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ORIGINAL ARTICLE

Is vascular remodelling in patients with chronic heart failure exaggerated?

Robert Pietschner[1], Agnes Bosch[1], Dennis Kannenkeril[1], Kristina Striepe[1], Mario Schiffer[1], Stephan Achenbach[2], Roland E. Schmieder[1]* and Julie Kolwelter[1,2]

[1]*Clinical Research Centre, Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; and* [2]*Department of Cardiology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany*

Abstract

Background Vascular remodelling of large arteries increases afterload of the left ventricle. The aim of this study was to analyse whether vascular remodelling and function under laboratory and 24-hour ambulatory conditions is impaired in patients with chronic heart failure (CHF) independently of cardiovascular risk factors.

Methods and results In this monocentric cross-sectional observational study, 105 patients with CHF and an ejection fraction ≤49% (CHF+) were compared to 118 subjects without CHF (CHF−). After adjustment for age, gender, arterial hypertension, hyperlipidaemia, type 2 diabetes, obesity and smoking, vascular function and structure parameters, as assessed by pulse wave analysis (SphygmoCor) and the UNEX EF device, respectively, between the CHF+ and the CHF− group differed for resting pulse wave velocity (PWV) (P = 0.010), 24-h ambulatory PWV (P = 0.011), central systolic blood pressure (cSBP) (P = <0.001), 24-h ambulatory cSBP (P = <0.001), resting central augmentation index (P = 0.002), and brachial intima–media thickness (P = 0.022). In CHF+ patients, higher levels of NT-proBNP, taken as a marker for the severity of CHF, were related to a higher PWV (r = 0.340, P = <0.001), a higher cSBP (r = 0.292, P = 0.005), and a trend to higher central pulse pressure (cPP) (r = 0.198, P = 0.058), higher 24-h brachial PP (r = 0.322, P = 0.002), and 24-h total peripheral resistance (s = 0.227, P = 0.041) after full adjustment for covariates.

Conclusions In CHF+ patients we observed augmented vascular remodelling and functional impairment compared with CHF− patients independently of cardiovascular risk factors, age, and gender, and the extent of vascular remodelling and impairment was related to the severity of CHF.

Keywords Heart failure; Vascular remodelling; Vascular function; Cardiovascular risk factors; Central haemodynamics

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**Correspondence to: Roland E. Schmieder, Head of the Clinical Research Centre, Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg (FAU), Ulmenweg 18, 91054 Erlangen, Germany. Email: roland.schmieder@uk-erlangen.de*

Introduction

Chronic heart failure (CHF) is a complex entity that is associated with a reduced quality of life, increased hospitalization rate, and higher total mortality.[1] The complexity of the underlying pathophysiology comprises a cascade of inflammatory processes and neuroendocrine activation that provokes vascular remodelling and endothelial dysfunction.[2] Major risk factors for developing CHF, such as age, arterial hypertension, hyperlipidaemia, type 2 diabetes mellitus (T2D), obesity, coronary artery disease, and smoking, cause per se vascular remodelling. Whether the vascular remodelling processes observed in CHF are related to the cardiovascular risk factors or exaggerate if CHF already exists is unknown.[3] For example, arterial hypertension is associated with remodelling of the small and large arteries and impaired vascular (endothelial) function but also is one of the major risk factors of CHF.[4,5]

Pulse wave velocity (PWV) is a measure of arterial stiffness, or the rate at which pressure waves move down the vessel. In addition, there are reflected pressure waves that move back towards the heart at the end of the systolic period. When pressure waves move faster through the arteries, the reflected waves will also move back quicker. PWV is known as an established standard in the evaluation of vascular remodelling and

function of the large arteries and has been found to be related to cardiovascular events in the Framingham Heart Study.[6] However, in patients with CHF, data from prospective studies about vascular remodelling of the large or small vessels are limited and provide discrepant results.[7,8] In the Framingham Heart Study, a relationship between new-onset CHF and increased PWV has been found, but not with other parameters of vascular remodelling obtained from the pulse wave analysis.[8] In contrast, in the Multi-Ethnic Study of Atherosclerosis (MESA), the ratio between the reflected and forwarded pulse pressure height, assessed by pulse wave analysis (also referred to as 'reflection magnitude'), was found to be predictive for new-onset CHF.[7]

Considering that one of the main strategies in the medical therapy of CHF is based on reducing the afterload of the left ventricle, which in turn is profoundly determined by vascular remodelling and function, the evaluation of vascular remodelling in CHF remains clinically important.[9]

We hypothesized that vascular remodelling is augmented in CHF+ patients independently of cardiovascular risk factors including age and gender. Further, we assessed the relationship between vascular remodelling and the severity of CHF.

Methods

Study design

In this monocentric cross-sectional observational study, patients with CHF (CHF+) and patients without CHF (CHF−), both having cardiovascular risk factors, were consecutively recruited from the outpatient department of Cardiology and Angiology of the University Hospital of Erlangen, Germany, and the Clinical Research Unit of the Department of Nephrology and Hypertension of the University Hospital of Erlangen, Germany, and have been included in various observational and interventional follow-up studies. Written informed consent was obtained from each subject before study inclusion. The studies were performed according to the Declaration of Helsinki and the principles of good clinical practice guidelines and were approved by the local ethics committee of the University of Erlangen-Nuremberg.

Study population

Patients with the clinical diagnosis of CHF in stable condition and with a mildly reduced ejection fraction (HFmrEF, LVEF 41–49%) or with a reduced ejection fraction (HFrEF; LVEF <40%) were included in the group CHF+.[10] Patients without the diagnosis of CHF but, like CHF+ patients, with cardiovascular risk factors such as arterial hypertension, hyperlipidaemia, T2D, obesity, and smoking were included in the group CHF−. Participants in both groups were aged between 18 and 85 years. Key exclusion criteria were any other form of diabetes than T2D, a glycosylated haemoglobin (HbA1c) of ≥10%, an estimated glomerular filtration rate of <30 mL/min/1.73 m^2, uncontrolled hypertension (defined by office blood pressure ≥160/100 mmHg), any history of stroke, transient ischaemic attack, instable angina pectoris, myocardial infarction within the last 6 months prior to study inclusion, or CHF in Stage IV according to the New York Heart Association (NYHA) IV.

Clinical parameters

At our clinical research centre demographic data including medical history were recorded, physical examination was performed, and fasting blood samples were drawn to assess in particular NT-proBNP and metabolic parameters. Office blood pressure (BP) and heart rate were measured in a standardized fashion in a seated position three times in intervals of 2 min after 5 min of rest, according to guideline recommendations.[11]

Vascular assessment

The measurement of the PWV and the recording of the arterial pulse wave were performed under resting conditions by applanation tonometry with the SphygmoCor System (SphygmoCor™ XCEL System; AtCor Medical, Sydney, Australia). First, brachial systolic and diastolic BP was measured with a conventional brachial oscillometric device. The SphygmoCor system then automatically generated the corresponding central waveform by a validated transfer function, from which the following vascular parameters were given: cSBP, cPP, and central augmentation index (cAIx).[12]

The SphygmoCor XCEL system also measured the aortic PWV by using a specialized cuff around the upper thigh and a tonometer held on the carotid artery by trained study nurses. Based on the transit time between the two measurement points and the measured physical distance, PWV was calculated and recorded by the SphygmoCor XCEL system that has been previously validated.[13]

BP and vascular function parameters were assessed under 24-h ambulatory conditions by a validated oscillometric brachial-cuff-based device (Mobil-O-Graph, I.E.M., Aachen, Germany).[14] Measurements were performed at an interval of 15 min during the day and at 30 min during the night. Vascular parameters such as 24-h cSBP, 24-h cPP, and 24-h cAIx were derived from the obtained pressure wave form of the brachial artery.

Vascular structure of the brachial artery

At our clinical research centre vascular structure was assessed by measuring the intima–media thickness (bIMT),

wall-to-lumen ratio (bWLR), and the wall cross-sectional area (bWCSA) of the brachial artery via the UNEX EF (UNEX EF 18G, Nagoya, Japan) device according to international standards.[15,16] Flow-mediated vasodilation in response to ischemic provocation was measured as a vascular function parameter by the same device.[16]

The UNEX system is a semi-automatic ultrasound system using H-type ultrasound probes with the advantage to measure always (since automatically corrected) the lumen diameter at a 90° angle to the vessel wall. A pneumatic cuff was placed around the upper arm, and two ECG leads were attached to the wrists. Continuous recordings of B-mode images and A-mode waves of the brachial artery in the longitudinal plane were obtained and were simultaneously synchronized with the ECG R-wave. The diameter of the brachial artery was scanned and recorded at baseline, before cuff inflation and continuously from the release point to 2 min after cuff deflation, in order to obtain the maximum diameter during reactive hyperaemia.

Statistical analysis

Prior to further analysis, normal distribution of the measured variables was tested using a histogram and the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± standard deviation (SD), not normally distributed data as median and interquartile range (IQR). A two-sided *P*-value < 0.05 was considered statistically significant. Comparison of data between the CHF+ and CHF− groups was performed by unpaired *t*-test for normally distributed data and Mann–Whitney *U* test for not normally distributed data. Chi^2 test was used to compare categorical variables like medical history, gender, and medical treatments between the two groups. We performed a univariate covariance analysis to adjust between the two study groups for potential covariates, such as age, gender, arterial hypertension, hyperlipidaemia, T2D, obesity, and smoking. NT-proBNP represents a not normally distributed parameter and was logarithmized prior to further calculations (lnNT-proBNP). Partial correlations were calculated by taking the covariates age, gender, arterial hypertension, hyperlipidaemia, T2D, obesity, and smoking into account. All analyses were performed using SPSS software, version 28.0.0.0 (IBM Corporation, Chicago, IL, USA).

Results

Clinical characteristics

A total of 223 patients were included in our analysis. Hundred and five patients had a clinical diagnosis of CHF [CHF+, mean left ventricular (LV) ejection fraction: 38 ± 8%, serum median NT-proBNP: 434.50 pg/mL (IQR: 219.00–1037.50)], and 118 patients had no CHF. In 68 of the 105 patients (65%), myocardial ischaemia was the predominant cause of CHF. Cardiovascular risk factors differed between these groups (*Table 1*). Office systolic ($P = 0.003$) and diastolic ($P = <0.001$) BP and 24-h ambulatory systolic ($P = <0.001$) and diastolic ($P = <0.001$) BP were lower in CHF+ patients (*Table 1*). CHF+ patients had lower levels of LDL ($P < 0.001$) and non-HDL ($P < 0.001$) as well as a lower estimated glomerular filtration rate ($P < 0.001$) and a higher urine albumin–creatinine ratio ($P < 0.001$) (*Table 2*). According to the study design,

Table 1 Clinical parameters of the study participants ($n = 223$)

Parameter	CHF+ ($n = 105$)	CHF− ($n = 118$)	*P* value
Age (years)	67 ± 9	54 ± 13	<0.001
Gender (% male)	79	58	0.001
Weight (kg)	86.3 ± 14.4	84.5 ± 17.4	0.397
Height (cm)	173.6 ± 8.0	174.0 ± 9.3	0.784
BMI (kg/m^2)	28.5 ± 3.8	27.9 ± 5.2	0.292
Office systolic BP (mmHg)	124 ± 19	133 ± 18	<0.001
Office diastolic BP (mmHg)	72 ± 9	81 ± 12	<0.001
Office heart rate (bpm)	66 ± 11	69 ± 12	0.038
24-h ambulatory brachial systolic BP (mmHg)	120 ± 15	130 ± 12	<0.001
24-h ambulatory brachial diastolic BP (mmHg)	73 ± 9	80 ± 10	< 0.001
24-h ambulatory brachial heart rate (bpm)	67 ± 11	72 ± 10	0.002
Smoking habit [*n* (%)]	59 (57.3)	39 (35.1)	0.002
Arterial hypertension [*n* (%)]	81 (77.9)	64 (55.2)	<0.001
Diabetes mellitus [*n* (%)]	26 (24.8)	29 (25)	0.968
Atrial fibrillation [*n* (%)]	43 (41)	-	-
Hyperlipidaemia [*n* (%)]	72 (70.6)	22 (19.1)	<0.001
Obesity, BMI > 30 kg/m^2 [*n* (%)]	39 (37.1)	40 (33.9)	0.675

BMI, body mass index; BP, blood pressure; CHF−, control group without chronic heart failure, CHF+, chronic heart failure patients with mid-range ejection fraction or reduced ejection fraction.
Data are given as X ± SD or number (*n*) and per cent (%).

Table 2 Laboratory parameters of the study participants

Parameter	CHF+	CHF−	*P* value
HbA1c (%)	5.9 ± 0.7	5.8 ± 0.8	0.363
Fasting plasma glucose (mg/dL)	104.1 ± 20.0	104.9 ± 28.6	0.820
Lipoprotein a (mg/dl)	23.2 ± 30.2	20.9 ± 28.6	0.555
Triglycerides (mg/dL)	123.9 ± 73.4	139.6 ± 97.3	0.184
Cholesterol (mg/dL)	178.5 ± 47.2	216.4 ± 42.4	<0.001
HDL (mg/dL)	48.9 ± 12.7	55.9 ± 15.4	<0.001
LDL (mg/dL)	112.3 ± 36.7	139.5 ± 31.1	<0.001
Non-HDL (mg/dl)	129.6 ± 43.9	158.0 ± 40.8	<0.001
Serum creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	<0.001
eGFR (mL/min/1.73 m^2)	62.3 ± 13.2	71.7 ± 16.4	<0.001
Urine albumin–creatinine ratio (mg/g)	1.1 ± 6.2	0.1 ± 0.1	<0.001

CHF−, control group without chronic heart failure; CHF+, chronic heart failure patients with mid-range ejection fraction or reduced ejection fraction; eGFR, estimated glomerular filtration rate, HbA1c: glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Data are given as X ± SD.

Table 3 Medication class prescription

Medication class	CHF+	CHF−	*P* value
Number of antihypertensive medication classes	2.96 ± 0.98	0.92 ± 1.18	<0.001
ACE inhibitors [*n* (%)]	49 (46.7)	18 (15.3)	<0.001
Angiotensin receptor blockers [*n* (%)]	48 (45.7)	32 (27.1)	0.005
Calcium channel blockers [*n* (%)]	18 (17.1)	22 (18.6)	0.862
Diuretics [*n* (%)]	61 (58.1)	20 (16.9)	<0.001
Aldosterone antagonists [*n* (%)]	56 (53.3)	2 (1.7)	<0.001
Beta-blockers [*n* (%)]	81 (77.1)	14 (11.9)	<0.001
ARNI [*n* (%)]	17 (16.2)	-	-
Statins, cholesterol absorption inhibitors [*n* (%)]	77 (73.3)	15 (12.7)	<0.001

ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor-neprilysin inhibitor; CHF−, control group without chronic heart failure; CHF+, chronic heart failure patients with mid-range ejection fraction or reduced ejection fraction.
Data are given as number (n) and per cent (%).

Table 4 Vascular parameters

Parameter	CHF+	CHF−	*P* value	Adj. *P* value[a]
Pulse wave velocity				
Pulse wave velocity (m/s) under resting conditions	8.62 ± 2.16	8.28 ± 1.94	0.233	0.010
24-h ambulatory pulse wave velocity (m/s)	9.39 ± 1.56	8.19 ± 1.65	<0.001	0.011
Pulse wave analysis under ambulatory conditions				
24-h ambulatory central systolic BP (mmHg)	114 ± 15	121 ± 14	0.007	<0.001
24-h ambulatory central pulse pressure (mmHg)	40.4 ± 13.1	40.7 ± 10.0	0.873	0.207
24-h ambulatory total peripheral resistance (s*mmHg/mL)	1.20 ± 0.20	1.25 ± 0.16	0.073	0.008
Pulse wave analysis under resting conditions				
Central systolic BP (mmHg) under resting conditions	117 ± 15	123 ± 16	0.004	<0.001
Central pulse pressure (mmHg) under resting conditions	41.5 ± 9.4	41.6 ± 12.3	0.930	0.011
Central augmentation index standardized at 75 bpm (%) under resting conditions	21.2 ± 11.8	13.7 ± 11.5	<0.001	0.002
Flow-mediated vasodilation				
Flow-mediated vasodilation (%)	6.3 ± 8.0	6.8 ± 4.7	0.656	0.413
Vascular range (−)	0.048 ± 0.079	0.052 ± 0.050	0.707	0.125
Difference between max− and base diameter (mm)	0.19 ± 0.30	0.20 ± 0.19	0.892	0.069
Vascular structural parameters of the brachial artery				
Intima–media thickness (mm)	0.30 ± 0.08	0.25 ± 0.06	<0.001	0.022
Wall-to-lumen ratio	0.073 ± 0.031	0.063 ± 0.013	0.002	0.013
Wall cross-sectional area (mm)	14.3 ± 3.8	13.1 ± 4.1	0.044	0.688

BP, blood pressure; CHF−, control group without chronic heart failure, CHF+, chronic heart failure patients with mid-range ejection fraction or reduced ejection fraction.
Data are given as X ± SD.
[a]Adj. *P* value: adjusted *P* value for age, gender, arterial hypertension, hyperlipidaemia, type 2 diabetes mellitus, obesity, and smoking.

medication was different between the two patient groups (*Table 3*).

Vascular assessment

After adjustment for age, gender, arterial hypertension, hyperlipidaemia, T2D, obesity, and smoking, PWV differed between the two groups under both standardized resting (P = 0.010) and 24-h ambulatory conditions (P = 0.011), indicative of an augmented impairment of vascular remodelling in CHF+ patients (*Table 4*). In accordance, the two groups differed in cSBP ($P < 0.001$), cPP (P = 0.011), and cAIx (P = 0.002) (*Table 4*). Regarding the 24-h ambulatory measurements, CHF+ patients had a different cSBP (P = <0.001), cAIx (P = 0.012), and total peripheral resistance (P = 0.008), compared with CHF− patients (*Table 4*).

There was no significant difference in FMD and vascular range after 5 minutes of ischaemia between the two groups (*Table 4*).

As expected, resting PWV and cSBP (r = 0.491, $P < 0.001$; *Figure 2A*) correlated with each other.

Vascular structure

After adjustment for age, gender, and the above-mentioned cardiovascular risk factors, vascular structural adaptation, as indicated by bIMT (P = 0.022; *Figure 1*) and bWLR (P = 0.013), was more pronounced in CHF+ patients, thereby suggesting eutrophic vascular remodelling (*Table 4*). We did not observe a significant difference in bWCSA between the two groups (*Table 4*).

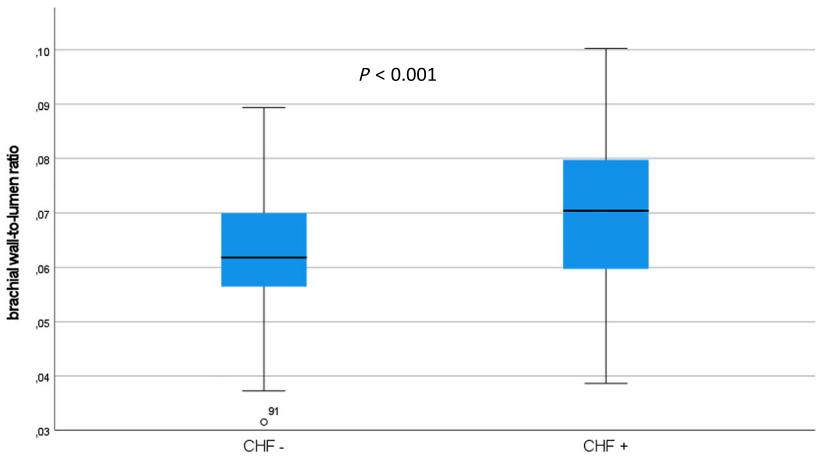
Interestingly, resting PWV was correlated to bIMT (r = 0.272, P = 0.012; *Figure 2B*).

Relationship between severity of CHF and vascular parameters

Higher serum NT-proBNP was associated with a higher PWV under resting laboratory conditions (r = 0.340, $P < 0.001$; *Figure 3A*), a trend towards a greater PWV under 24-h ambulatory conditions (r = 0.197, P = 0.075) and with greater cSBP (r = 0.292, P = 0.005; *Figure 3B*), after adjustment for age, gender, arterial hypertension, hyperlipidaemia, T2D, obesity, and smoking. We did not observe any significant relationship between CHF severity and vascular structural parameters.

Higher levels of serum NT-proBNP were associated with higher resting brachial systolic (r = 0.295, P = 0.004) and diastolic BP (r = 0.240, P = 0.012), as well as with higher 24-h ambulatory systolic BP (r = 0.309, P = 0.004) and peripheral PP (r = 0.322, P = 0.002).

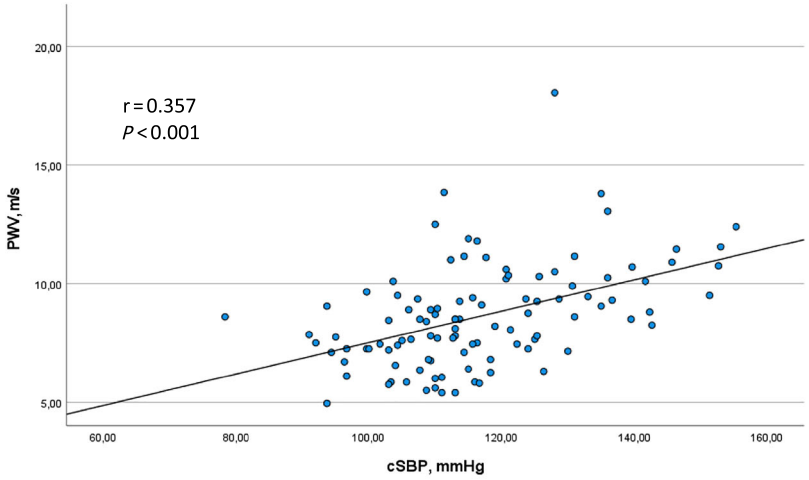
Figure 1 Comparison of brachial wall-to-lumen ratio between the study groups with CHF (CHF+) and without CHF (CHF−).



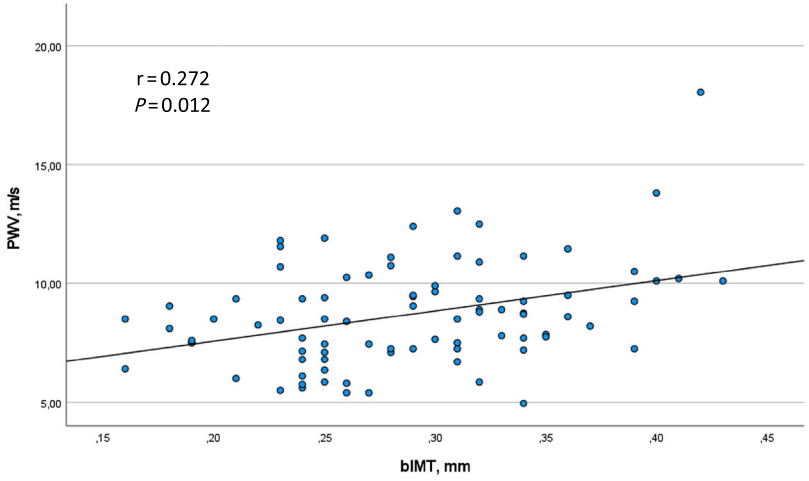
Abbreviations: CHF+: Chronic heart failure patients with mid-range ejection fraction or reduced ejection fraction, CHF-: Control group without chronic heart failure.

Figure 2 (A) Relationship between pulse wave velocity (PWV, m/s) and central systolic blood pressure (cSBP, mmHg) in the entire study population. (B) Relationship between pulse wave velocity (PWV, m/s) and brachial intima–media thickness (bIMT, mm) in the entire study population.

(A) Relationship between pulse wave velocity (PWV, m/s) and central systolic blood pressure (cSBP, mmHg) in the entire study population



(B) Relationship between pulse wave velocity (PWV, m/s)) and brachial intima-media thickness (bIMT, mm) in the entire study population



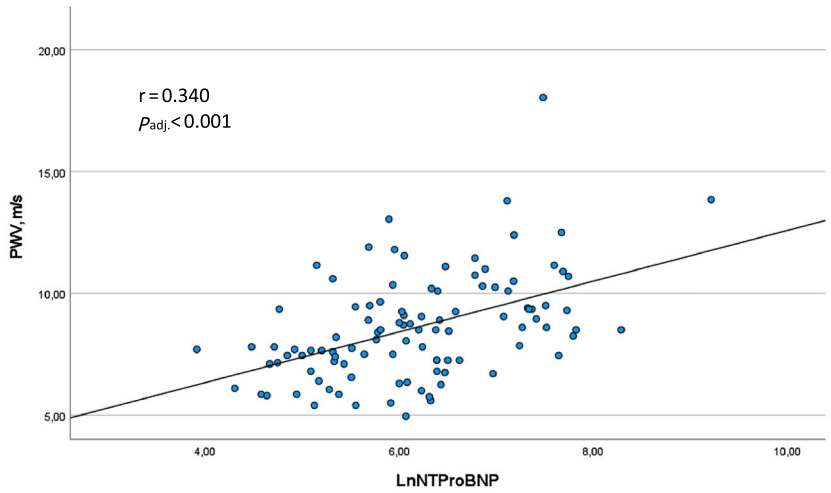
Discussion

Our principal result is that CHF+ patients had a greater degree of vascular remodelling despite a lower BP and a better lipid profile compared to CHF− patients. These findings were independent of cardiovascular risk factors including age and gender. In particular, our result that both PWV and cAIx were found to be more impaired in our CHF+ patients is of clinical importance, because these two vascular parameters have been reported to be strong independent predictors of cardiovascular events and all-cause mortality.[17] An accelerated PWV augments the haemodynamic load on the left ventricle, because the pulse waves are reflected earlier at vascular bifurcations and thus arrive already during late systole rather than during diastole. The increased systolic load leads to LV hypertrophy and myocardial fibrosis.[18] Consistently, experimental and human studies have found an association of increased late systolic load with diastolic dysfunction, impaired LV relaxation, and atrial dysfunction and with impaired systolic diastolic coupling.[19] Moreover, a direct link between increased PWV and new-onset heart failure has been reported in a community-based prospective study cohort.[8]

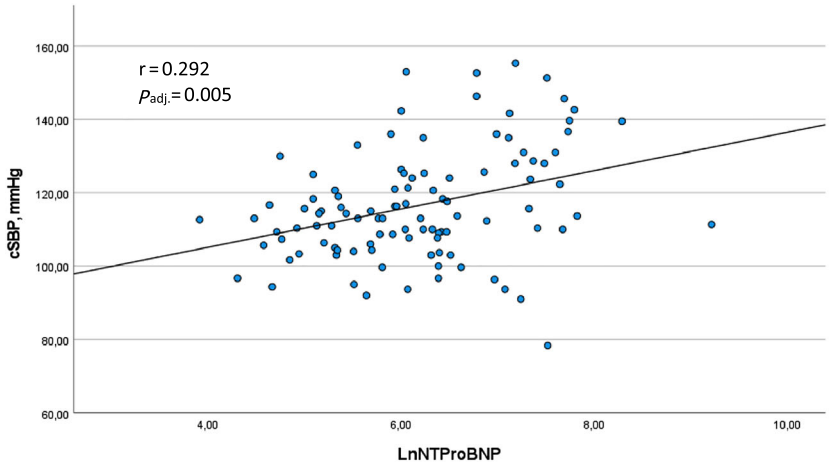
In accordance with our findings of increased PWV in CHF+ patients, we found cAIx to be increased in our CHF+ patients. The aortic cAIx represents the ratio of the augmentation of

Figure 3 (A) Relationship between serum NT-proBNP levels and pulse wave velocity (PWV, m/s) in the patient group with CHF, adjusted for age, gender, arterial hypertension, hyperlipidaemia, type 2 diabetes mellitus, obesity, and smoking. (B) Relationship between serum NT-proBNP levels and central systolic BP (cSBP, mmHg) in the patient group with CHF, adjusted for age, gender, arterial hypertension, hyperlipidaemia, type 2 diabetes mellitus, obesity, and smoking.

(A) Relationship between serum NT-proBNP levels and pulse wave velocity (PWV, m/s) in the patient group with CHF, adjusted for for age, gender, arterial hypertension, hyperlipidaemia, type 2 diabetes mellitus, obesity and smoking.



(B) Relationship between serum NT-proBNP levels and central systolic blood pressure (cSBP, mmHg) in the patient group with CHF, adjusted for for age, gender, arterial hypertension, hyperlipidaemia, type 2 diabetes mellitus, obesity and smoking.



systolic BP (difference between the two systolic peaks) to the total PP amplitude and is considered as a surrogate marker of arterial vascular stiffness.[20] Several human studies have described cAIx as an independent risk factor for cardiovascular disease.[21]

Additionally, bIMT was thicker and relative wall thickness (i.e. wall-to-lumen ratio) greater in CHF+ patients, indicative of more pronounced vascular remodelling in CHF+ patients.[22] This observation of increased vascular stiffness in CHF+ patients was independent of cardiovascular risk factors, age, and gender. In a clinical setting with 388 patients, a direct relationship has been demonstrated between bIMT, vascular function, and cardiovascular risk factors.[22] Similar observations have been made in patients with T2D, in whom an association between bIMT and coronary artery calcification was observed.[23]

In our project, we found a lower cSBP and total peripheral resistance in CHF+ patients. In CHF, afterload is

usually increased due to the activation of the sympathetic nervous system (among others).[24] Another mechanism of increasing the afterload of the LV consists in the release of angiotensin II through the activation of the renin–angiotensin–aldosterone system, which is therapeutically addressed by the administration of ACE inhibitors, ARBs, or angiotensin receptor-neprilysin inhibitors (ARNI), thereby lowering cSBP and total peripheral resistance.[25] Our CHF+ group took more antihypertensive and lipid-lowering medications, compared with the CHF− group, which may explain the lower cSBP and total peripheral resistance. Furthermore, in validation studies, brachial BP-derived central BP assessment has been shown to considerably underestimate invasive cSBP.[26]

PWV, bIMT, and cAIx represent more long-term parameters for the evaluation of vascular stiffness and function. Thus, our findings of increased PWV and a higher cAIx, together with a thicker bIMT wall-to-lumen ratio of the brachial artery, indicate a more progressed vascular remodelling in CHF+ patients compared to CHF− patients that was independent of cardiovascular risk factors, age, and gender.[22,27]

The second main result of this project refers to our CHF+ patient group. From our cross-sectional research setting, we observed that with greater severity of CHF as indicated by levels of NT-proBNP, vascular remodelling becomes more augmented independently of potential confounders and thereby may exacerbate the severity of CHF. Unfortunately, we do not have long-term observation in this patient group. We could not separate whether this association is related to the effects of the cardiovascular risk factors on both the myocardium and the vascular system or/and to the effect that greater vascular stiffness increases left ventricular afterload. It is well known that cardiovascular risk factors of the progression of CHF can lead to a worsening of arterial stiffness.[28] Our data support this concept that augmented vascular remodelling and impaired vascular function are associated with the progression of CHF and vice versa, thus proposing a vicious cycle of vascular and cardiac impairment. However, we cannot derive from our findings a causal relationship between vascular remodelling and severity of CHF.

One possible explanation of our findings is that neuroendocrine activation is the pathogenetic mechanism. In line with our findings, vascular stiffness is recognized as an independent and additional mediator for the progression of CHF.[20] Neuroendocrine activity (i.e. increased sympathetic tone and up-regulated renin–angiotensin–aldosterone system) has been described to increase progressively with severity of CHF but also to cause or exaggerate vascular remodelling in patients with CHF.[2,7,8] In a clinical setting of 27 patients with pheochromocytoma or paraganglioma, excess of catecholamines has been shown to be associated with vascular remodelling.[29] Likewise, experimental data documented that angiotensin II exerts hypertrophy of vascular smooth muscle cells and clinical data found that angiotensin II blockade reverses vascular remodelling in patients with arterial hypertension.[30]

We have to acknowledge certain limitations. One limitation is that the underlying project is a retrospective, monocentric, cross-sectional analysis, focusing on HFmrEF and HFrEF patients. Further longitudinal multicentric examination of vascular remodelling during the development and progression of CHF, including HFpEF patients, is needed. Additionally, patients with coronary artery disease as a cause of CHF are not discussed separately. The association of coronary calcification and bIMT will be an interesting topic of future research. However, we focused on the ensemble of CHF without differentiation in order not to distract from our main area of conflict. Moreover, we have not yet evaluated the neuroendocrine activation that may represent the key pathogenetic mechanisms for exaggerated vascular remodelling in CHF+ patients. This analysis of the underlying mechanisms of vascular remodelling in patients with CHF lies beyond the scope of the current study and will be subsequently addressed.

Conclusions

In CHF+ patients, we observed augmented vascular remodelling and functional impairment compared with CHF− patients independently of cardiovascular risk factors, age, and gender, and the extent of vascular remodelling and impairment was related to the severity of CHF, as assessed by NT-proBNP.

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Conflict of interest

None declared.

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