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Original Article

Study of endothelial function and vascular stiffness in patients affected by dilated cardiomyopathy on treatment with sacubitril/valsartan

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Abstract: Background: The multiple beneficial effects of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction are vastly known, but still no or few mentions have been made regarding its effects on endothelial dysfunction and arterial stiffness. Patients and methods: To understand more deeply if sacubitril/valsartan may have a role on endothelial function and arterial stiffness, 15 patients with dilated cardiomyopathy with reduced left ventricular ejection fraction (LVEF) were evaluated through transthoracic echocardiography, peripheral arterial tonometry (EndoPAT®) and applanation tonometry (SphygmoCor® Px system). These noninvasive exams were performed at the beginning of the study and after 6 months of sacubitril/valsartan treatment. Results: Aortic stiffness parameters didn't differ after 6 months of treatment. Augmentation pressure (P=0.889), augmentation index (P=0.906) and sphygmic wave velocity (P=0.263) increased slightly, but they weren't found to be statistically significant. Systolic, diastolic, and differential central arterial pressure didn't differ at the beginning and at the end of the study. RHI (reactive hyperemia index) increased significantly after 6 months (P=0.001) as well as augmentation index corrected for 75 bpm. Ejection fraction (32.21% ± 5.7 to 38.43% ± 8.4; P=0.010) and diastolic dysfunction degree (P=0.021) improved. There was an improvement in mitral regurgitation that wasn't statistically significant (P=0.116). TAPSE didn't change while pulmonary systolic arterial pressure increased, although not significantly (22.83 mmHg ± 4 to 27.33 mmHg ± 6; P=0.068) and within the normal range values. Conclusions: Even though in a study with a limited number of patients, sacubitril/valsartan improved endothelial function, left ventricular function, MR, and diastolic function significantly in patients with dilated cardiomyopathy and reduced LVEF. It showed no effects on vascular stiffness.

Keywords: Endothelial function, vascular stiffness, sacubitril/valsartan

Introduction

Heart failure is a clinical syndrome sustained by different risk factors, comorbidities and pre-existing conditions that can have a negative impact on the cardiac function with structural remodeling and fibrosis leading to a systolic and/or diastolic dysfunction. This condition leads to a number of signs and symptoms that impact the lives of the patients affected by it. Among the symptoms that most frequently are referred by the patients, the more invalidating are dyspnea, fatigue and reduced ability to exercise. Due to the high prevalence of this condition, especially in the elderly population, many steps forward have been made over the years to try and reduce its morbidity and mortality. In terms of treatment there has been a drastic evolution from diuretics as the only treatment available, to a multi-step approach to this syndrome. The main targets of heart failure therapy are the catecholaminergic system and the renin-angiotensin-aldosterone system. In fact, betablockers, ACE inhibitors or ARBs and mineralocorticoid receptor antagonists (MRAs) have been the mainstay of heart failure treatment for decades; they have been used to slow down the progression of fibrosis and remodeling. These drugs were the only ones that demonstrated efficacy in improving the symptoms

and reducing the hospitalization rate and mortality in these patients [1]. However, in the last few years a new treatment has emerged with the ability to radically change the natural history of this disease, so much that it is now preferred over ACEi/ARBs, whenever tolerated by the patients. With the arrival of sacubitril/valsartan finally a new target in the neuro-hormonal modulation was addressed.

In PARADIGM-HF trial sacubitril/valsartan reduced cardiovascular deaths and hospitalizations by 20% compared to enalapril. It also reduced the overall death and improved the quality of life. It demonstrated a progressive slowing of cardiac remodeling and progression of structural and functional dysfunction [2]. However, many of the mechanisms involved in these achievements are still not clear.

Different studies demonstrated that from the very first phases, endothelial dysfunction and vascular stiffness have a key role in the progression of the cardiac damage [3] and both the conditions are detectable in coronary arteries and in peripheral arteries of patients affected by acute and chronic heart failure, often present also following a heart transplant [4].

To expand the knowledge on this topic, the aim of our study was to evaluate the possible therapeutic effects of sacubitril/valsartan on endothelial function and arterial stiffness.

Materials and methods

Population of the study

The study was performed between April 2019 and August 2020 at the department of Cardiology of Spedali Civili (Brescia, Italy). This study was approved by the local ethics committee. During this time 15 patients with documented diagnosis of dilated cardiomyopathy with reduced left ventricular ejection fraction (LVEF) were enrolled. All participants provided written informed consent prior to enrolment in the study. Demographic, clinical and medication data at the beginning of the treatment with sacubitril/valsartan were obtained by medical records.

The patients were selected using the following criteria.

Inclusion criteria

- Caucasian ethnicity.
- Age ≥18 years.
- Dilated cardiomyopathy with LVEF <40%.
- Absence of recent acute coronary syndrome (6 months).

Exclusion criteria

- Non-Caucasian ethnicity.
- Age <18 years.
- Recent acute coronary syndrome (6 months).
- Congenital cardiomyopathy.
- Rheumatological or orthopedics diseases of the upper limbs that could somehow affect the use of EndoPAT®.

Study design

The study was a longitudinal prospective study. Instrumental examinations were performed to evaluate the endothelial function, the aortic stiffness and parameters of cardiac function at the moment of the enrollment in the study and subsequently after 6 months after the beginning of the therapy with sacubitril/valsartan in order to show the benefits of the drug. The patients were followed up in time with phone calls with the aim of ensuring therapy adherence and to agree on a control date at 6 months.

The procedures performed at the beginning and at the end of the study period were:

- Blood pressure measurements.
- Applanation tonometry through SphygmoCor Px system.
- Peripheral arterial tonometry through Endo-PAT 2000.
- Transthoracic echocardiography.

The parameters obtained at the end of the study were subsequently compared with the parameters detected at the time of enrollment.

Evaluation of the arterial pressure

The measurement of the arterial pressure was performed with an aneroid sphygmomanometer.

According to the guidelines of the Italian Society of Hypertension (SIIA) patients were seated comfortably, resting for 5 minutes in a quiet and pleasant environment. Subsequently, an adequate size pressure cuff was applied above the antecubital fossa, with the arm lied down and placed at the level of the cardiac plane. Overlapping legs and eloquence were avoided during the measurement. The pressure cuff was inflated in order to overcome the systolic arterial pressure and subsequently deflated with a velocity of 2-3 mmHg for second. Systolic arterial pressure, diastolic arterial pressure and systemic differential pressure were written down.

The procedure was also performed in the contralateral arm, in order to exclude arteriopathies, up to a total of 3 measurements; an average was then calculated. The registered data were used for the statistical processing.

Peripheral arterial tonometry

The evaluation of the endothelial function was obtained through peripheral arterial tonometry (PAT) using Endo-PAT 2000® device, produced by the Israelian Itamar Medical Ltd.

It's a non-invasive, quick and operator-independent procedure that can evaluate the peripheral microvascular endothelial function, using a specific software.

The device is based on the use of two probes that are placed at the distal phalange of the second finger of both hands. These probes have an external rigid coating and an internal system of neoprene inflatable membranes able to create a pressure of 70 mmHg.

The pressure produced by these membranes limits motion artifacts and prevents venous stasis related to a veno-arteriolar vasoconstriction reflex and the blood reflux, things that could compromise the results [5].

The patient is seated with both arms resting on special armrests in order to relax and stretch out the arms, limiting the finger movements and an aneroid sphygmomanometer is placed above the right antecubital fossa.

Once the probes are inflated, the test is performed through 3 different phases of 5 minutes each:

1. Basal phase: the system measures the magnitude of the sphygmic signal in the peripheric vascular system at rest for each finger.

2. Occlusive phase (ischemic): the pressure cuff (usually on the right arm) is inflated at a pressure of 50/60 mmHg above the systolic arterial pressure so to create an occlusion of the brachial artery. During this phase no signal is detected by the right finger probe while the left finger probe continues to create a signal.

3. Hyperemic phase: at the end of the 5 minutes, the pressure cuff is deflated. The magnitude of the hyperemic response is measured from the system at the right finger.

The software then analyzes the data obtained and is able to produce 3 endothelial functional indices:

1. Reactive Hyperemia Index (RHI), based on the sphygmic signal ratio between the experimental arm and the control arm during the reactive hyperemic phase, normalized for the same ratio calculated during the basal phase. The RHI cut off is 1.67 and lower values are a sign of endothelial dysfunction. However, in literature there are studies in which an RHI ≥2 has beenused as cut-off, so in our study we used both cut-off values. An RHI index between 1.67 and 2 was considered borderline.

2. Framingham reactive Hyperemia Index/Endoscore which is the natural logarithm of RHI. The cut off in this case is 0.51, with a LnRHI ≤0.51 that defines endothelial dysfunction.

3. Augmentation Index (Aix), the index of peripheral arterial stiffness. It is calculated by analyzing the shape of the wave of the signal impulses registered in phase 1 and is not necessarily related with endothelial dysfunction. The result is normalized for 75 bpm (Aix@75). Aix values lower than 17% reflect a normal condition, while values above this cut-off reflect an abnormal vascular stiffness.

Applanation tonometry

The non-invasive evaluation of the aortic stiffness parameters was obtained through the use of applanation tonometry with SphygmoCor Px system® (AtCor Medical®, Sydney, Australia). Applanation tonometry (AT) is a noninvasive, reproducible, and accurate representation of the aortic pressure waveform. Measurement of the aortic waveform can provide clinically useful information beyond brachial-measured blood pressure.

The exam consists in the application of a Miller tonometer at the target artery through which is possible to obtain a digital record of the pulse wave for 10 seconds.

The device software can calculate automatically the aortic stiffness related indices.

After the measurement of systemic arterial pressure, the pulse wave analysis (first phase of the study) is performed applying the tonometer on the right radial artery for 10 seconds, obtaining the pressure wave record.

The principal parameters acquired were:

1. Systolic, diastolic and average aortic pressure (PASao, PADao, PPao).

2. Augmentation pressure (AP), that refers to the difference of pressure between the moment at which the reflexed wave returns to the aortic bulb and the systolic peak, used for the calculation of the "augmentation index" (Aix).

3. Augmentation index (Aix) and Augmentation index corrected for 75 bpm rate (Aix@75), calculated through the formula deltaP/PP x 100 which is an expression of total peripheral resistances and vascular stiffness.

4. cfPWV (femoral-carotid pulse wave velocity).

Transthoracic echocardiography

The echocardiographic evaluations were performed using an ultrasound Vivid q device® (GE Heathcare, Milwakee, WI, USA), with a 3.5 MHz transducer. The digital data were stored on the machine hard disk for the online and offline analysis and transferred on a workstation (EchoPac®, Vingmed GE Healthcare, Milwakee, WI, USA) for the offline analysis. The images were acquired through apical (4 and 2 chambers) and parasternal windows, accordingly with the more recent guidelines [6] and an ECG was registered simultaneously at the echography session. All the exams were evaluated by a single operator, without any clinical knowledge of the patient.

1. Left ventricular ejection fraction (LVEF) was calculated with Simpson's biplane method [6].

2. Left ventricular diastolic function, accordingly with guidelines, was calculated with transmitral doppler influx and TDI in basal segments; 4 groups were defined through these parameters, each group with increasing diastolic dysfunction degrees [7]:

- Inversion of E/A ratio. This is the milder degree of diastolic function and is often named "altered ventricular relaxation". Patients are asymptomatic.

- The second degree of diastolic dysfunction is characterized by an increase of the left atrial filling pressure and often with atrium dilatation.

- The third degree represents severe diastolic dysfunction, characterized by a restrictive diastolic filling often leading to symptoms of advanced heart failure. When the patient performs a Valsalva maneuver the diastolic abnormalities seem to resolve. Therefore, it is named reversible restrictive diastolic dysfunction.

- This is the most severe form and represents a restrictive filing pattern which is not reversible.

3. The right ventricular systolic function was estimated by using tricuspid annular plane systolic excursion (TAPSE), as recommended by the guidelines [6].

4. The valvular abnormalities were evaluated following guidelines [8].

5. Systolic pulmonary artery pressure was obtained from the sum of the estimated right atrial pressure with the simplified Bernoulli equation applied on the velocity of the tricuspid regurgitation jet with continuous wave doppler.

Statistical analysis

After being tested for normality using graphics QQ plots, the continuous variables were expressed as an average ± standard deviation.

Table 1. Demographics characteristics and cardiovascular risk factors

Age (Years)	66.9 ± 7.4
Male sex	10 (66.7%)
Hypertension	8 (53.3%)
Type II diabetes	2 (13.3%)
Dyslipidemia	7 (46.7%)
Smoke	0
Cardiovascular familiarity	8 (53.3%)
Coronary artery disease	7 (46.7%)
Atrial fibrillation	4 (26.7%)
Cardiac resynchronization therapy	9 (60%)

Table 2. Patients' medications

Beta blockers	14 (93.3%)
Mineralocorticoid receptor antagonists	11 (73.3%)
Loop diuretics	10 (66.7%)
Thiazide diuretics	1 (6.7%)
Ivabradine	1 (6.7%)
Alpha-1 antagonists	2 (13.3%)
Statins	11 (73.3%)
Acetyl salicylic acid	6 (40%)
P2Y12 inhibitors	3 (20%)
Vitamin K antagonists	1 (6.7%)
Novel oral anticoagulants	3 (20%)

The categorical variables were instead expressed as rates (n) and percentage of the sample.

Ranks test with Wilcoxon sign to related samples was used to study the continuous variable differences before the administration of sacubitril valsartan and after 6 months of therapy.

The difference between proportions was performed with chi square test (or Fischer when possible).

Statistical analysis was performed by using software IBM SPS Statistics for Windows and the significant level was fixed at a p value < 0.05 with a two-tail test.

Results

Baseline characteristics

The study included a population of 15 patients affected by dilated cardiomyopathy, whose characteristics are listed in **Table 1**. The population included 10 men (66.7%) and 5 women (33.3%) and the average age was 66.9 years. Cardiovascular risk factors were considered, with a prevalence of 53.3% of hypertension and CV familiarity and a prevalence of 46.7% of dyslipidemia and coronary artery disease. Only two patients were diabetics, while 9 (60%) patients carried a resynchronization therapy device, 4 patients (26.4%) were affected by permanent atrial fibrillation. None of the patients declared to smoke.

Patients' medication was registered at the moment of data collection and it is listed in **Table 2**. Almost all patients (93.9%) were on therapy with beta blockers, while a lower percentage with MRAs and loop diuretics. Furthermore, 11 patients took statins and 9 of them also took antiplatelet therapy (6 on therapy with acetylsalicylic acid and 3 with P2Y12 inhibitors).

Clinical data

Clinical data were obtained at the beginning of the study and after 6 months through applanation tonometry (SphygmoCor®), peripheral arterial tonometry (EndoPAT®) and transthoracic echocardiogram as listed on **Table 3**.

Differences at 6 months in term of weight, BMI and body surface area resulted not significant, as also differences in term of systolic, diastolic, average and differential arterial pressure. Heart rate after 6 months was slightly lower compared with control, but without statistical significance.

Aortic stifness parameters

The data obtained with SpygmoCor® were not different at 6 months compared to baseline. Systolic, diastolic and differential central arterial pressure did not change and the slight increase of augmentation pressure (P=0.889), augmentation index (P=0.906) and sphygmic wave velocity (P=0.263) was not statistically significant.

Endothelial function

There was an important improvement in EndoPAT® data, which are related to endothelial dysfunction and peripheral vascular resistance. As depicted in **Table 3** and **Figure 1**, RHI values (reactive hyperemia index) at 6 months increased (P=0.001) as well as the augmentation index corrected for 75 bpm.

Table 3. Clinical data before and after treatment with sacubitril/valsartan

Clinical data	Before therapy	After therapy	*P* value
Weight (kg)	73.33 ± 13	74.47 ± 13	0.245
BMI (kg/m^2)	25.456 ± 4	25.817 ± 4	0.248
BSA (m^2)	1.837 ± 0.17	1.850 ± 0.17	0.155
Systolic arterial pressure (mmHg)*	121.69 ± 14.8	123.46 ± 16.8	0.528
Diastolic arterial pressure (mmHg)*	73 ± 8.5	73.85 ± 10.5	0.687
Average arterial pressure (mmHg)*	89.46 ± 9.5	90 ± 13	0.701
PP (mmHg)*	48.69 ± 9.5	49.62 ± 10.5	0.502
Heart rate*	69.69 ± 16	63.62 ± 5	0.155
SAP ao/central (mmHg)*	110.54 ± 13	112.38 ± 16	0.421
DAP ao/central (mmHg)*	74.08 ± 8	75 ± 10	0.666
PP ao/central (mmHg)*	36.46 ± 7	38.15 ± 10	0.208
AP (mmHg)	6.31 ± 9	9.23 ± 7.5	0.889
Aix-75 (%)	12.17 ± 22	16.25 ± 16.5	0.906
PWV (m/s)	8.089 ± 7	9.067 ± 2	0.263
RHI	1.516 ± 0.47	2.679 ± 1.13	0.001
Aix-75 PAT (%)	2.50 ± 27	-21.50 ± 25	0.006
EF (%)	32.21 ± 5.7	38.43 ± 8.4	0.010
Diastolic dysfunction	Number of patients*	Number of patients	0.021
Degree I	4 (28.6%)	11 (73.3%)	
Degree II	3 (21.4%)	3 (20%)	
Degree III	7 (50%)	1 (6.7%)	
Degree IV	0	0	
Mitral regurgitation	Number of patients*	Number of patients	0.166
Degree I	4 (33.3%)	10 (66.7%)	
Degree II	9 (60%)	4 (26.7%)	
Degree III	1 (67%)	1 (6.7%)	
Degree IV	0	0	
PAPs (mmHg)	22.83 ± 4	27.33 ± 6	0.068
TAPSE (mm)	18.33 ± 3.24	18.11 ± 2.26	0.888

*data obtained from 14 patients. Aix-75: augmentation index; AP: augmentation pressure; BMI: body mass index; BSA: body surface area; DAPao: aortic diastolic arterial pressure; EF: Ejection fraction; PAPs: systolic pulmonary arterial pressure; PPao: aortic pulse pressure; PWV: pulse wave velocity; RHI: reactive hyperemia index; SAPao: aortic systolic arterial pressure; TAPSE: tricuspid annulus plane systolic excursion.

Endothelial dysfunction evaluated with two different RHI cut off was performed at baseline and after 6 months. Considering RHI values <1.67, the number of patients with endothelial dysfunction at 6 months, after starting therapy was reduced from 9 (60%) to 4 (26.47%), while using a RHI cut off <2 patients with endothelial dysfunction at the end were 6 (40%) compared to 10 (66.7%) at baseline.

Echocardiographic data

Echocardiographic data are listed in **Table 3**.

There was a significant increase in ejection fraction (P=0.010) (**Figure 2**) and diastolic dysfunction degree (P=0.021) (**Figure 3**). At the end of the study, only 1 patient (6.7%) had third diastolic dysfunction degree, while 11 patients (73.3%) had a first diastolic dysfunction degree.

The improvement of mitral regurgitation was not statistically significant (P=0.116). However, the number of patients with moderate mitral regurgitation (II degree) were reduced from 10 to 6 and the number of patients with mild mitral regurgitation increased (I degree).

Systolic pulmonary artery pressure increased slightly at 6 months, but not in a statistically significant manner (P=0.068) and it was in the normality range. There was no global differen-

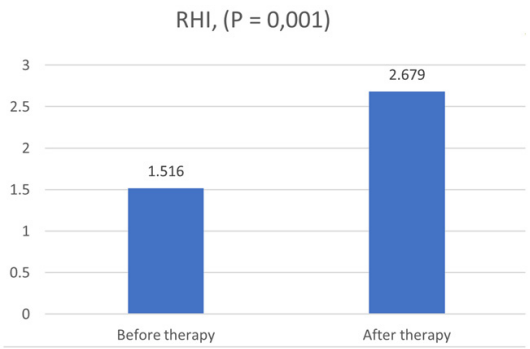

Figure 1. RHI improvement six months after introduction of sacubitril valsartan.

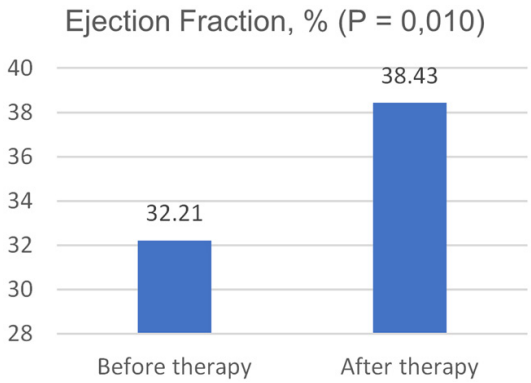

Figure 2. Ejection fraction six months after introduction of sacubitril valsartan.

ce in tricuspid annular plane systolic excursion and right ventricular function index.

Discussion

The aim of this study was unveiling the possible effects of sacubitril/valsartan on the vascular system, to assess whether there is an improvement in arterial stiffness and endothelial dysfunction in patients with dilated cardiomyopathy.

Hydrosaline retention, the increased neuro-hormonal activity and the functional abnormalities of endothelium are pathological conditions that concur to the progression of heart failure and to endothelial dysfunction as well as smoking, diabetes, hypertension, kidney disease, dyslipidemia and ageing [9]. These conditions, in association with the nitric oxide bioavailability reduction (main determinant of endothelial function) induce cardiac hypertrophy, fibrosis, ventricular remodeling and atherosclerotic plaques progression [1].

In this study the endothelial response was assessed in condition of reactive hyperemia, with the aim of estimating any endothelial functional change before and after 6 months of therapy with sacubitril/valsartan. A significant increase of RHI (reactive hyperemia index), calculated by peripheral arterial tonometry (endoPAT®) was observed, and a lower number of patients were affected by endothelial dysfunction, assessed with both cut off used in literature (RHI <1.67 and RHI <2). The improvements observed in this study may support the hypothesis that sacubitril/valsartan can improve endothelial function. Furthermore, it was observed an improvement of augmentation index, calculated with peripheral arterial tonometry (Aix-75 PAT), which is related to a reduction of vascular resistance, although with highly variable values.

This was the first study that assessed the potential efficacy of sacubitril/valsartan in this specific area. Only few evidence is present in literature and only on animal models. Kusaka et al, in a 2015 study proved that sacubitril/valsartan was better than valsartan alone in improving the acetylcholine-induced vasodilatation in rats fed with a high salt intake diet [10]. Seki et al, in a more recent study (2017) demonstrated an increase in bioavailability of nitric oxide in male hypertensive mice in whom heart failure had been induced through a surgical intervention of ischemia/reperfusion. In particular, nitric oxide increase was stable and more evident with sacubitril/valsartan compared to valsartan alone and this was related to a better endothelial-dependent response in term of stability of the maximum vasodilatation effect, that was instead reduced in the control group [11].

In this study the efficacy of sacubitril/valsartan might have been related to its hypotensive effect or to the increased level of vasoactive peptides. However, there are other drugs that can reduce blood pressure without giving any advantage in terms of endothelial function improvement. Moreover, in our study there was no significant pressure difference at 6 months. Therefore, it is possible to hypothesize that the improvement in endothelial function is related to the increased levels of natriuretic peptides, as a direct consequence of NEP inhibition by sacubitril/valsartan.

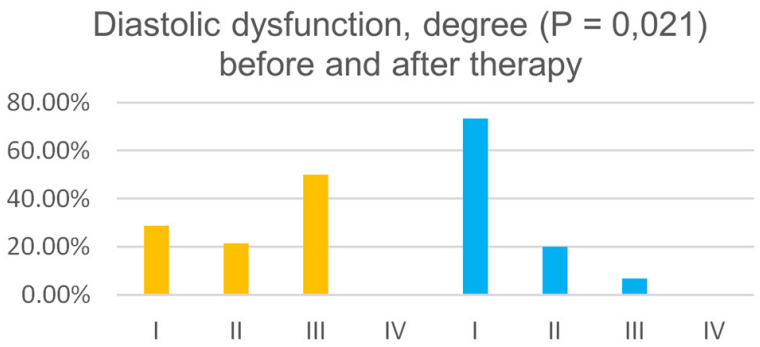

Figure 3. Diastolic degree disfunction six months after introduction of sacubitril valsartan.

There is some evidence that suggests a key role of these molecules in this pathway. In a recent study (2019) Bub KJ et al observed that the endothelial derived natriuretic peptide (CNP) has an important role in the regulation of vascular homeostasis: it can modulate the local blood flow at the vascular level, it can reduce platelet and leucocyte reactivity with antithrombotic and anti-inflammatory properties, and it can prevent development of atherosclerosis [12].

Other studies suggest a potential central role of CNP in angiogenesis and in the process of endothelization of damaged carotid arteries [13] after angioplasty [14] and of maintaining unaltered the capillary density after a myocardial infarction [15].

There are also some evidences regarding the atrial natriuretic peptide (ANP), that Barber et al' study demonstrated to be involved, together with CNP, in endothelial dependent vasodilatation in rabbit carotid arteries. When CNP was administered directly into the arterial lumen, it blocked neointimal vasal proliferation [16].

Less known is instead the physiological role of BNP. In an old study (2000) mice without this peptide did not develop hypertension, however they were more susceptible to cardiac fibrosis [17]. It's possible that BNP acts mainly as local factor, in a paracrine way, modulating the cell proliferation and tissue remodeling in heart as in other tissues, where is expressed after hypoxic response.

It's plausible that the effects of sacubitril/valsartan on endothelial function observed in our study may be due to some others vasoactive molecules, increasing after NEP inhibition.

In particular, in different studies it was demonstrated that bradykinin and P substance were able to stimulate the nitric oxide production, having a vasodilating role [18]. However, there may be even other molecules like calcitonin related gene peptide and adrenomedullin that may have a role in improving the endothelial function. Even if these peptides were believed to only have a role in vasodilatation which is endothelial independent. Finally, also angiotensin II, not being able to act on the AT-1 receptor, could in part explain the improvement of endothelial function and the slowing down of the process of remodeling and fibrosis, through the action induced by AT-2 receptor. The stimulation of this receptor can also improve bradykinin and nitric oxide synthesis [19].

Regarding the potential benefits on arterial stiffness, our study did not unveil an improvement of any parameter evaluated.

The aortic/central pressures (PASao/PADao/PPao), the pulse wave velocity (PWV) and the augmentation index (Aix75) resulted globally unchanged or slightly increased compared to baseline, although not statistically significant.

The EVALUATE-HF 2019 study evaluated the potential effects of sacubitril valsartan on aortic stiffness, compared to enalapril and did not demonstrate significative differences between the two treatments at 12 weeks, even though in both groups vascular stiffness parameters improved.

In the same study significative reductions in secondary echography endpoint have been observed, comprising left ventricle end-diastolic and end-systolic volumes and the E/e' ratio, suggesting an improvement in cardiac remodeling and in filling pressures.

Therefore, the benefits of sacubitril/valsartan therapy seem not to be related to a central aortic stiffness change, even though 12 weeks may be not enough to induce it.

It's known that endothelial dysfunction has an important role in worsening aortic stiffness [20], but many pathological conditions can lead to aortic stiffness, like the molecular alteration of vascular matrix.

However, the main determinants of stiffness are ageing [21], arterial hypertension [22] and metabolic syndrome, that lead to the molecular abnormalities described before. It's possible that sacubitril/valsartan, although improving endothelial function in our study, doesn't influence vascular stiffness parameters, hypothesis related also to the lack of improvement of pressure regimens of the patients enrolled.

It's important to underline that in a study on patients with isolated systolic hypertension, with a high level of arterial stiffness none of the anti-hypertensive drugs reduced aortic PWV significantly. This suggest that maybe patients with high grade of arterial stiffness could be less responsive to functional modifications induced by pharmacological treatment compared to patients with more distensible arteries [23]. Moreover, some encouraging data were obtained with non-pharmacological interventions. In a study lasted 4 months conducted on overweight and obese patients the weight loss reduced significantly aortic and carotid stiffness [24] and positive data were observed also following interventions targeted to modify the extracellular matrix, independently of the hemodynamic effect. These data suggest probably that other interventions rather than neuromodulation and pressure control with sacubitril valsartan are required to improve significantly the arterial stiffness.

Finally, as already demonstrated by the PARADIGM-HF study, sacubitril/valsartan in our study was able to improve functional and structural cardiac parameters, slowing the remodeling and the heart failure progression. There was a statistically significant improvement of ejection fraction and the degree of diastolic ventricular dysfunction. Moreover, although not significant, there was a positive trend of mitral regurgitation improvement, as already shown by some literature data, such as in the PRIME study (2019) that showed a better efficacy with sacubitril/valsartan than valsartan alone [25]. The tricuspid annular plane systolic excursion did not change. These results should be related to sacubitril/valsartan effect on reducing ventricular dilatation, a key characteristic of dilated cardiomyopathy. It wasn't observed an improvement of pulmonary arterial systolic pressure, which was actually slightly increased. However, it's important to make some considerations. First, this result was not statistically significant and, the values were within normal range. Secondly, it's important to consider the low sample size and the time since the beginning of the therapy that could not be enough to appreciate all the benefits of the drug, especially related to a complex parameter like pulmonary arterial systolic pressure.

The results of our study need to be considered keeping in mind the limits that our study present. First of all, the low number of patients (15). The study was performed only in our center. Moreover, the follow-up of 6 months may not be enough to observe effects that need a longer time to appear, especially for complex parameters like pulmonary arterial pressure and right ventricular function. Consequently, studies with a wider sample, multicentric, with a longer follow-up time are necessary to confirm the therapeutics effects of sacubitril/valsartan on endothelial function.

Conclusions

In conclusion, this study shows the possible role of sacubitril/valsartan in improving endothelial function significantly. This could mean a protective role on cardiac function and prevention of the remodeling process and consequently the progression toward heart failure, possibly preventing cardiovascular events. There was also an increased left ventricular function, and a mitral regurgitation and diastolic function improvement, as observed in PARADIGM-HF trial. Conversely, the drug seems to have no effects on vascular stiffness, which is probably a process related to different pathophysiological pathways. The results showed are comparable to previous literature data, such as the EVALUATE-HF trial.

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All participants provided written informed consent prior to enrolment in the study.

Disclosure of conflict of interest

None.

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