Stiff Heart and Stiff Arteries. Could We Soften Both?

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Abstract: Old age, female gender, hypertension (HTN), cardiac ischaemia, and arterial stiffness (AS) are the main determinants of a stiff heart, diastolic dysfunction (DD), and finally heart failure with preserved ejection fraction (HFpEF); however, several cardiac or extra-cardiac pathologies may also be involved. The combined ventricular-arterial stiffening (abnormal left ventricle-arterial coupling) is the main determinant of the increased prevalence of HFpEF in elderly persons, particularly women, and in younger subjects with HTN. Hospitalization and mortality rates in patients with HFpEF are similar to those of patients with heart failure with reduced EF (HFrEF). However, although the prognosis of HFrEF has improved over time, the optimal treatment of HFpEF remains unclear, because of the differences in the pathophysiology of the two syndromes. A number of new drugs have shown promise but they will not be commercially available for several years. For the time being, aggressive treatment of non-cardiac comorbidities is the only option available for the management of HFpEF. Treatment of anaemia, sleep disorders, chronic kidney disease, non-alcoholic fatty liver disease, atrial fibrillation, diabetes mellitus, and judicious use of diuretics are effective to some degree. Statin treatment deserves special attention, regardless of the presence of dyslipidaemia, because it has been shown, mainly in small studies, post hoc analyses, and in a large recent meta-analysis, that it is related to an improved quality of life and a reduction in HF-related mortality. We urgently need to utilize these resources to relieve a substantial number of patients suffering from HFpEF, a disease with an ominous prognosis.

Keywords: Heart stiffness, arterial stiffness, diastolic dysfunction, ventricular arterial coupling, heart failure with preserved ejection fraction, hypertension, statins.

1. INTRODUCTION

Heart stiffness or diastolic dysfunction (DD) or heart failure with preserved ejection fraction (HFpEF) is characterised by abnormalities of ventricular filling, including decreased diastolic distensibility and impaired relaxation [1]. DD represents an important pathophysiologic intermediate between hypertension (HTN) and heart failure (HF), and finally leads to HFpEF [2]. Up to 50% of patients with a history of HTN have evidence of DD [3], which represents an attractive target for HF prevention. However, no specific treatments have been definitively shown to improve DD to date [4]. During the last 20 years, HFpEF has turned into a serious health problem, accounting for practically half (40-71%) of all cases of HF [1-3] and affecting 11-35% of the general population, with most patients having a subclinical form of the disease [4].

The most common causes of HFpEF are old age, HTN, and cardiac ischaemia but other diseases can also lead to HFpEF [5]. Heart stiffening and decreased filling result in decreased ability of the heart to pump blood to the body [6]. Moreover, elevated filling pressure in the ventricles can result in both pulmonary and peripheral oedema [4]. The arteries were considered by the ancient Greeks as motionless conduits within which air flowed; later it was described that the blood circulates through them. At present, it has been established that when the heart contracts it generates a blood wave that travels through the arteries. The speed of the travel of this wave is called pulse wave velocity (PWV) and is related to the stiffness or compliance of the arteries [7-11]. Arterial stiffness (AS) is characterized by increased PWV and early return to the ascending aorta of reflected waves, during the systolic phase of the pressure waveform, increasing systolic blood pressure (BP); reflected waves in healthy people return during diastole and contribute to myocardial perfusion. Thus, central systolic aortic blood pressure (CABP), and consequently left ventricular (LV) afterload, is increased. This culminates in LV hypertrophy (and stiffness) and predisposes to LV systolic and diastolic dysfunction [7]. Furthermore, in patients with AS, CABP during the diastole is decreased, thus substantially reducing coronary artery perfusion [7].

The relationship between AS and PWV was first reported in 1808. Typical values of PWV in the aorta range from approximately 5 to > 15 m/s [7]. Increased aortic PWV has been shown to predict cardiovascular disease (CVD)-related and all-cause mortality in patients with end stage renal failure (ESRD), HTN and diabetes mellitus (DM) as well as in...
the general population [7-9]. Commercially available devices measure AS parameters, including the augmentation index (Alx) and PWV. These devices include the Complior, CVProfilor, PeriScope, Hanbyul Meditech, Mobil-O-Graph NG, Pulsecor, PulsePen and SphygmoCor. Heart is the primary site of damage caused by increased AS. Both arterial and LV stiffening may contribute to the transition from asymptomatic HF to overt HFpEF [7-10]. The functional interaction between the LV and arterial tree, termed ventricular–arterial coupling, is recognized as a key determinant of cardiovascular performance [10-14]. This arterio-myocardial coupling decline is further precipitated by the presence of other CVD risk factors leading to the development of HFpEF [5,14,15].

While tight BP control is a central component of HF prevention [16], the mechanisms by which BP control decreases HF risk are not yet fully clear. The extent to which anti-hypertensive therapy reverses arterial and LV stiffness, or affects ventricular–arterial coupling and LV energetic efficiency, is not yet well understood [17]. Thus, there is no widely accepted treatment for HFpEF with proven clinical benefit [9-14].

2. DIAGNOSIS OF HFpEF

According to recent ESC guidelines [18], HFpEF is diagnosed when 4 criteria are met: symptoms of HF, clinical signs of HF, preserved LVEF (>50, while EF 40-50% is in the grey zone) without LV dilatation and finally the existence of morphologic features (LV hypertrophy, left atrial dilatation) or functional characteristics indicating diastolic dysfunction and increased filling pressures [18]. In regard to diastolic function indices that should be carefully assessed, an increased ratio of transmural inflow E wave to average E′ of mitral annulus (E/e′) > 15 and a reduced average E′ wave of mitral annulus measured by Tissue Doppler imaging (< 9 cm/sec) both indicate elevated filling pressures [18].

3. TREATMENT OPTIONS

It has been proposed that HFpEF and HFrEF are part of the same HF continuum [19]. However, therapies with indisputable benefit in HFrEF have failed to show benefit in HFpEF [20,21], suggesting significant differences in the pathophysiology of these two entities. In the absence of proven treatments for HFpEF, it is important to understand potential differences in response to empiric HF therapies [22].

The aim of the treatment of HFpEF should be to relieve symptoms and prolong life [4]. Unfortunately, to date, studies of neuro-hormonal blockade in patients with HFpEF have failed to show a decline in mortality rates or a clear improvement in quality of life [4]. Although inhibitors of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system should continue to be used in the population of patients with HFpEF who have other comorbidities such as HTN, DM or CVD, the use of these drugs for the primary treatment of HFpEF is not supported from current evidence [4]. In contrast to HFrEF patients, who mainly die from CVD, the increased mortality in HFpEF is driven mainly by non-CVD causes [23]. The main causes of death among HFpEF patients are sudden cardiac death, HF, myocardial infarction, stroke and non-CVD causes [24]. Thus, it is possible to improve quality of life and increase survival in HFpEF patients by aggressive treatment of co-morbidities [25].

3.1. Lifestyle Measures

A recent pilot study in 14 hypertensive patients with HFpEF suggested that a sodium-restricted diet improves several key factors that contribute to heart failure [26]. The Dietary Approaches to Stop Hypertension diet (DASH) reduced office systolic BP (from 155 to 138 mmHg) and 24-hour systolic BP (130 to 123 mmHg) (both P=0.02) at 3 weeks and also induced a non-significant drop in central end-systolic BP (116 to 111 mmHg, P=0.12) [26]. Ventricular stiffness and relaxation indices improved, a trend toward lower energy for filling suggested increased diastolic efficiency, global contractility increased, effective arterial elastance decreased and ventricular-arterial coupling improved [26]. The findings of this short-term dietary intervention pilot study require confirmation in larger studies, but it is intriguing that large vessel AS, global LV contractility and ventricular-arterial coupling all significantly improved following DASH sodium-restricted diet in this cohort of elderly, obese patients [26]. Thus, salt restriction might prove a valuable tool in the management of HFpEF, although this has to be validated in larger long-term trials.

3.2. Pharmacotherapy

It has been suggested that besides the careful use of diuretics to improve symptoms there are no agents that improve the outcome of patients with HFpEF [27,28]. It has also been proposed that spironolactone could improve the prognosis of HFpEF. However, in the recently published Aldosterone Receptor Blockade in Diastolic HF (Aldo-DHF) trial, which included 422 patients with chronic HF, left ventricular (LV) ejection fraction of >50%, and echocardiographic evidence of LV DD, long-term aldosterone receptor blockade improved LV diastolic function but had no effect on maximal exercise capacity, HF symptoms, HF-related hospitalizations or quality of life [29].

A number of factors, including sex, body size, and age, are known to influence ventricular–arterial properties [30-33]. It is not entirely clear how these factors may influence the ventricular–arterial response to antihypertensive therapy [34]. This was evaluated in a combined analysis (n = 527) of the Valsartan in Diastolic Dysfunction (VALIDD) [35] and Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction (EXCEED) studies [36]. It was shown that angiotensin receptor blockers (ARB) reduce arterial and ventricular stiffness, improve ventricular–arterial coupling, reduce cardiac work and improve LV efficiency and systolic and diastolic function [36]. Interestingly, sex and body weight were important determinants of the change in the coupling ratio and of the improvement in cardiac efficiency; women and obese patients achieved smaller reductions in the coupling ratio and smaller improvements in cardiac efficiency than men and non-obese individuals. This suboptimal response in women (even after adjusting for age, body weight and change in systolic BP) and in obese men suggest that structural and functional changes may be less
reversible in these groups, possibly explaining their greater risk for HF [34]. Notably, the ratio of women to men affected by HFpEF is 2:1 [37] and obesity is also a major risk factor for HFpEF [38]. This combined analysis did not evaluate HF-related symptoms and did not have the power to assess survival.

3.3. Pharmacological Agents Under Development

Several drugs are in the pipeline, mainly in phase 2 and some in phase 3 studies, but they will not be commercially available for several years [39-57]. Detailed analysis of these agents is beyond the scope of the present review.

3.4. Management of Comorbidities of Patients with HFpEF

A promising strategy for the improvement of outcomes in patients with HFpEF is the aggressive treatment of noncardiac comorbidities [18,58,59]. Indeed, an important aspect of ventricular–arterial coupling is the detrimental impact of AS on LV diastolic function in different populations: in patients with chronic obstructive pulmonary disease (COPD), HTN, DM, ESRD, obstructive sleep apnea (OSA), liver dysfunction, anaemia, thyroid disorders and depression, which are all associated with increased morbidity and mortality [60]. Most of these noncardiac comorbidities share 2 common features: they may lead to LV dysfunction/HF [60,61] and they are associated with systemic inflammation [60,62]. The noncardiac comorbidity burden is higher in HFpEF patients than in those with HFrEF [63]. Therefore, aggressive management of comorbidities might result in larger benefits in HFpEF than in HFrEF [60]. The treatment of most of these comorbidities also has a beneficial effect on AS [64]. Accordingly, it appears that subcutaneous erythropoietin administration for anaemia might improve symptoms and survival in HFpEF patients with anaemia [65]. Tighter BP control (with judicious use of diuretics) may also reduce HF-related events [66]. The Hypertension In the Very Elderly Trial (HYVET) study regarding the treatment of HTN in patients > 80 years of age (n=3,845) provided evidence that antihypertensive treatment with indapamide with or without perindopril was beneficial [67]. There was a reduction in the incidence of stroke by (30%, p = 0.05), all cause mortality (by 21%, p = 0.02), CVD mortality (by 23%, p = 0.06), CVD events (by 34%, p = 0.001) and HF (by 64%, p = 0.001). [67].

Improvement of renal function with atorvastatin [68] and resolution of NAFLD with atorvastatin and rosuvastatin [69-74] are useful in the overall multifactorial approach of HFpEF [75] as well as of AS [76]. It appears that the above benefits are specific to these statins at appropriate doses and not a drug class effect.

Moreover, treatment of sleep-related disorders of breathing also appears to be beneficial in patients with HFpEF. Adaptive servoventilation (ASV) effectively attenuated nocturnal Cheyne-Stokes respiration (CSR) in patients with HFpEF and improved HF symptoms and cardiac function [77].

At an early stage, diabetic cardiomyopathy is manifested as HFpEF, which is detected in up to 75% of asymptomatic diabetic patients [78]. In several patients, HFpEF may progress to HFrEF, with a poor prognosis (annual mortality rate of 15-20%) [79]. Diabetic patients carry a 4- to 5-fold increased risk of HF [79]. In multivariable models, treatment with antidiabetic drugs, especially metformin, was associated with significantly lower risks of death or rehospitalization [79]. In contrast, thiazolidinediones should not be used in diabetic patients with established HF [80]. A reduction in deaths or hospitalizations was observed with metformin monotherapy vs sulfonylurea monotherapy [81], suggesting that metformin is both safe [82] and useful in HF [81,82]. The recently developed incretin-based therapies, such as glucagon-like peptide agonists and dipeptidyl peptidase-4 inhibitors, significantly improve cardiac function, including LV ejection fraction, and end-diastolic LV pressure, suggesting that they may represent a novel approach for the treatment of patients with T2DM-associated HF [83].

In a recent large trial in a national cohort of veterans with HF, the burden of 15 noncardiac comorbidities and their impact on hospitalization and mortality were compared between patients with HFpEF and those with HFrEF [25]. The cohort consisted of 2,843 patients with HFpEF and 6,599 with HFrEF followed-up for 2 years. Compared with patients with HFrEF, those with HFpEF were older and had higher prevalence of COPD, DM, HTN, anaemia, obesity, peptic ulcer disease and cancer but a lower prevalence of chronic kidney disease (CKD). Comorbidities had similar impact on mortality in patients with HFpEF compared with those with HFrEF, except for COPD, which was associated with a greater risk in patients with HFpEF [25]. These data showed that there is a higher noncardiac comorbidity burden associated with higher non-HF hospitalizations in patients with HFpEF compared with those with HFrEF. This suggests that aggressive management of comorbidities may have a greater effect on HFpEF [25].

3.5. Emerging Treatments

It is probable that chronic low-grade inflammation of the myocardium and arterial wall plays an important role in the pathogenesis of both HFpEF and AS, since it has been repeatedly associated with increased risk for clinically manifest HF in large cohort studies [60]. Impaired diastolic function is thought to be due to concentric remodelling of the heart along with increased stiffness of both the extracellular matrix and myofilaments [49]. In addition, oxidative stress and low-grade inflammation are thought to have a role in HFpEF progression, along with endothelial dysfunction and impaired nitric oxide(NO)-cyclic guanosine monophosphate kinase G (PKG) signalling [49]. The pathogenesis of AS that usually co-exists with HFpEF is also similar and is another key factor of the worsening of HF symptoms [84,85]. Statins may attenuate most if not all these adverse pathogenetic factors through their pleitropic effects [86,87].

A recent meta-analysis of 15 prospective studies (n=45,110) addressed the effects of statins in patients with HF [88]. The study included patients with both preserved and reduced EF and showed a reduction in all-cause mortality in patients treated with statins (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.61-0.83) and a reduction in rehospitalization rate for HF (RR 0.84, 95% CI 0.74-0.96) [88].
Statin treatment, however, had little impact on pump failure-related mortality, CVD mortality and sudden cardiac death. Atorvastatin treatment appeared to reduce all-cause mortality (RR 0.61, P=0.05) and rehospitalization for HF (RR 0.44, P=0.04) compared with non-atorvastatin statin therapy [88]. Thus, the statistical heterogeneity in the two outcomes could be partially accounted for by differences in the specific statin used [88].

A 2-year study reported the effect of statin treatment in 137 HFpEF patients in comparison to angiotensin converting enzyme inhibitor (ACE-I) or ARB, beta-blocker, or calcium channel blocker [89]. The latter treatments had no significant effect on survival; in contrast, treatment with a statin was associated with a substantial improvement in survival, independent of other predictors for death and differences in baseline clinical features [hazard ratio (HR) 0.20, 95% CI 0.06-0.62] [89]. After propensity matching, statin therapy was associated with both improved survival and a trend for fewer CVD-related hospitalizations [89].

Statin therapy was evaluated in another small study in 146 patients with HFpEF. Patients were assigned to statin therapy (n = 103) or not (n = 43) and were followed for 1 year [90]. Statin therapy was independently associated with reduced all-cause mortality (HR = 0.24, 95% CI 0.07-0.90, p<0.05) and CV rehospitalization rate (HR = 0.55, 95% CI 0.33-0.92 p < 0.05) [90]. In another long-term study [91], 270 patients with HFpEF were followed for over 5 years. Patients on statins demonstrated improved survival compared to patients not on statins (HR = 0.65, 95% CI 0.45-0.95, p = 0.029) [91]. Thus, statin therapy appears to be associated with improved survival in patients with HFpEF during mid- and long-term follow-up [91].

The results of the small studies described above suggest that statins may improve mortality in patients with HFpEF. Whether these findings are generalizable to a broader group of patients with HFpEF remains unclear. This was evaluated in a nationwide sample of 61,939 Medicare recipients ≥ 65 years of age who were hospitalized with a primary discharge diagnosis of HF [92]. From 54,960 patients finally included, only 16.7% received statins at discharge [92]. In a Cox proportional hazards model, discharge statin therapy was associated with significant improvements in 1- and 3-year mortality (HR 0.80, 95% CI 0.76 - 0.84 and HR, 0.82; 95% CI, 0.79-0.85, respectively). These results were independent from total cholesterol levels or presence of established CVD [92].

Statins also reduce AS in patients with dyslipidaemia [93-97], patients with or without CVD [98,99], postmenopausal women [100], patients with CKD [101], overweight and obese [102], patients with T2DM [103] or T1DM [104], healthy men [105], patients with rheumatoid arthritis [106] and elderly patients with HTN [107]. This effect of statins on AS is probably not a drug class effect, as suggested by the fact that the compound and the dose plays a significant role in the degree of AS reduction [98-107]. It seems that potent statins, such as atorvastatin and rosuvastatin, are more effective in reducing AS and consequently reducing excessive CVD risk [108]. This improvement in AS is probably one of the mechanisms through which statins improve HFpEF.

Recently, a new HFpEF paradigm has been proposed, with emphasis shifting from LV afterload excess to coronary microvascular inflammation [109]. This is supported by the fact that stiffness does not appear only in left ventricle [109]. Myocardial remodelling in HFpEF differs from the one observed in HFrEF, where remodelling is driven by loss of cardiomyocytes [109]. The new HFpEF paradigm proposes that comorbidities, plasma markers of inflammation and vascular hyperaemic responses should be included in diagnostic algorithms and intends to restore myocardial PKG activity with NO-donors, phosphodiesterase 5 inhibitors, and statins [109].

Despite the above data supporting the use of statins in HF, two large randomized trials, the Controlled Rosuvastatin Multinational Study in Heart failure (CORONA) trial [110] and the Gruppo Italiano per lo Studio della Sopravvivenza Nell’ Insufficienza Cardiaca Heart Failure (GISSI-HF) trial [111], which randomized patients to rosuvastatin 10 mg/d or placebo, did not show improved survival in patients with HF. However, both studies mostly included patients with HFrEF (100% in CORONA and 90% in GISSI-HF) [110,111]. In contrast to the latter studies, a prespecified post hoc analysis of the Treating to New Targets (TNT) study (n=10,001), were patients with coronary heart disease (CHD) were randomized to either 10 or 80 mg/d of atorvastatin, showed a substantial reduction in hard endpoints in patients with pre-existing HF [112]. Intensive treatment with atorvastatin 80 mg/d reduced hospitalizations for HF compared with the 10 mg/d dose. This benefit was more pronounced in patients with a history of HF (hospitalization for HF, 17.3 vs 10.6% in the 10- and 80 mg arms, respectively; HR 0.59, 95% CI 0.40 to 0.88, p = 0.009). The mechanism accounting for this benefit was not a reduction in recurrent CVD events or a difference in BP [112]. Patients with symptoms of advanced HF or a known ejection fraction < 30% were excluded from TNT; however, a part of the study population had pre-existing HF ascertained by questionnaire at the time of enrolment. Given the limited information on type of HF and LV function, generalizations of these findings should be made with caution. Furthermore, HF outcomes in TNT did not examine LV function and therefore included both HFrEF and HFrEF patients [112]. However, regardless of the type of HF, the 80 mg/d dose of atorvastatin reduced hospitalizations for HF by 41% over the 10 mg/d; this is a very important finding and it is probably related to the statin and dose used.

We reported similar findings in the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study [113]. Both in the original study and in a post hoc analysis, treatment with atorvastatin in 1,600 patients with CHD resulted in a reduction of 50% (95% CI 0.27-0.94, p = 0.021) in new or worsening cases of HF requiring hospitalization compared with usual care [113,114]. In GREACE, 63 of 800 patients treated with atorvastatin had HF at baseline. Among these patients, 10 were hospitalized for HF during the 3-year follow-up and showed a 2% increase in estimated glomerular filtration rate (eGFR) at 1 year compared with a 7.5% increase in those not hospitalized for HF (p = 0.002) [113]. Among the 800 patients receiving usual care, 55 had HF at baseline, and of those, 21 were hospitalized for HF during 3-year follow-up. These patients showed a 5% decrease in
eGFR at 1 year compared with a 1% increase in those not hospitalized for HF (p = 0.001) [113]. Therefore, the reduced risk for hospitalization for HF appears to be partly mediated by the improvement of renal function related to atorvastatin treatment [115]. These results are supported by the TNT findings [116], according to which improvement in kidney function may contribute to the beneficial effects of high-dose atorvastatin on HF hospitalization [116]. These findings suggest that the effects of statins in HF depend on the compound and dose used. Indeed, lipophilic statins appear to result in better clinical outcomes than hydrophilic statins in terms of HF-related events [117].

4. CONCLUSIONS
HFpEF is a major and growing public health problem in the Western world, currently accounting for half of all patients with HF. HFpEF has a multifactorial aetiology involving several interconnected physiological systems. For example, increases in AS, as seen in HTN and aging, can impair LV diastole. Ideally, the treatment of HFpEF should relieve symptoms and increase survival. The classical treatment of HFpEF did not improve survival and could not substantially reduce symptoms in patients with HFpEF. Further research is required to determine how to better target haemodynamic and cellular pathophysiology of diastolic and non-diastolic mechanisms of disease in order to reduce the substantial burden of morbidity and mortality in HFpEF, which is reaching epidemic proportions. Several drugs are in the pipeline but they will not be commercially available for several years. The aggressive treatment of comorbidities of both AS and HFpEF are at the present time the only available choice for the relief of the disease burden. Thus, drugs that improve ventricular-vascular coupling by targeting both ventricular and vascular stiffness (stiff heart and stiff arteries) may be of benefit in treating HFpEF, especially when combined with other drugs that target inflammation and cardiomyocyte stiffness. Treatment of anaemia, sleep disorders, CKD, NAFLD, atrial fibrillation, DM, and careful use of diuretics to reduce preload are effective to some degree. Statin treatment should also be implemented, regardless of lipid values, because it has been shown to substantially improve quality of life and survival in patients with HFpEF.

CONFLICT OF INTEREST
The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT
Declared none.

REFERENCES

[22] Schwartzzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilatation in heart failure with preserved or reduced ejection fraction implications of distinct patho-


[49] McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines of the ESC. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-847.


