

Role of the renin-angiotensin-aldosterone system in diastolic dysfunction and heart failure¹

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Summary

Heart failure with preserved left ventricular (LV) ejection fraction is commonly viewed as the consequence of diastolic dysfunction. Hypertension is the most common cause for the development of diastolic dysfunction and LV hypertrophy leading to symptomatic hypertensive heart disease. Strict blood pressure control therefore is mandatory to prevent diastolic heart failure in patients with hypertension. Besides the mechanical pressure load activation of the renin-angiotensin-aldosterone system (RAAS) essentially contributes to the progression of LV hypertrophy and diastolic heart failure in hypertensive heart disease. Inhibition of RAAS by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor (AT1) blockers reduces LV mass, cardiovascular events and incidence of atrial fibrillation in patients with hypertension and LV hypertrophy. Thus, in patients with LV hypertrophy, diastolic dysfunction or heart failure blood pressure should be tightly controlled by medical treatment usually including an ACE inhibitor or AT1 receptor antagonist although to date prognosis was not shown to be improved by RAAS inhibition in randomised studies including patients with heart failure and preserved ejection fraction.

Key words: diastolic dysfunction; heart failure; hypertension; hypertensive heart disease; renin-angiotensin-aldosterone system; RAAS

Introduction

Congestive heart failure is one of the most prevalent diseases with high hospitalisation rate in the western world [1]. Coronary heart disease and hypertension are the leading causes of heart failure. The heart failure syndrome has long been attributed to impaired systolic function, as found after myocardial infarction or in dilated cardiomyopathy. However, about half of patients with heart failure have

largely preserved systolic function [2]. Impaired relaxation, increased stiffness of the ventricle and abnormal diastolic filling are early features of diastolic dysfunction with still normal exercise tolerance. When the disease progresses exercise tolerance diminishes due to abnormally increased pulmonary pressure during exercise. Clinical signs of congestive heart failure occur when filling pressure increases further leading to higher left atrial pressure and size [3]. While patients with diastolic heart failure were thought to have a better prognosis [4–6], more recent studies suggest that outcome and mortality in patients with preserved ejection fraction is similar to patients with a reduced ejection fraction [7, 8].

Hypertensive heart disease

Among patients suffering from diastolic heart failure the most prevalent group are patients with hypertensive heart disease. While patients with heart failure secondary to myocardial infarction or dilated cardiomyopathy usually have an enlarged and dilated left ventricle (LV), patients with hypertensive heart disease present with LV hypertrophy and a normal LV chamber size [9]. Increased pressure load is an important stimulus for LV remodeling. Further, the activation of the renin-angiotensin-aldosterone system (RAAS) triggers LV remodeling. Both mechanisms induce myocyte hypertrophy leading to LV hypertrophy (for review see [10]). Perivascular and interstitial fibrosis reduces LV compliance resulting in diastolic dysfunction. Endothelial dysfunction and arterial remodeling contribute to the reduction of coronary perfusion and precipitate myocardial ischaemia which adds to the devel-

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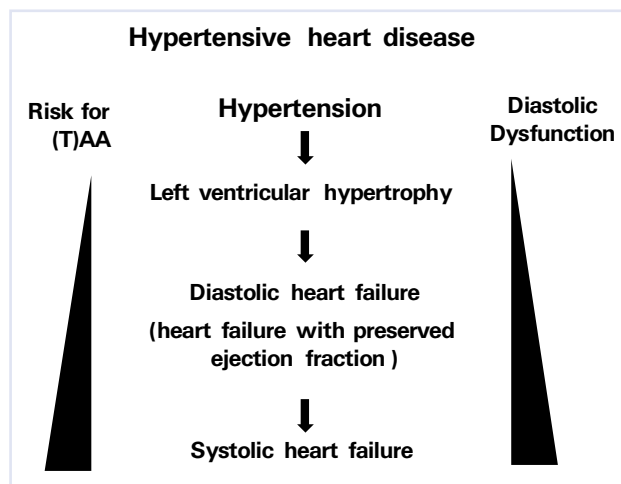
opment of diastolic and systolic dysfunction. Patients with hypertensive heart disease therefore present with a reduction of cardiac function associated with reduced coronary reserve. LV remodeling triggers electrical instability and thereby increases the risk of arrhythmia. Increased pressure load also causes dilation of the aorta and left atrium. Atrial fibrillation is present in a large proportion of patients with heart failure. Increased atrial size and neurohumoral activation can trigger atrial fibrillation in patients with diastolic dysfunction. The loss of atrial contraction, the irregular filling time of the ventricle and excessive ventricular rate worsen the negative clinical consequences of heart failure. Evidence suggests that heart failure patients with atrial fibrillation have worse prognosis compared to patients with sinus rhythm and atrial fibrillation is an independent risk factor for death in heart failure patients.

RAAS inhibition and LV hypertrophy

Early treatment strategies with aggressive blood pressure control in hypertensive patients should be standard to prevent progression of hypertensive heart disease as outlined in figure 1. The VALIDD study in which valsartan was not superior in reducing diastolic dysfunction in hypertensive patients without LV hypertrophy suggests that in early diastolic dysfunction lowering blood pressure improves diastolic function irrespective of the antihypertensive regimen [11, 12]. Blood pressure levels strongly correlate with LV hypertrophy as detected by echocardiography [13]; lowering blood pressure therefore is essential, however in patients with established LV hypertrophy various antihypertensive therapies differ markedly in their ability to reduce LV hypertrophy despite having similar effects on blood pressure. In a meta-analysis of

18 studies, calcium antagonists, ACE inhibitors and angiotensin receptor (AT1) blockers were significantly more effective in reducing LV hypertrophy than diuretics or beta-blockers [14]. Applying drugs that efficiently reduce LV hypertrophy in addition to lowering blood pressure is essential as the prognosis of the patient depends on the regression of LV hypertrophy [15]. Targeting RAAS activation by ACE inhibition, AT1 receptor blockade or mineralocorticoid receptor (MR) blockade belongs to the standard therapy in systolic heart failure to reduce mortality and morbidity [16, 17]. There is good experimental and clinical data that RAAS inhibition attenuates the progression of LV hypertrophy. In spontaneously hypertensive rats Brilla et al. demonstrated that ACE inhibitors reduce LV hypertrophy [18]. This findings were confirmed in patients with hypertensive heart disease, as lisinopril treatment for 6 months attenuated myocardial fibrosis and improved LV diastolic function compared to treatment with hydrochlorothiazide [19]. Long-term therapy with a different ACE inhibitor, perindopril, diminished periarteriolar fibrosis which was associated with a marked improvement in coronary reserve [20]. The LIFE study showed that AT1 receptor blockade with losartan compared to the beta-blocker atenolol significantly reduced cardiovascular morbidity and death in hypertensive patients with LV hypertrophy [21]. ACE inhibition as well as AT1 receptor blockade also reduced the incidence of atrial fibrillation in heart diseases [22], e.g., losartan prevented in the LIFE study the occurrence of atrial fibrillation and stroke in hypertensive patients with LV hypertrophy better than atenolol [23]. The MADRID study showed that the addition of the AT1 receptor blocker irbesartan significantly improved the maintenance of sinus rhythm when given in patients treated with amiodarone after cardioversion for atrial fibrillation [24]. In the 4E-left ventricular hypertrophy study, the combination of enalapril and the selective MR blocker eplerenone reduced LV mass more effectively than single therapy [25]. The ongoing ALDO-DHF trial will clarify whether spironolactone improves maximal exercise capacity and diastolic heart failure in patients with diastolic dysfunction. Inhibition of renin has also emerged as a new concept in blocking RAAS. The ALLAY study was designed as a double-blind, randomised, active-controlled trial in overweight patients with hypertension and LV hypertrophy. This study demonstrated that renin inhibition with aliskiren was as effective as AT1 receptor blockade in reduction of LV mass. Combination of renin inhibition and AT1 receptor blockade was not significantly more effective than single therapy [26]. Calcium antagonists are efficient in reduction of LV hypertrophy, however the combination therapy of amlodipine and benazepril was not significantly better than benazepril alone [27]. An ongoing trial evaluates the effects of systolic blood pressure lowering to different targets (less than 130 mm Hg vs less than 140 mm Hg)

Figure 1
Hypertensive heart disease progression.
TAA = tachyarrhythmia absoluta.



on diastolic function using valsartan and amlodipine in patients with hypertension and diastolic dysfunction (ClinicalTrials.gov identifier: NCT00523549). Another study done in Germany compares the efficacy and safety of valsartan in combination with amlodipine to losartan plus hydrochlorothiazide in patients with hypertension and left ventricular hypertrophy (ClinicalTrials.gov identifier: NCT00446563).

Outcome studies in patients with heart failure with preserved ejection fraction

Patients suffering from heart failure with preserved ejection fraction have a similar bad outcome as patients with reduced ejection fraction [8]. Major randomised studies in heart failure with preserved LV function investigated the effects of ACE inhibitors or AT1 receptor blockers, the role of MR blockade is addressed in ongoing studies (table 1). While the perindopril in elderly people with chronic heart failure (PEP-CHF) study could not demonstrate effects of perindopril treatment on long-term morbidity and mortality, improved symptoms and exercise capacity and fewer hospitalisations for heart failure in the first year were observed [28, 29]. After the first year, a large proportion of the patients received open-label ACE inhibition which prevents further conclusions from that study. In a prospective study including patients with normal or slightly impaired

ejection fraction surviving a first hospitalisation for heart failure, prescription of ACE inhibitor was associated with a significant decrease in long-term mortality [30].

In the CHARM preserved study comparing candesartan against placebo in patients with heart failure with ejection fraction >40% mortality did not differ between groups, but hospital admission for congestive heart failure was lower in the candesartan group [31]. The recently published I-PRESERVE study did not show a prognostic benefit of the AT1 receptor blocker irbesartan in heart failure with preserved ejection fraction [32, 33]. RALES has demonstrated the importance of additional blockade of the aldosterone pathway in heart failure [34]. Aldosterone levels correlate with the LV mass, indicating a role for aldosterone for LV hypertrophy [35]. MR blockade improves myocardial function in hypertensive heart disease [36] and there is evidence for a complementary and additive prognostic value of cortisol and aldosterone levels for total mortality in patients with systolic, but also diastolic heart failure [37]. The TOPCAT study, a multi-center, randomised, double blind placebo-controlled trial with the MR blocker spironolactone in 4500 patients with heart failure and left ventricular ejection fraction of >45% will help to clarify the role of MR blockade in heart failure with preserved ejection fraction (ClinicalTrials.gov identifier: NCT00094302).

Table 1

Randomised studies with RAAS-inhibitors in heart failure with preserved systolic function.

Trial	Drug	# Patients	Key entry criteria	Primary endpoints	Key results
PEP-CHF [28, 29]	Perindopril	850	>70 years treated with diuretics, no major LV systolic dysfunction, echo criteria of diastolic dysfunction	All-cause mortality and unplanned HF related hospitalisation with a minimum follow-up of 1 year	Trend to reduction in the primary outcome, fewer hospitalisation for HF and improved exercise capacity
CHARM-PRESERVED [31]	Candesartan	3025	EF ≥40%, NYHA II–III	Cardiovascular mortality and HF hospitalisation	No effects on cardiovascular death, but fewer hospitalisation
I-PRESERVE [32, 33]	Irbesartan	4133	>60 years, EF ≥45%, NYHA II–IV and HF hospitalisation ≤6 months or evidence of HF or diastolic heart failure	Composite outcome of death or hospitalisation	No effects on death or cardiovascular hospitalisation
TOPCAT	Spironolactone	4500	>50 years, EF ≥45%, signs and symptoms and prior hospital admission or elevated BNP levels	Composite of cardiovascular mortality, aborted cardiac arrest or hospitalisation for the management of HF	Ongoing
ALDO-DHF	Spironolactone	420	>50 years, EF ≥50%, NYHA II–VI, echo criteria of diastolic dysfunction	Exercise capacity and diastolic function (echo)	Ongoing

= number; BNP = brain natriuretic peptide; EF = ejection fraction; HF = heart failure; LV = left ventricle; LVH = left ventricular hypertrophy.

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