moderate MR	Lisinopril ($n = 12$) vs placebo ($n = 11$)	Change in myocardium physiology	Reduction in RF with lisinopril: −6.4 ± 3.5% vs + 3.7 ± 3.2%, $p < 0.05$; no change in LV volumes and mass. Reduction in LA volumes with lisinopril (subsequent analysis): maximum LA volume 88 ± 33 to 75 ± 23 mL, $p < 0.01$; minimum LA volume 46 ± 20 to 38 ± 16 mL, $p < 0.01$.
Tischler et al. 1998 [21]	Open-label	6 months	12	Severe MR due to MVP	Enalapril (no control)	Change in myocardium physiology, functional status	At rest: reduction in LVEDV (214 ± 67 to 189 ± 58 mL, $p < 0.001$); LVESV (69 ± 21 to 53 ± 16 mL, $p = <0.001$); total SV (145 ± 50 to 136 ± 44 mL, $p < 0.05$); RF (53 ± 10 to 44 ± 17%, $p < 0.05$); RVol ($p < 0.05$), increase in LVEF (67 ± 5 to 71 ± 4%, $p < 0.01$). After exercise: reduction in LVEDV (208 ± 60 to 184 ± 50 mL, $p < 0.01$); LVESV (49 ± 15 to 42 ± 13 mL, $p < 0.005$); total SV (159 ± 50 to 143 ± 41 mL, $p < 0.05$); RF (45 ± 13 to 35 ± 14%, $p < 0.05$); RVol ($p < 0.05$). No effect on exercise capacity, MR remained severe.
Enriquez-Sarano et al. 1999 [22]	Observational	561 ± 423 days	74	MR	RAAS inhibitors	Progression of MR	Reduction in afterload indices (systolic BP, LVESWS, peripheral vascular resistance) was determinant of MR regression (RVol, RF, EROA). No effect of treatment with RAAS inhibitors on MR progression despite a significant effect on systolic BP (− 8 ± 17 vs 0 ± 13 mmHg, $p = 0.043$), LVESWS (− 23 ± 34 vs + 1.2 ± 28 g/cm^2, $p = 0.003$).
Gupta et al. 2001 [23]	RCT	6 months	87	Mildly symptomatic rheumatic severe MR	Nicorandil vs enalapril	Change in myocardium physiology	Nicorandil vs enalapril Both decreased LVESV index: 57.4 ± 24.8 to 43.2 ± 20.7 mL/m^2, $p = 0.003$ vs 50.0 ± 19.0 to 40.4 ± 14.2 mL/m^2, $p = 0.006$; LV mass index: 218.0 ± 88.0 to 188.0 ± 76.0 g/m^2, $p = 0.05$ vs 217.2 ± 48.0 to

Table 1 (continued)

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
							186.2 ± 45.0 g/m^2, $p = 0.002$; LVESWS: 152.9 ± 29.0 to 126.0 ± 25.0 dyne/cm^2, $p = 0.001$ vs 150.0 ± 30.2 to 138.0 ± 9.0 dyne/cm^2, $p = 0.002$ Both improved LVEF: 63.8 ± 7.0 to 71.0 ± 6.7%, $p < 0.0001$ vs 63.2 ± 6.9 to 67.5 ± 6.4%, $p = 0.002$. Nicorandil more effective in absolute reduction of LVESV index: 13.3 ± 10.1 vs 9.6 ± 5.9 mL/m^2, $p = 0.02$ and absolute improvement of LVEF: 7.2 ± 4.7 vs 4.2 ± 2.6%, $p = 0.0005$.
Dujardin et al. 2001 [24]	Open-label	1 month	28	MR	Losartan 50 mg (no control)	Change in MR severity	Reduction in RVol: 77 ± 28 to 64 ± 26 mL, $p < 0.001$; EROA: 43 ± 16 to 37 ± 15 mm^2, $p < 0.001$; LVESWS: 173 ± 46 to 156 ± 44 g/cm^2, $p < 0.001$.
Harris et al. 2005 [25]	Open-label	6 months	26	Asymptomatic moderate to severe MR	Ramipril (no control)	Change in MR severity, LV size and functional status	No significant reduction in EROA: 45.3 ± 39.5 to 41.6 ± 34.7 mm^2, p = NS. Significant reduction in the hypertensive subgroup: 55.1 ± 26 to 37.4 ± 35.4 mm^2, $p = 0.03$. No significant change in LV size, exercise capacity, or functional status.
Sampaio et al. 2005 [26]	RCT	1 year	47	Mildly symptomatic moderate to severe MR due to rheumatic valve disease or MVP	Enalapril 20 mg × 2 ($n = 26$) vs placebo ($n = 21$)	Change in MR severity, myocardium physiology, and functional status	Enalapril significantly reduced: RVol: 257 ± 96 to 192 ± 84 mL, $p < 0.05$; MR jet area: 9.4 ± 2.4 to 6.9 ± 2.7 cm^2, $p < 0.05$; mitral inflow volume: 315 ± 98 to 250 ± 85 mL, $p < 0.05$; MROA: 2.0 ± 0.7 to 1.5 ± 0.7 mm^2, $p < 0.05$; RF: 80 ± 7 to 74 ± 9%, $p < 0.05$; LVEDD: 6.4 ± 0.5 to 6.1 ± 0.5 cm, $p < 0.05$; LVESD: 4.2 ± 0.4 to 4.0 ± 0.3 cm, $p < 0.05$; LA diameter: 4.8 ± 0.6 to 4.5 ± 0.6 cm, $p < 0.05$; LV mass index: 176 ± 45 to 160 ± 45 g/m^2, $p < 0.05$. No change in forward SV, systolic indices, and exercise capacity.
Sekuri et al. 2008 [27]	Open-label	6 weeks	27	Moderate MR due to rheumatic valve disease or MVP	Losartan 50 mg (no control)	Change in MR severity, myocardium physiology, and functional status	Increase in treadmill exercise time: 477.7 ± 147.9 to 559.6 ± 142.8 s, $p = 0.006$; metabolic equivalent values: 10.9 ± 2.9 to 12.4 ± 3.1, $p = 0.002$. Reduction in RVol: 29.3 ± 14.1 to 25.1 ± 14.8 mL, $p = 0.025$; increase in LVEF: 51.70 ± 13.37 to 54.11 ± 11.75%, $p = 0.015$. No change in MR orifice diameter, LV, and LA dimensions.
Strauss et al. 2012 [28]	Meta-analysis		18 studies	MR	RAAS inhibitors	Change in MR severity	In studies assessing daily therapy modest reduction in RVol: 8.3 mL (95% CI 1.5–15.2); RF: 7.7% (95% CI 4.9–10.6); LVEDV index: 11.5 mL/m^2 (95% CI 2.4–20.6).
Supino et al. 2014 [29]	Observational	Follow-up 7.9 ± 5.6 years	52	Asymptomatic or mildly symptomatic severe MR	Any indirect vasodilator ($n = 7$, 6 patients on ACEI/ARB, 1	Death or indication for mitral valve surgery	Vasodilator use vs no vasodilator use. No benefit with vasodilator use: average annual risk for endpoint: 17% vs 16%, p = NS. Modest benefit of vasodilator use in hypertensives: $p = 0.041$.

Table 1 (continued)

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
					patient on a-blocker) vs no vasodilator ($n = 45$)		Harm from vasodilator use in non-hypertensives: average annual risk for endpoint: 69% vs 15%, $p = 0.007$.
Beta-blockers							
Oh et al. 2007 [30]	Retrospective	Mean follow-up 20 months	134	Mildly symptomatic moderate to severe MR with LVEF > 50%	Beta-blockers, afterload reduction agents (ACEIs, CCBs, hydralazine)	Change in myocardium physiology	Use of beta-blockers was associated with LVEF worsening ($p < 0.02$) and use of afterload reduction drugs was associated with LVEF improvement ($p < 0.03$). No LVEF improvement from afterload reduction in patients receiving beta-blockers. Decrease in MR severity in patients that afterload reduction therapy was initiated during follow-up.
Varadarajan et al. 2008 [31]	Retrospective	NA	895	Severe MR with normal LVEF	Beta-blockers ($n = 281$) vs no beta-blockers ($n = 614$)	Mortality	Reduction in mortality: HR: 0.62 (95% CI 0.46–0.83), $p = 0.002$ (independent of the presence of hypertension and CAD).
Stewart et al. 2008 [32]	RCT (crossover)	2 weeks	25	Moderate or severe degenerative MR	Metoprolol vs placebo	Change in MR severity, myocardium physiology	Metoprolol significantly increased forward SV: 94 ± 20 vs 89 ± 21 mL, $p = 0.03$; LV pump efficiency: 18% (95% CI, 8 to 27%); and decreased LV work: 21% (95% CI, 16 to 27%). No effect on LVEF, RVol. Metoprolol increased LVEDV: 235 ± 48 vs 229 ± 50 mL, $p = 0.003$; LVESV: 85 ± 21 vs 81 ± 21 mL, $p = 0.01$.
Ahmed et al. 2012 [33]	RCT	2 years	38	Asymptomatic moderate to severe MR with normal LVEF	Metoprolol ($n = 19$) vs placebo ($n = 19$)	Change in myocardium physiology	Improvement with metoprolol in LVEF (annual rate): 0.47 ± 0.75 vs − 2.48 ± 0.75, $p = 0.006$; peak early filling rate (annual rate): 0.09 ± 0.06 vs − 0.18 ± 0.06 mL/s, $p = 0.001$. Numerically fewer patients in the metoprolol group had MV surgery (2 vs 6, p = NS). No benefit in LV volumes, LV mass, or LV systolic longitudinal strain rate.
Vasodilators							
Chatterjee et al. 1973 [34]	Open-label	NA	8	Clinically significant MR	I.V. sodium nitroprusside (no control)	Hemodynamic indices	Decrease in PCWP: 33 ± 1.8 to 16 ± 1.4 mmHg, $p < 0.005$; increase in forward cardiac index: 2.2 ± 3.5 to 3.3 ± 0.47 lt/min/m^2, $p < 0.005$; and forward SV index: 23 ± 4.4 to 36 ± 6.6 mL/m^2, $p < 0.005$.
Goodman et al. 1974 [35]	Open-label	NA	14	Significant MR	I.V. sodium nitroprusside (no control)	Hemodynamic indices	Decrease in PAMP: 27.4 ± 2.7 to 19.1 ± 2.4 mmHg, $p < 0.001$ LVEDP: 16.7 ± 1.6 to 9.3 ± 1.2 mmHg, $p < 0.001$, forward cardiac index: 2.2 ± 0.2 to 2.7 ± 0.2 lt/min/m^2, $p < 0.001$. In 10 patients, significant decrease in LVEDV: 196 ± 10 to 177 ± 10 mL, $p < 0.01$; LVESV: 90 ± 10 to 77 ± 9 mL, $p < 0.05$; RF: 57 ± 6 to 42 ± 6%, $p < 0.01$; RVol: 62 ± 8.7 to

Table 1 (continued)

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
							43 ± 7.2 mL, $p < 0.01$; and significant increase in forward SV: 45 ± 7.3 to 57 ± 7.7 mL, $p < 0.01$.
Harshaw et al. 1975 [36]	Open-label	NA	7	Severe MR	I.V. sodium nitroprusside (no control)	Hemodynamic indices	Decrease in RVol index: 73 ± 19 to 55 ± 12 ml/m^2*; RF: 70 ± 7 to 57 ± 6%*; PCWP: 29 ± 2 to 13 ± 1 mmHg*; LVEDP: 20 ± 3 to 9 ± 1 mmHg*. Increase in cardiac index: 2.2 ± 0.5 to 3.1 ± 0.4 lt/min/m^2*; forward SV index: 23 ± 4 to 34 ± 4 mL/m^2*.
Greenberg et al. 1978 [37]	Open-label	NA	10	Severe MR	I.V. hydralazine (no control)	Hemodynamic indices	Decrease in regurgitant stroke volume index: 40 ± 6 to 27 ± 6 mL/m^2, $p < 0.001$; increase in forward SV index: 22 ± 2 to 33 ± 3 mL/m^2, $p < 0.001$; no effect on LVEDV, LVEDP.
Greenberg et al. 1982 [38]	Open-label	NA	16	Severe MR	Hydralazine 50–225 mg (no control)	Hemodynamic indices	Acute effects on rest: increase in cardiac index (2.5 ± 0.1 to 3.7 ± 0.2 L/min/m^2, $p < 0.001$) and SV index (30 ± 2 to 39 ± 2 mL/m^2, $p < 0.001$); decrease in PAWP (18 ± 2 to 15 ± 2 mmHg, $p < 0.025$). Acute effects on exercise: increase in cardiac index (3.7 ± 0.3 to 4.9 ± 0.3 L/min/m^2, $p < 0.001$) and SV index (36 ± 3 to 45 ± 2 mL/m^2, $p < 0.005$), decrease in PAWP (27 ± 2 to 21 ± 1 mmHg, $p < 0.001$). Long-term effects: improvement in NYHA class in half of the patients.
Cacciapuoti et al. 1993 [39]	RCT	5 years	223	Hypertension, no mitral valve disease	Nifedipine ($n = 76$) vs enalapril ($n = 72$) vs atenolol ($n = 75$)	Mitral annular calcium, MR	Fewer patients on nifedipine developed mitral annular calcium and MR compared to enalapril and atenolol [2.6% vs 18% vs 20% ($p < 0.01$) and 0% vs 13.9% vs 17.3% respectively*]
Kelbaek et al. 1996 [40]	RCT	2 weeks	21	Moderate to severe MR	Nifedipine 20 mg × 2 ($n = 7$) vs isosorbide dinitrate 20 mg × 2 ($n = 7$) vs placebo ($n = 7$)	MR severity	*Acute effects* Nifedipine significantly reduced LVESV by 9% (95% CI for the difference 1–18 mL) and increased forward SV by 30% (46 to 60 mL, 95% CI for the difference 6–21 mL), no effect on RF, LVEDV. Isosorbide dinitrate significantly reduced LVEDV by 16% (217 to 192 mL, 95% CI for the difference 7–37 mL), LVESV by 20% (89 to 71 mL (95% CI for the difference 7–31 mL), no effect on RVol, RF, forward SV. *2-week effects* Nifedipine significantly reduced RVol by 20% (69 to 55 mL, 95% CI for the difference 6–31 mL), RF (49 to 38%, 95% CI for the difference 5–21%) and increased mean forward SV by 18% (62 to 73 mL, 95% CI 8–24 mL). Isosorbide dinitrate produced no significant hemodynamic effects.

Table 1 (continued)

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
Kizilbash et al. 1998 [41]	Open-label	NA	31	Moderate to severe MR	I.V. sodium nitroprusside (no control)	Change in MR severity, myocardium physiology	Decrease in LVEDV: 5.5 ± 0.8 to 5.3 ± 0.8 cm, $p < 0.0001$; LVESV: 4.3 ± 0.9 to 4.2 ± 0.9 cm, $p < 0.0001$; LVESWS: 121 ± 50 to 89 ± 36 dynes/cm^2, $p < 0.0001$ No effect on RF, RVol, VC width, EROA. Wide variability in response (in 52% improved MR severity, 26% worsened, 22% unchanged)
Secondary MR							
Weiland et al. 1986 [42]	Open-label	NA	14	Severe HF (mean LVEF: 16 ± 4%), 5 patients with mild or no MR (RF < 0.10), 9 patients with more severe MR (RF > 0.30)	I.V. nitroprusside (no control)	Hemodynamic indices	Nitroprusside increased forward CO in all patients with significantly greater increase in patients with RF > 0.30 (64 ± 34% vs 31 ± 17%, $p < 0.01$). Nitroprusside decreased mean RF in the same group (0.44 ± 0.12 to 0.26 ± 0.15, $p < 0.005$).
Stevenson et al. 1987 [43]	Open-label	48–72 h	15	Severe HF (mean LVEF: 19 ± 6%)	I.V. nitroprusside and furosemide, per os captopril, hydralazine, nitrates (no control)	Hemodynamic indices	Significant increase in forward SV with decrease in total SV probably due to decrease in MR flow: forward SV: 37 ± 14 to 52 ± 14 mL, $p < 0.01$; total SV: 74 ± 22 to 59 ± 20 mL, $p < 0.01$. Improvement in other hemodynamic indices: PAWP: 32 ± 8 to 16 ± 4 mmHg, $p < 0.01$ LVEDV: 390 ± 138 to 301 ± 126 mL, $p < 0.01$ LVESV: 316 ± 127 to 241 ± 111 mL, $p < 0.01$ RAP: 11 ± 6 to 5 ± 2 mmHg. No change in LVEF.
Stevenson et al. 1990 [44]	Open-label	96 h	10	LVEF < 25%, PCWP > 25 mmHg	I.V. nitroprusside and furosemide or bumetanide, per os captopril or hydralazine (no control)	Hemodynamic indices before and after treatment at rest and during exercise	Significant increase in forward SV without increase in total SV probably due to decrease in MR flow both at rest and exercise, significant decrease in PCWP, LVEDV both at rest and exercise, no change in LVEF. Increase in exercise time with therapy: 10 ± 4 to 16 ± 4 min, $p < 0.001$. *At rest* Forward SV: 38 ± 17 to 53 ± 16 mL, $p < 0.001$, PCWP: 36 ± 5 to 19 ± 3 mmHg, $p < 0.001$, cardiac index: 1.9 ± 0.6 to 2.6 ± 0.6 lt/min/m^2, $p < 0.005$, RAP: 20 ± 6 to 7 ± 3 mmHg, $p < 0.001$.
Hamilton et al. 1991 [45]	Open-label	6 months	14	HF NYHA III, IV (mean LVEF: 17 ± 4%) with MR	I.V. nitroprusside and diuretics for 48–96 h followed by per os captopril, enalapril, hydralazine,	Hemodynamic indices, MR and TR severity	Initial therapy (48–96 h) decreased MR severity, improvement sustained after 6 months: MR grade: 2 ± 1/3 to 1.1 ± 1/3 to 1.3 ± 1.1/3, $p < 0.01$; MR color flow fraction: 0.33 ± 0.16 to 0.13 ± 0.12 to 0.09 ± 0.11, $p < 0.01$; MR velocity volume index: 34 ± 21 to 17 ± 19 to 15 ± 14, $p < 0.01$. Similar results for TR severity: TR grade: 1.8 ± 0.7/3 to1.1 ± 0.9/3 to 0.6 ± 0.8/3, $p < 0.01$; TR color flow fraction: 0.36 ± 0.16 to 0.18 ± 0.18 to 0.18 ± 0.18,

Table 1 (continued)

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
					nitrates, diuretics (no control)		$p < 0.01$; TR velocity volume index: 27 ± 14 to 8 ± 10 to 5 ± 6, $p < 0.01$. Improvement in signs and symptoms of HF and hemodynamic indices: PAWP: 30 ± 6 to 17 ± 4 mmHg, $p < 0.01$; CO: 3.4 ± 0.9 to 5.4 ± 1.5 lt/min, $p < 0.01$; RAP: 13 ± 5 to 7 ± 4 mmHg, $p < 0.01$; PAMP: 42 ± 5 to 30 ± 7 to 30 ± 11 mmHg, $p < 0.01$; mean RA volume: 85 ± 23 to 64 ± 23 to 52 ± 14 cm^3, all $p < 0.01$; mean LA volume: 100 ± 25 to 80 ± 19 to 65 ± 15 cm^3, all $p < 0.01$.
Seneviratne et al. 1994 [46]	RCT	12 weeks	23	At least grade 2/4 functional MR, LVEF < 40% due to CAD	Captopril 100 mg ($n = 13$) vs placebo ($n = 10$)	Change in myocardium physiology	Captopril reduced MR area: 8.1 ± 2.1 to 1.8 ± 2 cm^2 vs 9 ± 2.4 to 7.1 ± 2.9 cm^2, $p < 0.01$; LA area: 30.1 ± 5.5 to 27.1 ± 41.1 cm^2 vs 31.9 ± 6.7 to 31.4 ± 5.4, $p < 0.05$; and increased SV: 43 ± 9.6 to 60 ± 13.4 mL vs 42 ± 10.4 to 49 ± 8.9 mL, $p < 0.01$; DT: 167 ± 43 to 243 ± 38 ms vs 175 ± 44 to 191 ± 61 ms, $p < 0.01$. Trend for decrease in LVEDD: 6.4 ± 0.3 to 6.1 ± 0.4 cm vs 6.4 ± 0.5 to 6.5 ± 0.6 cm, $p = 0.06$.
Levine et al. 1997 [47]	Open-label	6 months	99	Impaired systolic LV function	Uptitration of ACEIs and nitrates	Change in myocardium physiology, functional status	Intensified therapy with ACEIs and nitrates improved MR severity: grade 2.1 ± 1.3/4 to 1.4 ± 1.3/4, $p = 0.0002$; increased LVEF: 21 ± 9 to 30 ± 13%, $p < 0.001$); reduced LVEDD (6.6 ± 0.9 to 6.3 ± 1 cm, $p = 0.002$). Sustained reduction of MR severity in patients with longer follow-up (3.1 ± 1.9 years): 1.9 ± 1.5/4 to 1.1 ± 1.3/4, $p = 0.01$.
Levine et al. 1998 [48]	Open-label	12 months	19	At least grade 3/4 functional MR due to impaired systolic LV function	High doses of lisinopril and isosorbite nitrate (no control)	Change in myocardium physiology, functional status	Decrease in MR severity (to grade 0–1/4) in 8 patients LVEDD ≤ 6.8 cm predicted MR improvement with a 83% sensitivity and specificity In the whole cohort, improvement in LVEF: 20 ± 6 to 30 ± 10%, $p = 0.0005$; NYHA class: 3.0 ± 0.7 to 1.6 ± 0.2, $p < 0.0001$; HF-related hospitalizations: 2.3 ± 0.5 to 0.6 ± 0.2, $p = 0.01$.
Lowes et al. 1999 [49]	RCT	4 months	59	Symptomatic HF with LVEF < 35%	Carvedilol ($n = 36$) vs placebo ($n = 23$)	Change in myocardium physiology	Carvedilol improved MR severity assessed by MR ratio (defined as MR jet area/LA area): 0.26 ± 0.04 to 0.20 ± 0.04 vs 0.28 ± 0.05 to 0.41 ± 0.08, $p = 0.02$ Carvedilol also improved LVEF: 21 ± 1 to 31 ± 2% vs 19 ± 2 to 20 ± 2%, $p = 0.0001$ and reduced LV wall thickness: 1.31 ± 0.04 to 1.22 ± 0.06 cm vs 1.33 ± 0.04 to 1.41 ± 0.04 cm, $p = 0.02$, LV mass: 276 ± 15 to 247 ± 17 g vs 301 ± 28 to 340 ± 28 g, $p = 0.01$.
Capomolla et al. 2000 [50]	Observational	6 months	90	HF with LVEF < 40%	Carvedilol group ($n = 45$) vs		Carvedilol significantly reduced RVol: 16 ± 13 vs 47 ± 24 mL, $p = 0.0003$, EROA: 0.13 ± 0.1 vs 0.51 ± 0.27 cm^2,

Table 1 (continued)

Study	Design	Follow-up duration	Participants	Condition	Drug intervention	Primary outcome	Outcomes
					control group ($n = 45$)	Change in myocardium physiology	$p = 0.00001$, LVEDV index: 135 ± 38 vs 143 ± 52 mL/m^2, $p = 0.003$, LVESV index: 93 ± 37 vs 107 ± 39 mL/m^2, $p = 0.00001$, LVESD: 56 ± 9 vs 65 ± 10 mL, $p = 0.006$, and increased LVEF: $29 \pm 9\%$ vs $25 \pm 7\%$, $p = 0.004$, DT: 196 ± 63 vs 132 ± 45 ms, $p = 0.0001$, forward SV: 77 ± 15 vs 61 ± 13 mL, $p = 0.004$.
Okura et al. 2016 [51]	Retrospective	NA	296	Moderate to severe MR due to CAD	Any RAAS inhibitor ($n = 130$ patients) vs no RAAS inhibitor ($n = 166$ patients)	Survival, event-free survival	Use of RAAS inhibitors was associated with significantly better survival ($p = 0.006$) and event-free survival ($p = 0.02$). No use of RAAS inhibitors independent predictor of cardiac events ($p = 0.048$).
Kim et al. 2017 [52]	Retrospective	NA	551	At least mild MR due to CAD	Any RAAS inhibitor ($n = 395$ patients) vs no RAAS inhibitor ($n = 156$ patients)	All-cause mortality, cardiac death, and composite of cardiac death and heart failure	Use of RAAS inhibitors was associated with significantly lower all-cause mortality (9% vs 25%, $p = 0.001$), cardiac mortality (3% vs 13%, $p = 0.009$), and incidence of the composite of cardiac death and heart failure (7% vs 20%, $p = 0.025$).

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BP* blood pressure, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CI* confidence interval, *CO* cardiac output, *DT* deceleration time, *EROA* effective regurgitant orifice area, *FU* follow-up, *HF* heart failure, *HR* hazard ratio, *I.V.* intravenous, *LA* left atrium/left atrial, *LV* left ventricle/left ventricular, *LVEDD* left ventricular end-diastolic diameter, *LVEDP* left ventricular end-diastolic pressure, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic diameter, *LVESV* left ventricular end-systolic volume, *LVESWS* left ventricular end-systolic wall stress, *MR* mitral regurgitation, *MROA* mitral regurgitation orifice area, *MVP* mitral valve prolapse, *NA* not available, *NS* non-significant, *NYHA* New York Heart Association, *PAMP* pulmonary artery mean pressure, *PAWP* pulmonary artery wedge pressure, *PCWP* pulmonary capillary wedge pressure, *RA* right atrium/right atrial, *RAP* right atrial pressure, *RAAS* renin-angiotensin-aldosterone system, *RCT* randomized controlled trial, *RF* regurgitation fraction, *RVol* regurgitation volume, *SV* stroke volume, *TR* tricuspid regurgitation, *VC* vena contracta

*p value for the specific comparison is not provided

MR and Hypertension: Associations

Several studies have evaluated the association of hypertension with development and progression of MR. As for studies that made no distinction between primary and secondary MR, a recent longitudinal cohort study conducted by Rahimi et al. examined the electronic medical records of 5.5 million adults in the UK and the investigators demonstrated a continuous association between MR and BP values. During follow-up (mean time 10 years), 28,655 patients were diagnosed with MR (0.52%), a proportion that implies that clinically severe cases were mainly included in the examined medical records and not asymptomatic patients with mild disease, who are the vast majority of MR cases [53]. A 20 mmHg increase in systolic BP was associated with a 26% higher risk for MR [adjusted hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.23–1.29] and a 10 mmHg increase in diastolic BP was linked to a 24% higher risk for MR (adjusted HR 1.24, 95% CI 1.20–1.28). When analysis was performed after adjustment for CAD, MI, and HF, association between hypertension and MR was only slightly attenuated (adjusted HR 1.22, 95% CI 1.20–1.25), indicating that the mediating effect of causes of secondary MR was small. The relationship between BP values and MR risk was consistent in all age subgroups, but in younger patients the increase in risk was higher for the same BP increase [53••]. Towards this direction, severity of MR was independently associated with a history of hypertension, among other parameters, in a large study with cardiac ultrasound measurements ($n = 6851$ participants) [11•]. Presence and severity of MR were as well related to higher systolic BP and history of hypertension in the Strong Heart Study, however, in multivariate analysis association between hypertension and presence of MR lost statistical significance [9]. In addition, no association between hypertension and incidence of severe MR necessitating surgical treatment was observed in a recent study that compared 181 patients operated for MR with 717 matched controls [67•]. Similarly, a Japanese study with 313 AF patients did not demonstrate significant difference in the prevalence of hypertension between subjects with no/mild MR and individuals with moderate/severe primary or secondary MR [68].

As far as studies that assessed the relationship between hypertension and primary MR are concerned, the Framingham Study reported that, after exclusion of patients with MI and HF, the independent determinants of MR were age, lower body mass index (BMI), and arterial hypertension [odds ratio (OR) 1.6, 95% CI 1.2–2.0 for hypertension] [2]. Moreover, two older studies reported a higher prevalence of MR in hypertensive patients compared to healthy controls of similar age (36.1% vs 27%, $p < 0.01$ in the Italian study that enrolled 130 hypertensives and 100 controls, 69% vs 35%, $p < 0.05$ in the smaller Japanese study) [12, 13]. Another study compared 54 patients with severe MR due to mitral valve prolapse (MVP) with 117 patients with uncomplicated MVP across an 11-year follow-up period. Authors reported that patients with severe MR had higher rate of hypertension and, among severe MR patients, those who underwent surgery were more likely to be hypertensives; however, similar to the Strong Heart Study, in multivariable analysis, associations were no longer significant [63]. A strong association between pre-existing hypertension and primary chordae tendinae rupture (CTR) was demonstrated by Juang et al. in a large retrospective study that included 351 patients with primary (idiopathic) CTR, 143 patients with secondary CTR, and 1053 controls (no CTR). The prevalence of hypertension was significantly higher in the primary CTR group (50.9% vs 14.6% in the secondary CTR group vs 14.9% in the control group, $p < 0.001$, OR after correction for age: 3.6 and 6.6 for secondary CTR group and control group respectively, both $p < 0.001$) [69]. Similar results were reported in a smaller study with 98 patients (68 with primary CTR and 30 with secondary CTR) [70]. The impact of hypertension on the prognosis of patients with a history of mitral valve repair due to degenerative MR has also been examined. David et al. found that hypertension was independently associated with recurrent moderate or severe MR in a cohort of 606 patients (HR 1.82, 95% CI 1.13–2.94, $p = 0.013$) [71•], whereas it did not achieve statistical significance as a predictor of mitral valve dysfunction in a smaller Korean study ($p = 0.059$) [72].

In terms of functional MR, hypertension may constitute a major risk factor, either per se or through precipitation of clinical entities such as HF, CAD, HF, and AF that predispose to mitral valve pathology. Albeit, no association between hypertension and presence or severity of secondary MR in either HFpEF or HFrEF was observed in a recent large registry with 4842 HF patients [59•]. On the other hand, a closer relationship between hypertension and pure annular dilation (generally observed in secondary MR cases) compared to other causes of severe primary or secondary MR, mainly MVP and CAD, was found by Glower et al. in a study with 535 patients that needed mitral valve repair [73]. Furthermore, in a cohort of AF patients referred for ablation, Gertz et al. reported that rates of hypertension were higher in patients with moderate or severe secondary MR compared to those with mild or less MR (62% vs 43%, $p = 0.05$). After adjustment, hypertension lost its association with MR; however, the multivariable model included parameters that may be influenced by increased BP (namely LA and mitral annulus dimensions and persistent AF) [58•]. Finally, hypertension seems to affect mitral valve functionality in hypertrophic cardiomyopathy (HCM). Aslam et al. evaluated 122 hypertensive and 74 normotensive patients with HCM and no primary valvular diseases in a study where LV wall thickness, LV end-diastolic diameter (LVEDD), LV ejection fraction (LVEF), and resting LV outflow tract obstruction were similar in both groups.

Authors suggested that hypertensive patients had a significantly higher prevalence of systolic anterior motion of the mitral valve (52% vs 19%, $p = 0.02$); no multivariable analysis was performed in this study [74].

Mitral annulus calcification (MAC) is another condition that predisposes to MR [75] and some studies have linked MAC to hypertension. In a cohort of 5694 subjects of the Framingham Study, systolic BP was independently associated with MAC [76]. Along this line, Boon et al. suggested that hypertension prevalence was increased (adjusted OR 2.72, 95% CI 1.92–3.86) in patients with MAC compared to controls in a study that used echocardiographic data of 8160 patients [77] and Aronow et al. reported similar findings in univariate analysis in a cohort of 531 elderly patients [78]. On the other hand, in the Multi-Ethnic Study of Atherosclerosis (MESA), no significant association between hypertension and MAC (after adjustment for other risk factors) was observed; nevertheless, hypertension was related to MAC severity [79].

Some studies have reported that presence of both hypertension and MR may produce an additive impact on LV geometry. According to a sub-analysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study that included 939 patients with hypertension and left ventricular hypertrophy (LVH), presence of mild/moderate valvular (aortic or mitral) regurgitation was associated with increased sex-adjusted LV internal dimensions, LV mass index, and LA diameter, suggesting a higher prevalence of structural heart abnormalities [80]. In another study with 85 patients who underwent mitral valve repair, presence of hypertension (after adjustment) was negatively correlated with post-operative left ventricular mass index regression and LA volume index regression [81]. However, a larger study with 530 patients with mitral valve repair found no relationship between hypertension and pre-operative LV mass index or post-operative LV mass index regression [82].

In summary, pathophysiologic considerations and data from observational and retrospective studies support association between hypertension and MR. Nevertheless, randomized studies are lacking, whereas findings are not consistent and common risk factors, e.g., age, may act as confounders. Therefore, the net effect of hypertension on MR incidence and severity remains uncertain.

Treatment with Antihypertensive Agents in MR: Pathophysiology

Optimal antihypertensive treatment in hypertensives with MR is not clearly defined. Certain lines of evidence suggest a possible beneficial effect of specific antihypertensive agents on MR severity independent of BP lowering. Thus, specific pathophysiologic associations might guide the medical treatment strategy in this valvular disease.

Chronic severe MR causes volume overload; preload is increased due to the regurgitant volume (RVol) and as a compensatory response to maintain adequate forward stroke volume (SV), LV is dilated (elevated end-diastolic and end-systolic diameter) and, according to Laplace's law ($T = P \times r/2 \times h$, where T is wall stress, P is pressure, r is radius, and h is wall thickness), LV wall stress increases. Thereby, afterload is augmented independent of the presence of hypertension; mitral regurgitation itself does not produce elevated BP values [83••–85]. The aforementioned hemodynamic disturbances, along with activation of neurohormonal mechanisms, i.e., the renin-angiotensin-aldosterone system (RAAS) [86] and the sympathetic nervous system [87–89], result in LV remodeling and systolic dysfunction [90, 91]. In addition, LV dilation, regardless of its etiology (primary MR, systolic dysfunction, or both), causes tethering of the mitral annulus and displacement of papillary muscles with further MROA increase and MR worsening resulting in a vicious cycle ("MR begets MR") [55•, 92].

These pathophysiological considerations provide a rationale for the use of drugs that interfere in these mechanisms (RAAS inhibitors, beta-blockers, vasodilators, diuretics) in non-hypertensive MR patients with normal systolic LV function. Preload reduction decreases LV end-diastolic volume (LVEDV), thereby MR orifice area, and improves workload conditions; afterload reduction decreases mean pressure gradient, therefore MR volume, and may increase forward SV; inhibition of RAAS and sympathetic system may prevent LV remodeling [14, 83••]. Experimental data suggest that cellular and hemodynamic alterations are present in early stages of the disease [93]; thereby, reversal of these abnormalities may be beneficial. Thus, medical therapy could attenuate MR severity, delay disease progression, and postpone surgical therapy in non-severe MR patients or in severe MR patients not fulfilling criteria for surgery [28••], where a strategy of watchful waiting has been found to be safe [94]. It may also improve symptoms and outcomes in high surgical risk or inoperable severe MR patients.

On the other hand, others argue that medical therapy has no place in normotensive MR patients with normal LVEF, because afterload is not increased and LV systolic dysfunction has not yet occurred, situations met at advanced stages of the disease [83••–85, 90]. Moreover, antihypertensive agents that reduce preload and/or afterload may worsen MR in MVP and hypertrophic obstructive cardiomyopathy (HOCM), where LV is not dilated, and inadequate LV filling or intense vasodilation may result in augmented LV outflow tract gradients and increased systolic anterior motion of the mitral valve [14, 83••]; thus, these drugs should be used with great caution in these patients.

Importantly, vasodilating therapy could mask presence of symptoms and/or LV dysfunction, thus potentially resulting in unnecessary delay of surgery [95, 96], which has been related

to adverse prognosis [4••]. However, the rationale of administering medical therapy in MR patients is based on the consideration that vasodilators will delay occurrence of symptoms through reduction (or delaying of increase) in MR magnitude [14, 28••, 83••]. Therefore, patients will not be exposed to the adverse effects of disease progression and any delay in surgery will occur as a result of MR regression. Furthermore, there is no evidence suggesting that asymptomatic MR patients chronically on vasodilating agents (e.g., hypertensives) have worse MR-related outcomes. Of course, this therapeutic strategy requires close clinical and echocardiographic monitoring allowing for prompt detection of features necessitating mitral valve repair or replacement.

In contrast, the clinical value of medical therapy is better established in primary MR with severely impaired systolic LV function; these patients should receive HFrEF treatment similar to all patients with reduced LVEF and according to heart failure and valvular heart disease guidelines [4••, 60]. Low LVEF at the time of surgery is a major determinant of adverse outcomes, especially if valve repair is not feasible, and mitral valve intervention in these patients confers no certain survival benefit [4••, 97–100]. Thus, in this group of MR patients, who generally carry poor prognosis, medical therapy is the first-line treatment choice and, in presence of high burden of comorbidities that increase surgical risk, often the only one applicable [4, 97]. Towards this direction, medical therapy is considered mandatory in secondary MR, particularly when caused by HFrEF [3, 4, 60, 101]. Afterload reduction with vasodilators (in non-hypotensive patients) is also considered useful in acute MR for initial stabilization and may act as a "bridge" to surgical treatment [3, 4, 90, 101]. A summary of mechanisms possibly linking MR and hypertension and suggesting potential beneficial effects of antihypertensive agents on MR patients is shown in Fig. 1.

The predominant role of surgical therapy in the management of severe primary MR makes conduction of relevant studies difficult and existing data are scarce. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, and, to a lesser extent, vasodilators have been tested in clinical trials, but most of them were non-randomized with relatively few patients and results have been inconsistent.

Primary MR

ACEIs and ARBs

Only small clinical trials ($n < 100$ patients in all studies), with the majority of them being non-randomized, have evaluated the effects of ACEIs and ARBs on regurgitation severity and LV remodeling and function in patients with primary MR and normal LV systolic function. The first

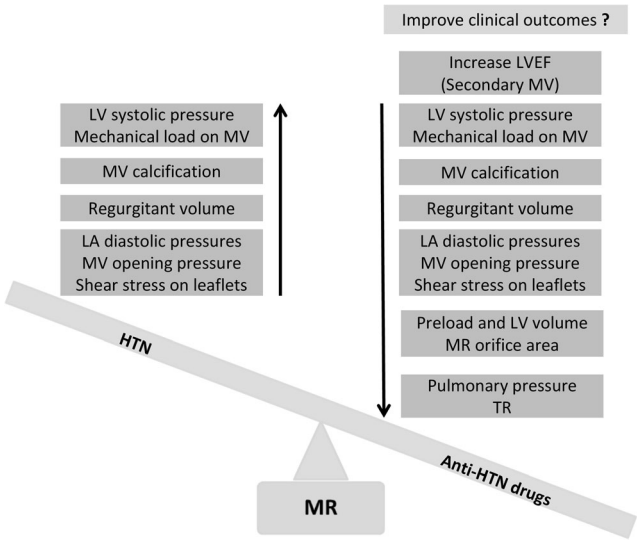

Fig. 1 Summary of the detrimental mechanisms linking mitral regurgitation (MR) and hypertension and the salutary effects of antihypertensive drugs in these patients. LV left ventricle, MV mitral valve, LA left atrium, LVEF left ventricle ejection fraction, MR mitral regurgitation, TR tricuspid regurgitation

evidence that ACEIs could be beneficial in MR was derived more than three decades ago, where captopril reduced regurgitation fraction (RF) in a small sample of 10 patients [15]. Another observational study reported that 1-year treatment with quinapril reduced RF, LV mass, LVEDD, and LV end-systolic volume (LVESV) in 12 symptomatic patients with chronic moderate to severe MR of mixed etiologies [17]. Moreover, 4-week treatment with ramipril in 11 symptomatic patients with mild to severe MR due to MVP significantly reduced RVol, but had no effect on LV volumes and mass [18]. Six-month treatment with enalapril was evaluated in two small studies with MR patients due to MVP and results were conflicting. Tischler et al. reported a significant reduction in LVEDV, LVESV, RF, RVol, total SV both at rest and after exercise, and an increase in LVEF at rest [21], while Harris et al. found no changes in MR severity, LV and LA dimensions, exercise capacity, or functional status [25]. Albeit, subgroup analysis in the latter study indicated a significant reduction in MR severity in the hypertensive subgroup (baseline systolic BP > 140 mmHg), expressed as a reduction of effective regurgitant orifice area (EROA), suggesting an important role of afterload reduction and obtaining BP values within the "normal" range [25]. Two other studies tested losartan in MR with positive results: Sekuri et al. reported decreased RVol, increased LVEF, and improved exercise capacity after 6-month treatment [27] and Dujardin et al. claimed that 1-month treatment with losartan decreased the degree of MR with a substantial variability among participants, which was independent of BP reduction [24]. In addition, an interesting study that

examined the progression of MR in 74 patients suggested that reduction in afterload indices, i.e., systolic BP, LV end-systolic wall stress (LVESWS), and peripheral vascular resistance, was a major determinant of MR regression. However, treatment with RAAS inhibitors had no effect on MR progression, since these individuals had similar changes of RVol, RF, and EROA compared to the other patients despite a significant decrease in systolic BP and LVESWS [22].

Regarding evidence from randomized studies, Wisenbaugh et al. reported that 6-month treatment with 25 mg captopril three times daily had no effect on LV end-systolic diameter (LVESD), LVEDD, or LVEF compared to placebo in 32 asymptomatic or mildly symptomatic patients with chronic isolated MR, mainly due to rheumatic disease [16]. Another randomized controlled trial (RCT) tested lisinopril vs placebo in 23 asymptomatic patients with moderate MR and normal LV systolic function for a follow-up period of 1 year. Lisinopril reduced MR severity assessed by RF, but not LV volumes or LV mass [19]. The same research team demonstrated a few years later a significant reduction in LA volume in the treatment group [20]. Gupta et al. conducted the largest RCT evaluating ACEIs in MR and enrolled 87 mildly symptomatic patients with severe MR of rheumatic etiology, who were randomly assigned to enalapril and nicorandil [23], a vasodilator that is currently used in refractory stable angina [102]. After 6 months, both enalapril and nicorandil achieved a significant reduction in LVESV index, LV mass index, and LVESWS, while they increased LVEF. Nicorandil was more effective than enalapril in LVESV index absolute reduction as well as in LVEF absolute improvement [23]. Sampaio et al. also investigated the effects of 1-year treatment with enalapril in another randomized placebo-controlled study with 47 mildly symptomatic patients with moderate to severe MR of mixed etiologies. Enalapril significantly reduced LVEDD, LVESD, LV mass index, and LA diameter. Indices of MR severity were as well improved, since there was a significant reduction in RVol, MROA, RF, MR jet area, and mitral inflow volume. No improvement in forward SV, systolic function indices, or exercise capacity was observed [26]. Finally, a meta-analysis summarized evidence and concluded that RAAS inhibitors reduced RF, RVol, and LVEDV index by a modest degree in primary MR [28••].

It should be emphasized that the aforementioned clinical studies present several limitations. The sample size was relatively small in most studies, follow-up was rather short, few of them were randomized, there was heterogeneity regarding the etiology of MR, and, most importantly, there was lack of reported clinical outcomes referring to cardiovascular events, hospitalization, mitral valve intervention, or mortality. Moreover, most of the positive results in hemodynamic indices were not consistent across all trials, i.e., some studies showed improvement in specific indices and other studies in others. Therefore, there is no strong evidence supporting the use of RAAS inhibitors in MR. However, the majority of clinical trials and a recent meta-analysis reported a reduction of either RVol or LV dimensions with RAAS inhibition in MR patients, implying that larger scale trials are warranted. Importantly, in studies where baseline BP was higher, the results were more promising [14, 27] compared to those with low baseline BP [16]. In addition, in at least one prospective study the hypertensive subgroup was more likely to benefit from antihypertensive treatment in terms of reduction in MR severity [25]. These observations suggest that treatment of hypertension might exert an important, favorable role in the management of MR. Supporting this notion, a recent observational prospective study among 52 patients with severe MR assessed for a mean follow-up of 7.9 years the association between chronic use of vasodilators (7 patients, of which 5 were on ACEI, 1 on ARB, and 1 on alpha-blocker) and adverse events, defined as death or indication for valve surgery, and established a weak benefit only in the hypertensive subjects of the enrolled population [29•].

Beta-blockers

Limited studies have evaluated the possible benefits of beta-blockade treatment in the setting of MR. A large retrospective observational cohort study investigated the effect of beta-blocker treatment on survival in 895 patients (32% on beta-blocker therapy, 70% hypertensives in the beta-blocker group) with chronic severe MR and normal LVEF. Use of beta-blockers was associated with significantly higher survival, independently of the presence of hypertension, systolic heart dysfunction, and CAD. This was the largest study to evaluate the effect of medical therapy on severe primary MR, but it was not a randomized one [31]. On the other hand, a retrospective study that examined the effect of beta-blockade and afterload reduction agents (ACEIs, calcium channel blockers, and/or hydralazine) in 134 mildly symptomatic patients with moderate to severe MR and LVEF > 50% reported that use of beta-blockers was associated with a decline in LVEF, while use of vasodilators was related to LVEF improvement only in the absence of beta-blockade exposure. A reduction in MR severity was observed in patients that treatment with vasodilators was initiated during follow-up [30]. More recently, a randomized placebo-controlled trial evaluated the effect of metoprolol on LV dimensions and function in 38 patients with chronic

moderate to severe isolated degenerative MR and normal LVEF. After 2 years of treatment, authors reported modest beneficial effects on LVEF and LV diastolic function assessed by peak early diastolic filling rate, but no effect on LV volumes, LV mass, or LV systolic longitudinal strain rate. Six patients in the placebo group and two patients in the treatment group had mitral valve surgery during follow-up; however, difference was non-significant [33]. Another small RCT suggested that 2-week treatment with metoprolol in 25 patients with moderate or severe degenerative MR increased forward SV and LV pump efficiency and decreased LV work, but did not reduce RVol and slightly increased LV dimensions [32]. As clinical outcomes have not been adequately investigated, no safe conclusions can be derived until larger randomized trials are released.

Other Vasodilators

Evidence from other antihypertensive-vasodilating agents in patients with MR is also scarce and is derived from small old studies. Short-term treatment with intravenous hydralazine significantly increased forward SV and decreased RVol, but had no effect on LVEDV and LV filling pressure in a small study with 10 severe MR patients [37]. Similarly, the same agent tested in 16 patients produced a significant reduction in pulmonary artery wedge pressure and increase in cardiac index and SV index both at rest and exercise in the acute phase. Long-term treatment (mean duration 13 months) resulted in marked improvement in symptoms in half of the patients [38]. Three other small studies ($n < 15$ patients with severe primary MR) reported that intravenous nitroprusside sodium improved various hemodynamic parameters, such as RVol, RF, LV filling pressures, LVEDV, LVESV, forward SV index, and pulmonary artery pressure [34–36]. In addition, Kizilbash et al. reported that nitroprusside significantly reduced LVEDD, LVESD, and ESWS in 31 patients with moderate or severe MR, but had no effect on vena contracta width, EROA, RVol, or RF, despite improvement in MR severity in 16 participants [41]. A small randomized placebo-controlled trial with 23 moderate to severe MR patients evaluated the effects of nifedipine and isosorbide dinitrate on hemodynamic parameters in the acute phase and after 2-week treatment. Isosorbide dinitrate acutely decreased mean LVEDV and LVESV with no effect on RVol and these results were attenuated after 2-week treatment. On the other hand, nifedipine acutely reduced LVESV and increased forward SV and, after 2-week treatment, decreased RVol and RF and increased forward SV [40]. Finally, an interesting RCT by Cacciapuoti et al. that enrolled 223 hypertensive patients without mitral valve disease examined the effect of different antihypertensive agents (nifedipine, enalapril, and atenolol) on the prevention of MAC and subsequent MR. Authors suggested that significantly fewer patients in the nifedipine group developed MAC after 5 years compared to the enalapril and atenolol group, while no patient on nifedipine had MR compared to 10 patients receiving enalapril and 13 patients receiving atenolol [39]. Overall, data from non-ACEI/ARB vasodilators in MR patients are extracted from old studies with few patients that examined mostly short-term effects; thus, no essential conclusions can be drawn.

Secondary MR

In secondary (functional) MR, the valve is usually structurally normal and its insufficiency is caused by LV dilation, ischemia, and/or LA dilation due to MI, CAD, HFrEF, HFpEF, or AF [3, 4, 55, 60, 101]. As opposed to primary MR, a beneficial effect of treatment with antihypertensive agents on both valve function and clinical outcomes is well established [3, 4, 101]; however, this benefit is mainly attributed to a favorable impact of medical therapy on the underlying disease [91]. The dynamic nature of MR orifice, which decreases with LV volume reduction, probably facilitates a favorable response to vasoactive drugs [14]. Treatment with RAAS inhibitors was associated with significantly better survival and event-free survival in a Japanese registry that included 296 patients with MI and at least moderate MR [51•] and similar results were observed in another retrospective study from Japan with 551 patients with MI and at least mild MR [52]. Moreover, Levine et al. suggested that high dose of ACEI (enalapril) combined with nitrates reduced MR severity, along with an increase in LVEF and a decrease in LVEDD, in 99 patients with impaired systolic LV function [47]. The same research group tested the effects of high doses of lisinopril and isosorbide dinitrate in patients with at least grade 3/4 functional MR and observed a decrease in MR severity only in patients with less dilated LV [48]. Capomolla et al. compared 45 patients with HF and impaired LVEF treated with carvedilol to 45 matched controls and reported decreased MR volume and EROA in the treatment group, along with an improvement in LVEF and forward SV and a reduction in LVESD, LVEDV index, and LVESV index [50]. In addition, diuretics and vasodilators have been found to attenuate secondary MR in older small studies that assessed hemodynamic indices in individuals with congestive heart failure and severely depressed LVEF [42–45]. As for randomized data, captopril improved functional MR evaluated by mitral regurgitant area in a RCT with 23 HF patients [46]. Regarding beta-blockers, carvedilol reduced MR severity assessed by MR ratio (defined as MR jet area/LA area), while it increased

LVEF and decreased LV mass, in a randomized placebo-controlled trial that enrolled 59 patients with HF due to systolic LV dysfunction [49]. Overall, medical treatment of the underlying cause (dilated cardiomyopathy, CAD) is considered mandatory in functional MR [3, 4, 60, 101].

Acute MR

Surgical intervention is the only effective treatment in acute severe MR and should be performed promptly with concomitant treatment of the underlying cause (e.g., myocardial ischemia, infection). No studies have assessed the impact of specific drugs in acute MR. However, it is common belief that medical therapy may offer valuable time for patient stabilization and preparation of surgery. Provided that the patient is not hypotensive, vasodilators and diuretics are administered, as they reduce preload and afterload, therefore diminish regurgitant volume, LV filling pressures, and LV size, and increase forward stroke volume and relief from pulmonary congestion. Nitroprusside is the drug of choice and it has been suggested that it can administered even in hypotensive patients along with inotropic agents [3, 4, 90].

Summary

In summary, hypertension and mitral regurgitation are both common entities, with high prevalence in the general population and increased rates in elderly patients. Certain pathophysiologic considerations support an association between hypertension and primary MR, while hypertension is an established risk factor for diseases that precipitate to secondary MR, i.e., CAD, HF, and AF. Although there is circumstantial evidence suggesting a link between hypertension and MR incidence and severity, findings are inconsistent and may be confounded by common risk factors, such as age; thus, a causal relationship has not been established. The role of antihypertensive agents on MR treatment remains as well uncertain. Most relevant studies, including a meta-analysis, have evaluated the potential therapeutic role of ACEIs and ARBs in primary MR patients, whereas beta-blockers and vasodilators have also been studied. Regrettably, these studies, in their majority, were small, non-randomized, and with short follow-up. Some positive results in hemodynamic and echocardiographic indices have been reported; however, neither these findings were consistent nor any benefit on hard clinical outcomes was assessed. Therefore, no safe conclusions can be drawn. Lastly, no studies have investigated whether achieving specific and/or lower than widely recommended BP values could be beneficial for MR patients.

Currently, there is general agreement that antihypertensive therapy should be administered in hypertensives according to relevant guidelines [6]. Patients with severely depressed LVEF (< 35%) and either primary or secondary MR should receive the routine therapy of HFrEF with an ACEI (or ARB), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and, if needed, loop diuretic [60]. It is as well clear that in subjects with severe MR and normal (> 60%) or mildly/moderately depressed LVEF (35–60%), medical therapy cannot substitute surgical therapy when indicated [3••, 4••]. In normotensive severe MR patients without severe systolic LV dysfunction and no indication (or at high risk) for surgical intervention, the role of medical therapy is a matter of debate, since research data are scarce and conflicting. Recommendations are generally in accordance with HF guidelines' suggestions for the management of asymptomatic systolic LV dysfunction, that is, no medication for normal LV function, use of ACEIs for mild/moderate systolic LV dysfunction, and concomitant use of beta-blockers in case of history of MI [60]. Thus, American Heart Association valvular disease guidelines suggest that medical therapy should be administered in patients with severe symptomatic MR and LVEF < 60% if surgery is not an option [3••]. European Society of Cardiology valvular disease guidelines recommend use of ACEIs in patients with HF not suitable for surgery or if symptoms persist after surgery and use of beta-blockers and MRAs as appropriate [4••]. Prophylactic use of ACEIs/ARBs, beta-blockers, MRAs, or vasodilators in symptomatic or asymptomatic patients with severe MR and normal systolic LV function or non-severe MR patients is not recommended, as there is no robust evidence to support this strategy [3••, 4••]. Despite these recommendations, a recent survey demonstrated that things are different in real-world practice: two-thirds of physicians prescribe medical therapy (mainly ACEIs/ARBs and beta-blockers) in order to delay MR progression or decrease its severity [5••].

Conclusions

Circumstantial evidence indicates a possible association between hypertension and MR incidence and severity. While certain studies have provided encouraging results regarding beneficial effects of antihypertensive agents on hemodynamic indices and LV remodeling, no sufficiently powered randomized trials have assessed the potential favorable impact of medical treatment on cardiovascular outcomes. Therefore, hypertension should be treated in these patients according to contemporary recommendations. Randomized, controlled studies are warranted to

elucidate the precise role of antihypertensive therapy on treatment and overall therapeutic strategy of MR.

Compliance with Ethical Standards

Conflict of Interest The authors report no relationships that could be construed as a conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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