Role of the renin–angiotensin–aldosterone system and inflammatory processes in the development and progression of diastolic dysfunction

Sebastiano SCIARRETTA*, Francesco PANENI*, Francesca PALANO*, Diana CHIN*, Giuliano TOCCI*, Speranza RUBATTU*† and Massimo VOLPE*†

*Department of Cardiology, II Faculty of Medicine, University of Rome “La Sapienza”, S. Andrea Hospital, Via di Grottarossa 1035-1039, 00100 Rome, Italy, and †Istituto Di Ricovero e Cura a Carattere Scientifico Neuromed, Via Atinense 18, 86077 Pozzilli (IS), Italy

ABSTRACT

Left ventricular diastolic dysfunction represents a frequent clinical condition and is associated with increased cardiovascular morbidity and mortality. Diastolic dysfunction is the most common cause of HF-PSF (heart failure with preserved ejection fraction). Therefore it becomes important to understand the pathophysiological mechanisms underlying diastolic dysfunction, as well as the effective therapeutic strategies able to antagonize its development and progression. Among the complex pathophysiological factors that may contribute to the development of diastolic dysfunction, the RAAS (renin–angiotensin–aldosterone system) has been shown to play a significant role. Paracrine and autocrine signals of the RAAS promote structural and functional changes in the heart largely linked to increased myocardial fibrosis. Enhanced and dysregulated activity of the RAAS also contributes to the development of volume overload and vasoconstriction with subsequent increases in left ventricular diastolic filling pressures and a higher susceptibility of developing CHF (congestive heart failure). More recently, it has also been suggested that the RAAS may play a role in triggering myocardial and vascular inflammation through the activation of different cell types and the secretion of cytokines and chemokines. RAAS-induced myocardial inflammation leads to perivascular myocardial fibrosis and to the development or progression of diastolic dysfunction. For these reasons pharmacological blockade of the RAAS has been proposed as a rational approach for the treatment of diastolic dysfunction. In fact, ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin II receptor blockers) and AAs (aldosterone antagonists) have been demonstrated to delay the development and progression from pre-clinical diastolic dysfunction towards CHF, as well as to reduce the morbidity and mortality associated with this condition.

Key words: diastolic dysfunction, ejection fraction, heart failure, inflammation, myocardial fibrosis, renin–angiotensin–aldosterone system (RAAS).

Abbreviations: AA, aldosterone antagonist; ACE, angiotensin-converting enzyme; ACEI, ACE inhibitor; AngII, angiotensin II; ANP, atrial natriuretic peptide; AP-1, activator protein-1; ARB, AngII receptor blocker; AT1R, AngII type 1 receptor; AT2R, AngII type 2 receptor; BP, blood pressure; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHF, congestive heart failure; CRP, C-reactive protein; CTGF, connective tissue growth factor; EF, ejection fraction; EGFR, epidermal growth factor receptor; ERK, extracellular-signal-regulated kinase; FAK, focal adhesion kinase; HF-PSF, heart failure with preserved EF; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; LV, left ventricular; LVH, LV hypertrophy; LVM, LV mass; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP, metalloproteinase; NF-κB, nuclear factor κB; IκB, inhibitor of NF-κB; NYHA, New York Heart Association; PAI-1, plasminogen activator inhibitor-1; PDGFR, platelet-derived growth factor receptor; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; PICP, C-terminal propeptide of procollagen type I; PLC, phospholipase C; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SILVHIA, Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol; STAT, signal transducer and activation of transcription; TDI, tissue Doppler imaging; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases; TNF-α, tumour necrosis factor-α; VALIDD, VALsartan In Diastolic Dysfunction; VCAM-1, vascular cell adhesion molecule-1; VSMC, vascular smooth muscle cell; WMI, wall motion index.

Correspondence: Professor Massimo Volpe (email massimo.volpe@uniroma1.it).
INTRODUCTION

Over the last two decades the attention of physicians on LV (left ventricular) diastolic dysfunction has progressively increased, and a growing body of evidence has been developed to better characterize epidemiological, pathophysiological and therapeutic aspects of this frequent cardiac function abnormality. Diastolic dysfunction represents a common finding in different clinical conditions, such as arterial hypertension, diabetes, obesity and ischaemic heart disease, and its prevalence has been growing proportionally with age [1,2]. Diastolic dysfunction is associated with increased cardiovascular morbidity and mortality [3–7]. In fact, impaired cardiac diastolic function strongly affects prognosis, and it represents a pre-clinical cardiac alteration which is highly predictive of cardiovascular events [3–7]. Diastolic dysfunction also represents a key determinant of high-risk clinical conditions, such as atrial fibrillation and, more importantly, HF-PSF [heart failure with preserved EF (ejection fraction)]. Although it is associated with a better prognosis than heart failure with overt systolic dysfunction, HF-PSF is responsible for increased morbidity and mortality, and increases in healthcare expenditure ([4,8], but see [8a]).

On the basis of these considerations, it has become important to identify both the pathophysiological basis of diastolic dysfunction as well as the effective therapeutic strategies able to antagonize its development and progression.

Several pathophysiological mechanisms have been advocated to explain the morphological and functional alterations described in patients with diastolic dysfunction. Among the different factors, the RAAS (renin–angiotensin–aldosterone system) appears to play a major role in determining the development of LV diastolic dysfunction and its progression towards HF-PSF. Paracrine and autocrine signals of the RAAS promote heart remodelling through the development of LVH (LV hypertrophy) and myocardial fibrosis. Moreover, enhanced and dysregulated activity of the circulating RAAS contributes to the development of volume overload and vasoconstriction, with consequent increases in LV diastolic filling pressures and a state of venous congestion [9,10].

More recently, the RAAS has also been found to be primarily involved in myocardial and vascular inflammation through the activation of different cell types and the secretion of cytokines and chemokines. This tissue inflammation leads to myocardial fibrosis and changes in LV structure and geometry, thus contributing to the development of diastolic dysfunction [11]. For these reasons pharmacological blockade of the RAAS has been proposed as a rational approach for the treatment of diastolic dysfunction.

Over the last two decades several investigations [12–22] have shown a beneficial effect of RAAS inhibition in terms of the regression of diastolic function abnormalities [12,13,15–21]. Moreover, RAAS inhibition was found to reduce the high morbidity and mortality associated with HF-PSF [14,22]. Obviously, further studies are required to better define the prospective beneficial effect of this type of drug in patients with diastolic dysfunction, and indeed this topic is under active investigation [23,24].

This article reviews the evidence supporting the importance of the RAAS in the development of diastolic dysfunction, focusing on the relevant molecular mechanisms relating the RAAS with the pathogenesis of cardiac diastolic abnormalities, with particular emphasis on the involvement of inflammation in this process. The potential advantages of pharmacological antagonism of the RAAS on cardiovascular morbidity and mortality in patients with diastolic dysfunction or HF-PSF will also be discussed.

PATHOPHYSIOLOGY AND DEFINITIONS: FROM DIASTOLIC DYSFUNCTION TO HF-PSF

The definition of LV diastolic dysfunction refers to the presence of abnormalities in the relaxation and filling of the left ventricle. This is secondary to an alteration in diastolic active relaxation; or due to changes in LV myocardial structure or geometry; or it can be associated with the impairment of elastic properties involved in diastolic filling [25]. Although an impairment of diastolic function is constantly observed in the presence of LV systolic dysfunction, diastolic dysfunction may also develop when systolic function is preserved, which is also known as ‘isolated’ diastolic dysfunction [1]. Myocardial alterations represent the most important and frequent causes underlying diastolic dysfunction; these include: functional alterations of myocytes, abnormal myofilament structure and function, and pathological remodelling of the extracellular matrix [26,27].

Assessment of diastolic dysfunction has long been assessed by cardiac catheterization based on recordings of LV diastolic pressures and measurements of indexes of LV relaxation as the peak dP/dt and tau (time constant of relaxation). Invasive assessment of diastolic dysfunction, however, is expensive and not applicable to routine clinical diagnosis of diastolic dysfunction. Thus echocardiographic assessment of diastolic dysfunction represents a reproducible non-invasive tool which provides reliable information at a relatively low cost. Echocardiographic flow and myocardial Doppler measurements allow the recording of early and late trans-mitral diastolic flow velocities, pulmonary vein flow velocities, and early and late myocardial relaxation velocities. On the basis of echocardiographic evaluation, diastolic dysfunction is usually divided into three patterns characterized by a progressively higher severity: the delayed relaxation pattern, which is represented by an alteration of the early
LV active relaxation properties, and the pseudonormal and restrictive patterns of diastolic dysfunction, which represent more severe degrees of diastolic dysfunction, with a progressive increase in LV filling pressure, also characterized by an increase in LV stiffness [1,28].

Diastolic dysfunction has high clinical prevalence, given that it is a common finding in arterial hypertension, ischaemic heart disease and diabetes mellitus, and it increases proportionally with age [1,2]. In MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) [29] and the Strong Heart Study [3], the prevalence of diastolic dysfunction in the general population was estimated to be approx. 11 and 19 % respectively. In the Olmsted County Study, the prevalence of diastolic dysfunction was approx. 20 % in healthy subjects, exceeding 45 % when hypertension or ischaemic heart disease were considered [7]. Recently, APROS-diadys (Assessment of PRevalence Observational Study of Dia-stolic Dysfunction) conducted on a population of 2545 elderly healthy hypertensive subjects found that 25 % of individuals of over 50 years of age had diastolic dysfunction, as assessed by conventional echocardiography [2].

Diastolic dysfunction is associated with an increase in cardiovascular morbidity and mortality [3–7], representing a pre-clinical cardiac marker, highly predictive of the development of cardiovascular events. Indeed, findings from the Cardiovascular Health Study and Strong Heart Study demonstrated that diastolic dysfunction is an independent predictor of cardiovascular events, the level of risk growing proportionally with the severity of dysfunction [3,5]. In addition, in the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study, which was conducted in hypertensive subjects, the presence of impaired diastolic function was associated with an increased occurrence of cardiovascular events, independently from LVH [6].

On the other hand, diastolic dysfunction itself also predisposes to high-risk clinical conditions such as HF-PSF [30]. For this reason, when diastolic dysfunction is associated with signs or symptoms of CHF (congestive heart failure), it is frequently defined as ‘diastolic heart failure’. HF-PSF (or diastolic heart failure) refers to a clinical status of CHF in patients with normal or mildly depressed systolic function. The presence of LV relaxation abnormalities is usually observed in patients with HF-PSF [30], and asymptomatic diastolic dysfunction was found to be predictive for the occurrence of HF-PSF [31]. On the basis of a recent consensus, HF-PSF can be diagnosed according to the presence of signs or symptoms of CHF in subjects with a normal or mildly depressed systolic function (EF > 50 %), associated with invasive haemodynamic or echocardiographic signs of elevated LV filling pressures or in the presence of LV relaxation abnormalities or structural abnormalities associated with high levels of BNP (brain natriuretic peptide) [32].

Epidemiological studies have shown that CHF accounts for approx. 550000 new cases per year in the U.S.A. [33], its incidence in hypertensive patients being comparable with that of stroke [34]. Among subjects with CHF, a percentage ranging from 13–74 % present with HF-PSF [1]. HF-PSF represents a serious condition which is responsible for increased morbidity and mortality worldwide ([4,8], but see [8a]), as demonstrated in the Olmsted, Framingham and Helsinki Aging studies [7,35,36]. The severity of HF-PSF was found to be proportional to myocardial fibrosis [37]. It has also been observed that asymptomatic diastolic dysfunction or HF-PSF predisposes to the development of overt systolic dysfunction in several studies [31,32,38,39]. A subtle reduction in LV long-axis shortening (assessed by TDI (tissue Doppler imaging)) has also been reported in patients with HF-PSF compared with subjects with asymptomatic diastolic dysfunction [40].

For these reasons, a better understanding of the pathophysiological mechanisms underlying diastolic dysfunction represents an important research objective. This is also in view of the need to optimize therapeutic strategies aimed at antagonizing diastolic dysfunction and reducing the cardiovascular risk of subjects presenting with this cardiac abnormality.

**ROLE OF THE RAAS AND INFLAMMATORY PROCESSES IN THE DEVELOPMENT AND PROGRESSION OF DIASTOLIC DYSFUNCTION**

A pathophysiological contribution of the RAAS has been advocated in the development of myocardial structural and functional abnormalities, and impairment in LV diastolic filling, mainly by acting through autocrine and paracrine signals (Figure 1) [41–43]. In fact, the RAAS modulates cellular growth, proliferation and differentiation, contributing to cardiomyocyte hypertrophy, cardiac fibrosis and remodelling.

AngII (angiotensin II) modulates cellular growth and hypertrophy through the activation of MAPks (mitogen-activated protein kinases), which include ERK1/2 (extracellular-signal-regulated kinase 1/2), JNK (c-Jun N-terminal kinase) and p38 MAPK [44,45].

ERK1/2 represents the most commonly involved kinase in the AngII-mediated hypertrophic response in cardiomyocytes and VSMCs (vascular smooth muscle cells), mainly through EGFR (epidermal growth factor receptor) phosphorylation, following the binding of AngII to AT1R (AngII type 1 receptor) [44–47]. PDGFR (platelet-derived growth factor receptor) and the insulin receptor are also involved in AngII-mediated hypertrophic responses through MAPK and PLC (phospholipase C) (Figure 1). A cross-talk of AT1R with EGFR, PDGFR and insulin receptors has also been described [48–50]. Moreover, under conditions of increased cellular...
stress, AngII induces the activation of JNK and p38 MAPK via ASK-1 (apoptosis signal-regulating kinase-1) [45]. The latter is a crucial protein, mediating the activation of JNK and p38 MAPK in the presence of an increased production of ROS (reactive oxygen species) [51].

A persistent activation of the RAAS also promotes and maintains the accumulation of the extracellular matrix responsible for increased myocardial stiffness and impaired diastolic function, [10,52,53]. In fact, RAAS activation, mostly through the binding of AngII to AT1R and the interaction between aldosterone and its intracellular receptor, stimulates fibroblasts to produce fibrillar collagen type I and III, which progressively accumulates, leading to a derangement of the tissue structure, independent of changes in arterial BP (blood pressure) (Figure 1) [54–56]. AngII and aldosterone also contribute to myocardial fibrosis through the modulation of MMPs (metalloproteinases), their tissue inhibitors [TIMP (tissue inhibitor of metalloproteinases)] and collagenases expression [57]. In fact, AngII was found to influence the transcription of MMPs via AP-1 (activator protein-1) and NF-κB (nuclear factor κB) signalling pathways. It has also been demonstrated that AngII and aldosterone induce both NF-κB and AP-1 activation in rat cardiomyocytes and
fibroblasts, with an increase in collagen type I production and a decrease in MMP-1 expression [58]. Similarly, an increase in nuclear translocation of cytoplasmic NF-κB, followed by an increase in MMP-9 transcription, was observed in neonatal rat ventricular myocytes stimulated by AngII [59]. On the other hand, AngII-induced up-regulation of MMP-2 and MMP-14 is mediated by the JAK (Janus kinase)/STAT1 (signal transducer and activation of the transcription 1) pathway [60] (Figure 1).

The RAAS has also been shown to favour cardiac remodelling by triggering subclinical tissue inflammation in the cardiovascular system through paracrine actions [61–63]. In fact, increased levels of tissue AngII and aldosterone in the context of arterial hypertension and myocardial infarction are responsible for increased vascular permeability, tissue leucocyte infiltration, activation of different myocyte signalling pathways and an increased burden of oxidative stress and cytokine secretion, which consequently lead to cardiac perivascular and tissue fibrosis, myocyte hypertrophy and, subsequently, diastolic dysfunction [11,27,56] (Figure 1). In fact, after the migration into the vessel intima, macrophages and lymphocytes move into the cardiac perivascular space [11,64] and produce cytokines, including TNF-α (tumour necrosis factor-α) and IL-6 (interleukin-6), and growth factors, such as TGF-β (transforming growth factor-β), which promote and maintain inflammation locally and stimulate fibroblasts to produce collagen [65–68]. The latter progressively accumulates thereby leading to increased myocardial stiffness and diastolic dysfunction (Figure 1). Moreover, increased oxidative stress products and cytokines directly stimulate the growth of myocytes with the subsequent development of hypertrophy [65–70] (Figure 1).

TGF-β appears to be the most important cytokine for the development of diastolic dysfunction due to RAAS-induced perivascular inflammation. It has been reported that AngII directly stimulates the secretion of TGF-β [71], increasing TGF-β transcription and protein synthesis in cardiomyocytes and cardiac fibroblasts [65,72,73]. Moreover, AngII enhances TGF-β receptor expression in cardiac fibroblasts, allowing a strong responsiveness towards its profibrotic actions. TGF-β favours fibrosis through the binding to its receptor and activation of the Smad3 signalling pathway, which sequentially enhances matrix protein and TIMP expression [74]. Moreover, TGF-β may up-regulate the expression of CTGF (connective tissue growth factor), a well-known profibrotic molecule, in both cardiac myocytes and cardiac fibroblasts. TGF-β-induced CTGF expression is mediated by the activation of PD98059, a MEK1 (MAPK/ERK kinase 1) inhibitor, that in turn stimulates the synthesis of CTGF mRNA. The up-regulation of CTGF results in an increase in the synthesis of fibronectin, type I collagen and PAI-1 (plasminogen activator inhibitor-1), leading to further fibrosis and cardiac stiffness [75]. Accordingly, selective antagonism of TGF-β was also found to be associated with a regression of diastolic dysfunction [76]. AngII may also induce CTGF expression via calcineurin-dependent pathways [77].

At the cellular level, AngII and aldosterone promote vascular inflammation through an increase in cellular ROS production, mainly by the activation of NADPH oxidase [45,56]. ROS enhance NF-κB transcription and degradation of its cytoplasmic inhibitor IκB (inhibitor of NF-κB) [78]. NF-κB in turn promotes the expression of adhesion molecules, such as E-selectin, ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1), and chemokines, including MCP-1 (monocyte chemoattractant protein-1) and IL-8, in endothelial cells and VSMCs, thus promoting leucocyte adhesion and transmigration in the vascular wall [79–81]. Of note, it has been reported that an increase in vessel wall stretch through the activation of NADPH oxidase and NF-κB may also increase adhesion molecule expression by endothelial cells and lead to up-regulation of endothelial cell secretion of pro-inflammatory cytokines, independently of AngII [82,83].

AngII signalling also re-organizes inflammatory cell cytoskeletal structure and regulates the formation of focal adhesion complexes, thus promoting migration and adhesion in the vascular wall [84,85]. FAK (focal adhesion kinase) is mainly involved in the adhesion process, in fact it is highly expressed in the arterial media and VSMCs [86]. AngII binding to AT1R rapidly activates FAK, favouring inflammatory cell adhesion to the extracellular matrix, thus facilitating activation of several cytoskeletal proteins.

Accordingly, experimental evidence in animal models has shown that the inhibition of the RAAS reduces vascular inflammation and related cardiac fibrosis [55,87–93]. In fact, valsartan attenuated the expression of MCP-1, TNF-α, IL-6 and IL-1β, and infiltration of leucocytes and macrophages in injured arteries through the inhibition of the AT1R and possibly by an indirect stimulation of AT2R (AngII type 2 receptor) [87]. In SHRs (spontaneously hypertensive rats), the AT1R antagonists losartan and telmisartan attenuated the expression of MCP-1 and its receptor in the aorta and peripheral blood monocytes, thus lowering MCP-1 serum levels [88]. Furthermore, irbesartan reduced AngII-mediated oxidative stress, inflammation and cardiomyopathy in Ace2-null mice [89]. In pressure-overloaded rat hearts, inhibition of macrophage infiltration obtained by blocking ICAM-1 not only abolished the production of TGF-β and fibroblasts activation, but was also able to prevent the development of reactive myocardial fibrosis [90]. In the same animal model, the observed increase in BP was associated with a rapid local activation of tissue ACE (angiotensin-converting enzyme), associated with increased expression of ICAM-1 and MCP-1 as well.
Pathophysiological mechanisms depending on RAAS activity and the related inflammation in the development and progression from diastolic dysfunction towards CHF

Consistent with these experimental observations, we have recently demonstrated that increased markers of inflammation are independently associated with reduced diastolic function in humans [94]. In fact, we observed that hypertensive patients with the metabolic syndrome had a significant impairment in diastolic function assessed by TDI and also had higher plasma levels of TGF-β1, TNF-α, CRP (C-reactive protein) and PICP (C-terminal propeptide of procollagen type I) compared with those hypertensive patients without the metabolic syndrome. Most remarkably, these markers of fibrosis and inflammation were independently and directly related to a greater impairment of the TDI indexes of diastolic function [94]. The relationship between increased serum levels of PICP and CRP and the impairment of diastolic function has been confirmed recently [95,96].

Finally, RAAS activation also contributes to the progression from diastolic dysfunction towards the development of CHF [97]. In the presence of impaired LV filling, a reduction in cardiac output following precipitating events, such as lung disease, infections, anaemia or arrhythmias, activates the RAAS further, thus promoting LV remodelling and fluid retention. These pathological changes, in turn, lead to volume overload with enhanced ventricular filling pressures associated with symptoms and signs of venous congestion. In addition, vasoconstriction and the increased adrenergic tone secondary to the
Table 1  Main findings derived from the studies with RAAS inhibitors in humans

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Setting</th>
<th>n</th>
<th>Systolic function</th>
<th>Drug</th>
<th>Time</th>
<th>Key finding(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietz et al. [12]</td>
<td>1993</td>
<td>Hypertension</td>
<td>12</td>
<td>n.r.</td>
<td>Cilazapril</td>
<td>6 months</td>
<td>LVM reduction by 30%, improvement in left ventricle relaxation, and left atrial size reduction</td>
</tr>
<tr>
<td>Yalcin et al. [13]</td>
<td>2000</td>
<td>Hypertension</td>
<td>24</td>
<td>n.r.</td>
<td>Perindopril</td>
<td>6 months</td>
<td>LVM reduction, improvement in left ventricle relaxation, and reduced ANP levels</td>
</tr>
<tr>
<td>PEP-CHF [14]∗</td>
<td>2006</td>
<td>HF-PSF</td>
<td>850</td>
<td>WMI ≥ 1.4</td>
<td>Perindopril compared with placebo</td>
<td>25 months</td>
<td>Improvement in NYHA class, and reduction in hospitalization during the first year of treatment</td>
</tr>
<tr>
<td>LIFE [15]∗</td>
<td>2002</td>
<td>Hypertensive heart disease</td>
<td>728</td>
<td>EF ≥ 40%</td>
<td>Losartan compared with atenolol</td>
<td>1 year</td>
<td>Superiority of losartan in regression of LVM, and improvement in diastolic function</td>
</tr>
<tr>
<td>Giulla et al. [16]∗</td>
<td>2004</td>
<td>Hypertensive heart disease</td>
<td>219</td>
<td>n.r.</td>
<td>Losartan compared with atenolol</td>
<td>36 weeks</td>
<td>Superiority of losartan in reducing biochemical markers of collagen and left ventricle fibrosis assessed by echo-reflectivity</td>
</tr>
<tr>
<td>Dietz et al. [17]</td>
<td>2002</td>
<td>Hypertensive heart disease/diastolic dysfunction</td>
<td>34</td>
<td>EF ≥ 50%</td>
<td>Losartan</td>
<td>12 months</td>
<td>Regression of myocardial stiffness and fibrosis (biopsy) associated with diastolic dysfunction</td>
</tr>
<tr>
<td>Warner et al. [18]∗</td>
<td>1999</td>
<td>Diastolic dysfunction</td>
<td>20</td>
<td>EF &gt; 50</td>
<td>Losartan compared with placebo</td>
<td>2 weeks</td>
<td>Increased exercise tolerance and improved quality of life</td>
</tr>
<tr>
<td>Mattioli et al. [19]</td>
<td>2004</td>
<td>Hypertensive heart disease</td>
<td>140</td>
<td>EF ≥ 50%</td>
<td>Telmisartan</td>
<td>1 year</td>
<td>Reduction in LVM, improvement in LV diastolic filling and reduction in left atrial volumes</td>
</tr>
<tr>
<td>SILVHIA [20,96]∗</td>
<td>2003</td>
<td>Hypertensive heart disease</td>
<td>115</td>
<td>≥ 45%</td>
<td>Irbesartan compared with atenolol</td>
<td>48 weeks</td>
<td>Major benefit of irbesartan on the regression of LVM and reduction in PICP levels</td>
</tr>
<tr>
<td>VALIDD [21]∗</td>
<td>2007</td>
<td>Diastolic dysfunction</td>
<td>384</td>
<td>&gt; 50%</td>
<td>Valsartan compared with placebo</td>
<td>38 weeks</td>
<td>No significant differences between the two arms regarding diastolic function and BP-dependent improvement in LV relaxation</td>
</tr>
<tr>
<td>CHARM [22]∗</td>
<td>2003</td>
<td>HF-PSF</td>
<td>3023</td>
<td>&gt; 40%</td>
<td>Candesartan compared with placebo</td>
<td>37 months</td>
<td>Candesartan reduced cardiovascular events and hospitalizations for heart failure</td>
</tr>
<tr>
<td>Grandi et al. [102]∗</td>
<td>2002</td>
<td>Hypertension</td>
<td>34</td>
<td>PSR &gt; 1.9 s</td>
<td>Canrenone compared with placebo</td>
<td>6 months</td>
<td>Reduction in LVM and improvement in left ventricle relaxation</td>
</tr>
</tbody>
</table>

Activation of the RAAS significantly contribute to the worsening of diastolic function through increases in heart rate and afterload [25,98] (Figure 2).

**PHARMACOLOGICAL ANTAGONISM OF THE RAAS IN DIASTOLIC DYSFUNCTION**

The negative effects exerted by activation of the RAAS on diastolic function support the rationale of blocking this hormonal system, especially in patients with arterial hypertension. In recent years, experimental studies and clinical trials have been conducted to assess the therapeutic efficacy of ACEIs (ACE inhibitors), ARBs (AngII receptor blockers) and AAs (aldosterone antagonists) in improving LV diastolic filling or in delaying the progression of diastolic dysfunction towards the onset of diastolic heart failure. Most of the observations achieved in these studies showed a clear benefit of these drugs, both in humans and in animal models [12–22,99,100] (Table 1).

Experimental studies have shown that both acute and chronic administration of ACEIs exert favourable effects on diastolic ventricular performance. The intra-coronary infusion of enalapril significantly improved LV relaxation in dogs with LVH [99]. Similarly, chronic administration of the ACEI temocapril ameliorated diastolic performance in rats with ventricular hypertrophy, with a lower incidence of heart failure when compared with controls [100]. Accordingly, in two human studies, administration of cilazapril or perindopril induced improvements in LV relaxation, associated with reductions in left atrial dimensions [12,13]. With regard to perindopril, a reduction in plasma levels of ANP (atrial natriuretic peptide) was also reported, suggesting a decrease in ventricular...
filling pressure in patients with diastolic dysfunction [13]. Nevertheless, pharmacological actions of ACEIs beside reduced AngII production also include increased plasma concentrations of bradykinin, which also exerts anti-fibrotic effects [101]. Finally, the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) study, which investigated the effect of perindopril in patients with HF-PSF, showed an improvement in the NYHA (New York Heart Association) class as well as a reduction in hospitalization during the first year of treatment [14]. HF-PSF was diagnosed on the basis of the presence of CHF and a preserved or mildly depressed systolic function \([\text{EF} \geq 40 \text{ or WMI (wall motion index)} \geq 1.4]\), associated with echocardiographic evidence of diastolic dysfunction or cardiac damage (left atrial dilation or LVH).

Most of the evidence supporting a beneficial effect of blocking the RAAS in diastolic dysfunction is derived from the use of ARBs. The LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study [15], which compared losartan with atenolol, showed a clear advantage of losartan in terms of regression of LVH and improvement in diastolic function. Accordingly, losartan was more efficient compared with atenolol in reducing serum markers of collagen synthesis and myocardial echo-reflectivity [16]. Moreover, 12 weeks of treatment with losartan in hypertensive patients with different grades of myocardial fibrosis was associated with the regression of myocardial stiffness and diastolic dysfunction associated with a marked reduction in the amount of myocardial collagen, particularly in those subjects who had more severe fibrosis [17]. Losartan also improved exercise tolerance in patients with echocardiographic evidence of LV diastolic dysfunction [18]. Similarly, a study conducted with telmisartan demonstrated an improvement in LV diastolic filling and a reduction in left atrial dimensions in hypertensive subjects with mild-to-moderate LVH [19]. Accordingly, in the SILVHIA (Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol) trial, which compared irbesartan with atenolol in hypertensive subjects, the investigators found that irbesartan had a major benefit on the regression of LVM (LV mass) and an improvement in diastolic function, the latter associated with a significant reduction of serum PICP levels [20, 96]. On the other hand, in the VALIIDD (VALsartan In Diastolic Dysfunction) trial, in which 384 hypertensive patients were randomized to valsartan or placebo for 38 weeks, valsartan was not found to be associated with a significant improvement in diastolic function at the end of the study compared with placebo [21]. The improvement in LV filling observed in both arms was mainly related to the degree of BP reduction [21].

With regards to HF-PSF, the preserved arm of the CHARM (Candesartan in Heart Failure Assesment of Reduction in Mortality and Morbidity) study, which evaluated the efficacy of candesartan added to standard medical therapy in patients with HF-PSF, showed that candesartan significantly reduced the rate of cardiovascular events and hospitalizations for acute heart failure, albeit not reducing cardiovascular mortality [22]. HF-PSF was defined according to the presence of CHF associated with a preserved or mildly depressed systolic function \([\text{EF} \geq 40 \%]\).

The ongoing I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) study [23] has been designed to assess the efficacy of irbesartan in reducing cardiovascular morbidity and mortality in patients with HF-PSF. This trial is the largest trial conducted in subjects with HF-PSF defined according to more restrictive inclusion criteria than CHARM-Preserved (\([\text{EF} < 45 \% \text{ and NYHA class II–IV associated with previous hospitalization for CHF, or NYHA class III–IV and signs of cardiac damage}]\)). It is likely that the results of this trial will help to clarify the effective role of ARBs in HF-PSF.

In addition, the ongoing TOPCAT (Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart) study will provide important information on the approaches to HF-PSF. It was designed to assess the benefit of the administration of spironolactone to 4500 patients with HF-PSF. Clear benefit of AAs in diastolic dysfunction are already available. Indeed, it was demonstrated that when canrenone was added to ACEI and calcium antagonists in hypertensive subjects there was a greater improvement in diastolic function, independently from BP reduction [102].

**CONCLUSIONS**

Diastolic dysfunction represents a very frequent alteration in ventricular function which is associated with increased cardiovascular morbidity and mortality. In particular, diastolic dysfunction itself represents a crucial determinant of high-risk clinical conditions such as HF-PSF.

Current evidence suggests that the RAAS significantly contributes to the development of diastolic dysfunction and plays an important role in its progression towards CHF by promoting an increase in collagen production with a subsequent enhancement of myocardial fibrosis and stiffness. Dysregulated activation of the RAAS may also trigger a state of subclinical vascular and myocardial inflammation which, in turn, contributes to an increase in myocardial fibrotic disarray. Thus over the last two decades the use of drugs which antagonize the RAAS has been tested in the setting of both pre-clinical diastolic dysfunction and HF-PSF, and several large studies have shown a clear benefit in the use of ACEIs, ARBs and AAs in these clinical conditions.

On the basis of these studies, drugs blocking the RAAS should currently be suggested as an appropriate therapeutic approach in diastolic dysfunction and HF-PSF.
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