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Echocardiographic evaluation of the effects of sacubitril–valsartan on vascular properties in heart failure patients

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Abstract

Increased vascular stiffness is known to be an independent predictor of mortality in patients with heart failure with reduced ejection fraction (HFrEF). The effects of sacubitril–valsartan on vascular structure and function have not been systematically studied in this patient population. We hypothesized that aortic distensibility (AD) and fractional area change (AFAC), as assessed by 2D transthoracic echocardiography (TTE), would improve over time in HFrEF patients on sacubitril–valsartan therapy, due to the vasodilatory properties of the medication. We prospectively studied 30 patients with HFrEF (25 < EF < 40%) on optimal guideline-directed medical therapy who were subsequently started on sacubitril–valsartan. Patients underwent serial 2D TTE imaging at baseline, 3 and 6 months following therapy initiation. Ascending aortic diameters were measured 3 cm above the aortic valve in the parasternal long-axis view and used to calculate AD and AFAC, two markers of vascular compliance. For reference, we also measured AD and AFAC in 30 healthy, age and gender-matched controls at a single time point. Normal controls had significantly higher values of AD and AFAC than HFrEF patients at baseline (AD: 4.0 ± 1.1 vs. 2.2 ± 0.9 cm²dyne⁻¹10⁻³, $p < 0.0001$ and AFAC: $18.8 \pm 3.7\%$ vs. $10.3 \pm 4.3\%$, $p < 0.0001$). In HFrEF patients on sacubitril–valsartan, both indices of aortic compliance progressively improved towards normal from baseline to 6 months: AD from 2.2 ± 0.9 to 3.6 ± 1.5 cm²dyne⁻¹10⁻³ ($p < 0.0001$) and AFAC from 10.3 ± 4.3 to $13.7 \pm 4.1\%$ ($p < 0.0001$). In conclusion, AD and AFAC are decreased in patients with HFrEF and gradually improve with sacubitril–valsartan treatment. The echocardiographic markers used in this study may become a useful tool to assess the effectiveness of sacubitril–valsartan therapy in HFrEF patients.

Keywords

Aortic distensibility; Vascular stiffness; Aorta; Entresto

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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Introduction

Increased arterial stiffness is one of the earliest detectable signs of adverse structural and functional remodeling within the vessel wall [1]. It has been associated with increased morbidity and both all-cause and cardiovascular mortality in hypertensive and diabetic patients [2, 3]. In addition, increased vascular stiffness has been shown to be an independent predictor of mortality in patients with heart failure with reduced ejection fraction (HFrEF) [4].

Several medication classes including beta blockers, ACE inhibitors, and aldosterone receptor antagonists have been shown to reduce mortality in HFrEF. The most recent therapy to demonstrate a mortality benefit in HFrEF is sacubitril–valsartan, an angiotensin receptor blocker-neprilysin inhibitor (ARNI) which is currently recommended as a replacement for an ACE inhibitor or an ARB in patients with NYHA Class II or III symptoms [5]. In the PARADIGM-HF trial, sacubitril–valsartan was shown to be more effective than enalapril at reducing mortality or hospitalization for patients with NYHA Class II or greater HFrEF [6]. Sacubitril–valsartan causes the degradation of several endogenous vasoactive peptides, including neprilysin, which blocks the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and adverse vascular remodeling. Its beneficial effects on vascular remodeling via the renin–angiotensin–aldosterone system and natriuretic peptide axis may explain its positive effects on mortality in HFrEF patients.

To date, no echocardiographic biomarkers are widely used to monitor the effects of sacubitril–valsartan on vascular structure and function in this patient population. Non-invasive measurement of aortic compliance using AD and AFAC, both obtained from two-dimensional transthoracic echocardiography (TTE), has been shown to have a high degree of accuracy when compared with more invasive measurements [7, 8]. In this study, we hypothesized that in patients with HFrEF treated with sacubitril–valsartan, the degree of AD and AFAC measured by TTE will progressively increase over time, due to the vasodilatory and afterload-reducing effects of the drug on the vessel wall.

Methods

Patients and study design

This was a prospective, single-arm cohort study. Inclusion criteria included: 18 years of age or older, congestive heart failure with NYHA Class II-IV symptoms with left ventricular ejection fraction $\geq 25\%$ and $\leq 40\%$, on an ACE-inhibitor or angiotensin receptor blocker dose equivalent to Enalapril > 10 mg/day, on a beta blocker for at least 4 weeks (unless contraindicated), and optimized dosing of other heart failure medications. Exclusion criteria were as follows: history of angioedema related to previous ACE-inhibitor or angiotensin receptor blocker (ARB) therapy, $\text{eGFR} < 30$ mL/min/1.73 m², serum potassium > 5.2 mmol/L, symptomatic hypotension of SBP < 100 mmHg at the time of screening, acute decompensated heart failure, history of severe pulmonary disease, active malignancy, and requirement for treatment with both ACE-inhibitor and ARB.

We initially enrolled 45 patients from a tertiary care medical center in Chicago, Illinois. Subsequently, 5 patients were excluded due to early drug discontinuation and 10 subjects due to echocardiographic windows that precluded measurement of ascending aortic diameters, resulting in a total of 30 study patients (Table 1). Each patient was started on a maximally tolerated dose of sacubitril–valsartan at either 97/103 mg twice daily (n = 22) or 49/51 mg (n = 8).

TTEs were obtained at baseline, 3 months, and 6 months after initiation of therapy. In addition, 30 age- and gender-matched healthy patients with normal TTEs were identified and used as normal controls (Table 1). The study was approved by the Institutional Review Board and written informed consent was obtained from all study patients prior to enrollment.

Echocardiographic measurements

Ascending aortic diameters were measured from leading edge to leading edge at 3 cm distal to the aortic root at end-diastole and end-systole in the parasternal long-axis view, as recommended by the 2015 American Society of Echocardiography (Fig. 1) [9]. All patients were in normal sinus rhythm at the time of image acquisition. These measurements were used to calculate AD and AFAC for each study subject at baseline, 3 months, and 6 months. AD and AFAC was also calculated for age and gender-matched controls at a single time point.

AD was defined as the relative cross-sectional diameter change for a given pressure step at a fixed vessel length. AD is obtained by calculating the difference in the diameter of the ascending aorta at end-systole and end-diastole and dividing by the diameter at end-diastole as well as the pulse pressure, and multiplying by a correction factor of 2000 [1, 10]. Brachial pulse pressure measured at the time of TTE acquisition was used as a surrogate for aortic pulse pressure. AFAC is defined as the percent change of the cross-sectional area (CSA) of the vessel between end-systole and end-diastole, calculated as the difference in the CSA at end-systole and end-diastole divided by the CSA at end-systole, multiplied by a correction factor of 100 [7]. Table 2 contains the formulas used to calculate AD and AFAC.

Other echocardiographic parameters including left and right ventricular ejection fractions, left ventricular end-systolic and end-diastolic volumes, as well as blood pressures were also measured at baseline, 3 months, and 6 months for each HFrEF patient. In order to investigate the effect of blood pressure changes on AD and AFAC, we performed multiple linear regressions to analyze the relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) and AD and AFAC, respectively.

To assess inter-observer variability, all echocardiographic measurements were repeated by a second independent observer blinded to all prior measurements. Both observers were blinded to the patients' treatment status, past medical history, and current medications.

Statistical analysis

A paired *t* test was performed to compare AD and AFAC at baseline, 3 and 6 months in HFrEF patients on sacubitril–valsartan. An unpaired *t* test was used to compare AD and

AFAC between HFrEF patients and normal controls. A p value of less than 0.05 was considered to be statistically significant. Inter-observer variability was quantified by calculating an intra-class correlation (ICC) coefficient, as well as the absolute difference between pairs of repeated measurements as a percentage of their mean.

Results

We initially enrolled 45 patients. Subsequently, 5 patients were excluded due to early drug discontinuation and 10 subjects due to echocardiographic windows that precluded measurement of ascending aortic diameters, resulting in a total of 30 study patients (Table 1).

Figure 2 shows an example of changes in both AD and AFAC seen in one patient over the course of 6 months of sacubitril–valsartan treatment, reflecting progressive improvement in aortic compliance.

Figure 3 summarizes these changes in the entire study group. At 3 months, AD increased from 2.2 ± 0.9 at baseline to $3.2 \pm 1.8 \text{ cm}^2\text{dyne}^{-1}10^{-3}$ ($p = 0.003$) and AFAC from 10.3 ± 4.3 to $12.6 \pm 4.6\%$ ($p = 0.014$). This trend continued through the 6-month time points, showing a progressive increase in AD from 2.2 ± 0.9 to $3.6 \pm 1.5 \text{ cm}^2\text{dyne}^{-1}10^{-3}$ ($p < 0.0001$) as well as in AFAC from 10.3 ± 4.3 to $13.7 \pm 4.1\%$ ($p < 0.0001$). The statistically significant improvement in AD and AFAC was observed regardless of sacubitril–valsartan dose, as well as presence or absence of hypertension, diabetes, or ischemic heart disease.

Healthy age and gender-matched controls with normal TTEs had significantly lesser degrees of AD and AFAC than the HFrEF patients at baseline (AD: 4.3 ± 2.6 vs. $2.2 \pm 0.9 \text{ cm}^2\text{dyne}^{-1}10^{-3}$, $p = 0.001$, and AFAC: $18.8 \pm 7.7\%$ vs. $10.3 \pm 4.3\%$, $p < 0.0001$). Over the course of 6 months, both indices of aortic compliance progressively improved towards normal, as summarized in the previous paragraph.

Other echocardiographic parameters, including left and right ventricular ejection fractions, left ventricular end-systolic and end-diastolic volumes, all demonstrated improvement over the course of 6 months on sacubitril–valsartan (Table 3).

Average mean arterial pressure for the HFrEF patients at baseline, 3 months, and 6 months was 101 ± 15 , 92 ± 15 , and $88 \pm 12 \text{ mmHg}$, respectively (Table 4). The SBP of the HFrEF patients improved from 137 ± 18 , to 123 ± 18 , to 119 ± 15 at baseline, 3 months, and 6 months, respectively, and DBP improved from 84 ± 15 , to 77 ± 14 , to 72 ± 12 during the same time period. Average mean arterial pressure in the normal control group was $92 \pm 10 \text{ mmHg}$.

Linear regression analyses of the relationships between blood pressure and each index of aortic compliance depicted a moderate linear relationship between SBP and AD ($r = 0.50$; $p < 0.001$); however, all other measures of blood pressure including DBP ($r = 0.15$; $p < 0.20$) and MAP ($r = 0.30$; $p < 0.01$) showed weak linear relationships with AD. The correlation coefficients between SBP and AFAC ($r = 0.29$; $p < 0.02$), DBP and AFAC ($r = 0.21$; $p < 0.07$), and MAP and AFAC ($r = 0.25$; $p < 0.03$) were similarly weak.

Our assessment of inter-observer variability demonstrated good reliability between observers, with $9.2 \pm 7.3\%$ variability and an intraclass correlation coefficient of 0.80.

Discussion

Our study showed that AD and AFAC progressively improve with sacubitril–valsartan therapy. We demonstrated that normal controls have significantly higher values of AD and AFAC compared to HFrEF patients, and that treatment with sacubitril–valsartan helps to gradually normalize these two indices of aortic compliance, starting as early as 3 months following therapy initiation. For reference, we compared our data to previously published values for aortic distensibility in normal controls, and confirmed that measurements obtained in our control subjects were similar to previously published reference values [8, 10].

The aorta serves both as a conduit and reservoir for blood. The aorta stores half of the ejected blood volume and pushes the remaining volume into the peripheral circulation during diastole, a concept known as the Windkessel effect. With aging, stress, and the presence of cardiovascular risk factors, the elastic fibers within the aortic wall become disrupted, resulting in increased aortic stiffness [11]. Chirinos et al., also demonstrated the concept of pulsatile load, which suggests that wave reflections that arise in the peripheral arteries return to the proximal aorta during mid to late systole and contribute to left ventricular afterload. These authors also showed that increased arterial wave reflections are associated with an increased risk for cardiovascular events and the development of heart failure symptoms [12]. It has thus been suggested in the literature that reducing aortic stiffness may become an important therapeutic target in patients with heart failure [13].

Current evidence-based therapies for HFrEF, as endorsed by the 2013 ACC/AHA Guidelines as well as subsequent updates, include ACE inhibitors (or angiotensin receptor blockers in ACE inhibitor intolerant individuals) and beta blockers, both of which have been shown to have mortality benefit in this patient population [5, 14]. In patients with persistent symptoms, mineralocorticoid receptor antagonists are recommended, and have also been shown to improve mortality [5, 14, 15]. In 2014, the PARADIGM-HF study demonstrated that sacubitril–valsartan confers a mortality benefit in HFrEF patients with NYHA Class II–IV symptoms compared to enalapril [6]. Additional evidence-based therapies are recommended for those who remain symptomatic and for other specific patient populations (i.e. ivabradine, hydralazine and isosorbide dinitrate) [5, 14].

Important molecular targets in HFrEF include neurohormonal modulation of the renin–angiotensin–aldosterone system, as seen with ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid antagonists [16]. Beta blockers act by reducing catecholamine stimulation and myocardial oxygen demand, thereby decreasing the rate of adverse remodeling caused by cardiac myocyte hypertrophy and supply–demand mismatch [15]. Natriuretic peptide inhibitors act on the natriuretic peptide axis, blocking degradation of natriuretic peptide by neprilysin, resulting in increased natriuresis and vasodilation, decreased interstitial fibrosis, and improved vascular fitness [6].

A number of studies have investigated the relationship between sacubitril–valsartan and arterial stiffness in the setting of hypertension. The multicenter, randomized, double-blind PARAMETER study found that after 12 weeks, sacubitril–valsartan significantly reduced both central aortic and brachial blood pressures (measured using a specialized non-invasive blood pressure cuff), compared to olmesartan, in elderly patients with systolic hypertension and stiff arteries (defined as a pulse pressure of > 60 mmHg) [17]. Schmieder et al., also randomized patients with hypertension and elevated pulse pressure to sacubitril–valsartan versus olmesartan, and found that there was a significantly larger reduction in central pulse pressure in the sacubitril–valsartan group compared to the olmesartan group at 52 weeks. This study also showed improvement in AD in both groups (measured by cardiac MRI), however no significant difference in mean AD change between groups [18]. The results of these two studies, which both used non-invasive methods to measure AD and both showed improvements on sacubitril–valsartan over time, are corroborated by the results of our echo-based study.

Recent literature has also demonstrated an association between heart failure and increased vascular stiffness. Tsao et al., showed that increased aortic stiffness, reflected as higher carotid-femoral pulse wave velocities, was associated with an increased risk of developing symptomatic heart failure [19]. Similarly, increased aortic root remodeling has also been shown to be associated with increased risk of heart failure, likely secondary to concurrent ventricular-vascular remodeling in patients with enlarged aortic roots [20]. A recent meta-analysis by Vlachopoulos et al. showed that increased aortic stiffness, as measured by pulse-wave velocity, is a strong predictor of adverse cardiovascular events as well as all-cause mortality, particularly in subjects with higher cardiovascular risk [21]. Taken together, these studies demonstrate an important link between aortic stiffness, symptomatic heart failure, and all-cause mortality. These studies provided the impetus for our current study, aimed at identifying non-invasive imaging-based indices, AD and AFAC, capable of tracking the effects of novel drug therapy on aortic compliance.

Though pulse-wave velocity remains the gold standard non-invasive modality for measuring vascular stiffness [1], the advantage of TTE-based measurement is that it is more widely available, less cumbersome for the patient and provider, and provides a large amount of additional diagnostic information. Based on the results of this proof-of-concept study, future studies can be performed to test our hypothesis using other non-invasive methods of measuring vascular compliance, including pulse-wave velocity and velocity-encoded magnetic resonance imaging.

The results of our linear regression analyses investigating the relationship between blood pressure and AD and AFAC showed only weak to moderate relationships, the majority of which were established with statistical confidence reflected by low p-values. These results suggest that while changes in blood pressure, particularly SBP, likely play a role in changes in AD and AFAC, they are not likely to be the sole determining factor of aortic compliance. The pathophysiology of vascular stiffness is known to be multifactorial and is influenced by chronic kidney disease, diabetes, microvascular disease, and aging, as well as a host of other medical conditions and environmental factors [11]. Therefore, the improvements in AD and AFAC observed in our study are unlikely to be solely attributable to changes in blood

pressure, but rather to sacubitril–valsartan’s beneficial pleiotropic effects on the vascular bed and overall hemodynamics.

Limitations

While the size of our study is small, it is the first study to longitudinally examine echocardiographic markers of vascular structure and function in HFrEF patients on sacubitril–valsartan. In addition, we used brachial pulse pressure as a surrogate for aortic pulse pressure, which could have been affected by the amplification phenomenon between central and peripheral arteries [1]. Thus, it is possible that the brachial pulse pressure used in our analysis minimally overestimated the actual central pulse pressure, leading to a slight underestimation of AD. To offset this limitation, the second marker we used to measure aortic compliance, AFAC, is calculated independently of pulse pressure, and has been shown to significantly correlate with pulse-wave velocity [7]. Lastly, we did not follow our control group over time, as this group did not have echocardiograms performed at regular time intervals. However, the control group served as a useful reference for normal AD and AFAC values in healthy patients, and closely resembled values previously published in the literature [8, 10].

Conclusion

This study showed that sacubitril–valsartan has beneficial effects on AD and AFAC as measured by TTE, and that this effect gradually increases from baseline to six months. By routinely measuring ascending aortic diameters at end-systole and end-diastole on TTE, AD and AFAC can be calculated, serving as physiologic biomarkers of drug effect on vascular function. Future research is needed to confirm these results using other well-validated methods of measuring vascular compliance, including but not limited to pulse-wave velocity and velocity-encoded magnetic resonance imaging. Finally, longer term follow-up is required to assess the durability of this beneficial effect of sacubitril–valsartan on vascular structure and function.

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Fig. 1.

Transthoracic echocardiography-based measurements. Ascending aortic diameters were measured 3 cm distal to the aortic root at end-diastole and end-systole, from leading edge to leading edge, in the parasternal long-axis view, and used to calculate aortic distensibility and fractional area change, two markers of vascular compliance. *AoD* diameter of ascending aorta at end-diastole, *AoS* diameter of ascending aorta at end-systole

Fig. 2.

Example of changes in aortic distensibility (AD) and aortic fractional area change (AFAC).

In this individual patient with HFrEF treated with sacubitril–valsartan (97/103 mg twice daily), both AD and AFAC progressively improved from baseline (top row) to 3 months (middle row) to 6 months (bottom row). *AoD* diameter of ascending aorta at end-diastole (left), *AoS* diameter of ascending aorta at end-systole (right), *BP* blood pressure, *AD* aortic distensibility, *AFAC* fractional area change of ascending aorta

Fig. 3.

Changes in aortic distensibility (AD) and aortic fractional area change (AFAC). Both AD and AFAC progressively improved towards normal from baseline to 6 months: AD from 2.2 ± 0.9 to 3.6 ± 1.5 cm²dyne⁻¹10⁻³ ($p < 0.0001$) and AFAC from 10.3 ± 4.3 to $13.7 \pm 4.1\%$ ($p < 0.0001$). Normal controls had significantly higher aortic compliance than HFrEF patients at baseline (AD: 4.0 ± 1.1 vs. 2.2 ± 0.9 cm²dyne⁻¹10⁻³, $p < 0.0001$ and AFAC: $18.8 \pm 3.7\%$ vs. $10.3 \pm 4.3\%$, $p < 0.0001$)

Table 1

Baseline characteristics of HFrEF patients and normal controls

	HFrEF patients (n = 30)	Normal controls (n = 30)
Age (years)	56 ± 12.6	56 ± 12.6
Gender (% female)	43.3%	43.3%
Race (% African American)	56.7%	43.3%
Race (% white)	33.3%	26.7%
Race (% Asian)	6.7%	3.3%
Race (% other)	3.3%	26.7%
BSA (m ²)	2.1	1.9
NYHA class II (%)	79.3%	0%
NYHA class III (%)	20.7%	0%
% Ischemic cardiomyopathy	26.7%	0%
Hypertension (%)	53.3%	0%
Coronary artery disease (%)	36.7%	0%
Diabetes mellitus (%)	30.0%	0%
Atrial fibrillation (%)	20.0%	0%
ICD (%)	63.3%	0%

Table 2

Markers of aortic stiffness

Variable	Formula
Pulse pressure	Systolic blood pressure–diastolic blood pressure
Aortic cross-sectional area (cm ²)	$\pi \cdot (\text{Aortic Diameter}/2)^2$
Aortic distensibility (cm ² dyne ^{−1} 10 ^{−3}) [1, 8]	$2 \cdot [(\text{Aortic End-Systolic Diameter} - \text{Aortic End-Diastolic Diameter}) / (\text{Aortic End-Diastolic Diameter} \cdot \text{PP})] \cdot 1000$
Aortic fractional area change (%) [7]	$(\text{Aortic End-Systolic CSA} - \text{Aortic End-Diastolic CSA}) / (\text{Aortic End-Systolic CSA}) \cdot 100$

CSA cross-sectional area, PP pulse pressure

Table 3

Echocardiographic parameters of HFrEF patients over the course of treatment

Echo parameter	Baseline	3 months	6 months
Left ventricular ejection fraction (%)	32.0 ± 7.0	34.8 ± 7.4	36.8 ± 7.8
Right ventricular ejection fraction (%)	48.0 ± 10.4	49.9 ± 9.0	50.7 ± 6.8
Left ventricular end-diastolic volume (mL)	255 ± 75	227 ± 62	216 ± 70
Left ventricular end-systolic volume (mL)	178 ± 65	151 ± 55	140 ± 60

Table 4

Blood pressure measurements in the HFrEF patients over the course of treatment

Parameter	Baseline	3 months	6 months
Systolic blood pressure	137 ± 18	123 ± 18	119 ± 15
Diastolic blood pressure	84 ± 15	77 ± 14	72 ± 12
Mean arterial pressure (MAP)	101 ± 15	92 ± 15	88 ± 12