

Autonomic dysfunction is associated with cardiac remodelling in heart failure patients

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Abstract

Aims Orthostatic hypotension (OH) is a cardinal sign of autonomic dysfunction and a common co-morbidity in heart failure (HF). The role of autonomic dysfunction in the development of structural cardiac anomalies in HF patients has not been sufficiently explored. We aimed to assess relations between orthostatic blood pressure (BP) responses during active standing and echocardiographic changes in a series of patients admitted for HF.

Methods and results One hundred and forty-nine patients hospitalized for HF [mean age: 74 years; 30% women; ejection fraction (LVEF) $40 \pm 16\%$] were examined with conventional echocardiograms and active-standing test. Associations of cardiac remodelling parameters with the difference between supine and standing (after 3 min) systolic/diastolic BP were examined. Systolic BP decreased (-1.1 ± 15 mmHg), whereas diastolic BP increased ($+1.0 \pm 9.5$ mmHg) after 3 min of active standing. A total of 34 patients (23%) met conventional OH criteria; i.e. systolic/diastolic BP decreases by $\geq 20/10$ mmHg. In the multi-variable linear regression analysis, adjusted for traditional cardiovascular risk factors and LVEF, a decrease in systolic BP upon standing was associated with greater left atrial volume [β per -10 mmHg: 2.37, standard error (SE) = 1.16, $P = 0.043$], and greater left ventricular mass (β per -10 mmHg: 5.67, SE = 2.24, $P = 0.012$), but not with other echocardiographic parameters. No significant associations were observed between signs of cardiac remodelling and decrease in diastolic BP.

Conclusions Orthostatic decrease in systolic BP among older HF patients is associated with structural cardiac changes such as increased left atrial volume and left ventricular mass, independently of traditional risk factors and left ventricular dysfunction.

Keywords Autonomic dysfunction; Orthostatic hypotension; Left ventricular hypertrophy

Received: 17 May 2017; Revised: 7 August 2017; Accepted: 25 August 2017

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Introduction

Orthostatic hypotension (OH) is characterized by an abnormal decrease of blood pressure (BP) in standing position. It is a sign of cardiovascular (CV) autonomic dysfunction, which is typically caused by an impaired circulatory adaptation to the reduction of central blood volume that occurs in standing position.¹

In prospective population-based studies, OH has been associated with increased risk of mortality and CV morbidity.^{2–4} It has also been demonstrated that prevalent OH may precede the development of heart failure (HF) and atrial fibrillation (AF).^{5–8} The mechanisms behind these associations remain

elusive, but we have recently demonstrated that the presence of OH among middle-aged adults predicts the development of left ventricular hypertrophy (LVH) independently of traditional risk factors such as hypertension.⁹ Since the prevalence of LVH in large meta-analyses has been associated with a 1.5- to 3.5-fold increase in CV morbidity, a 1.5- to 6.8-fold increase in risk of overall mortality,¹⁰ and a 2.5-fold increased risk of HF development,¹¹ longitudinal association of OH with LVH⁹ highlights the importance of OH detection in high-risk populations.

The prevalence of OH in patients with HF remains uncertain. Reported data vary from 8% to as much as 83% among elderly patients hospitalized due to HF exacerbation.¹²

Moreover, data on relations between impaired orthostatic homeostasis and presence of structural cardiac abnormalities in patients diagnosed with HF are very sparse.

In this study, we examined a consecutive series of patients hospitalized for HF with BP measurements during active standing and standard echocardiography. Orthostatic BP changes were studied in relation to echocardiographic parameters of cardiac remodelling.

Methods

Study population

The Heart and Brain Failure Investigation (HARVEST) study is an ongoing study undertaken in patients hospitalized for the diagnosis of HF in the city of Malmö, Sweden.¹³ The inclusion criteria for the HARVEST study are admission to the department of internal medicine or cardiology for treatment of newly diagnosed or exacerbated chronic HF. The only exclusion criterion is the inability to deliver oral or written consent. In cases of severe cognitive impairment, defined as a mini mental test examination score <13 points, the relatives are instead being informed and asked for permission on the patient's behalf.

Between March 2014 and November 2016, a total of 220 consecutive patients hospitalized for HF were included. Of those, 172 underwent technically adequate transthoracic echocardiograms (ultrasound cardiogram) and clinical examination including active standing test. After exclusion of subjects with missing data, the final study sample consisted of

149 subjects (*Figure 1*). The study was approved by the Ethical Review Board at Lund University, Sweden. A written informed consent was obtained from all participants.

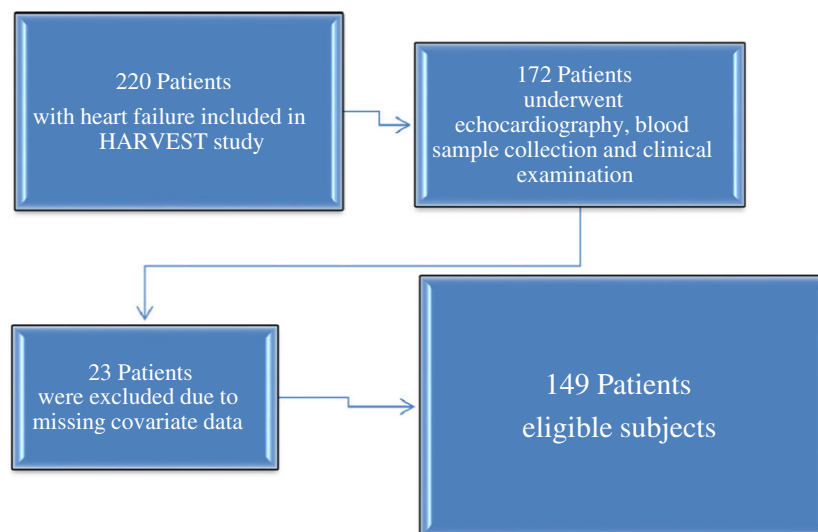
Clinical assessment

Upon the hospitalization and subsequent admission to the clinical wards, study participants were examined with anthropometric measurements and blood samples were drawn after overnight fast. Body mass index (BMI) was calculated as kilograms per square metre, and data regarding the study participants' medication were collected. Body surface area was calculated according to the DuBois formula.¹⁴ Prevalent diabetes was defined as either self-reported diagnosis of type 2 diabetes or use of antidiabetic medication or fasting plasma glucose (FPG) >7 mmol/L. Hypertension was defined as either systolic BP (SBP) \geq 140 mmHg and/or diastolic BP (DBP) \geq 90 mmHg. Atrial fibrillation (AF) was defined as prevalent AF on an electrocardiogram at the time of hospitalization.

Assessment of orthostatic hypotension

Baseline SBP and DBP were obtained after 10 min of rest in the supine position. A validated automated BP monitor (Boso Medicus, Bosch + Sohn GmbH u. Co. KG, Jungingen, Germany) was used. The upper arm cuff of appropriate size was placed on the right side, and the arm was supported at the heart level. Two measurements were performed with an interval of 30 s, and the mean value was calculated. After 10 min of supine rest, the patient was asked to stand up, and

Figure 1 Flowchart of the process of patient selection.



following 3 min of active standing, a mean of two BP measurements was calculated. The cuff was positioned at the heart level. The change in BP was calculated as delta SBP (Δ SBP) = standing SBP – supine SBP and delta DBP (Δ DBP) = standing DBP – supine DBP. OH was defined as a decrease in SBP of 20 mmHg or a decrease in DBP of 10 mmHg within 3 min of standing.

Laboratory assays

Analyses of high-density lipoprotein (HDL) and plasma glucose were carried out at the Department of Clinical Chemistry, Skåne University Hospital in Malmö, participating in a national standardization and quality control system. Low-density lipoprotein (LDL) was calculated according to the Friedewald equation.

Echocardiography

Conventional transthoracic echocardiographs were obtained using a Philips IE33 (Philips, Andover, MA, USA) with a 1–5 MHz transducer (S5-1) or with a GE Vingmed Vivid 7 Ultrasound (GE, Vingmed Ultrasound, Horten, Norway) with a 1–4 MHz transducer (M3S). All studies were performed by experienced sonographers. Cine loops were obtained from standard views (parasternal long axis, apical four- and two-chamber views). Measurements were done offline using Xcelera 4.1.1 (Philips Medical Systems, The Netherlands) according to the recommendations of the American Society of Echocardiography.¹⁵ Internal left and right ventricular dimensions were measured from a parasternal long-axis view at end-diastole. Measurements of wall thickness were obtained in a two-dimensional end-diastolic parasternal long-axis view. Left ventricle mass (LVM) was calculated according to the Devereux formula: $LVM(g) = 0.8\{1.04\{[(LVEDD + IVSd + PWD)^3 - LVEDD^3]\} + 0.6$.¹⁶ Left ventricular volumes were calculated using the biplane Simpson method of discs, by manual tracing (papillary muscles included in the cavity) in two-dimensional end-diastolic and end-systolic frames defined as the largest and smallest left ventricular cavities, respectively, in apical four- and two-chamber projections. Ejection fraction (EF) was calculated automatically from end-diastolic volumes (EDV) and end-systolic volume (ESV) using the following formula: $EF = (EDV - ESV)/EDV$. For assessment of left atrium (LA) volumes, the biplane area-length method was used: $LA \text{ volume} = (0.85 \times \text{area apical four-chamber area} \times \text{apical two-chamber area})/(\text{shortest atrial length})$. The values were indexed to body surface area. The LA endocardial borders were manually traced in both apical four-chamber and two-chamber views. Right atrium volumes were obtained using a single-plane disc summation technique in a dedicated apical four-chamber view.

Statistics

The variables are presented as means (\pm standard deviation) or median (25th–75th interquartile range). Before analyses, all variables that were not normally distributed were log-transformed (FPG, HDL, and LDL). All other covariates, including the echocardiographic parameters, were normally distributed. The cross-sectional associations of echocardiographic parameters {increased LVM, cardiac chamber volumes, and echocardiographic parameters of systolic ventricular function [left ventricular ejection fraction (LVEF)]} in relation to SBP change (Δ SBP) and DPB change (Δ DBP) upon 3 min of active standing were studied using linear regression models adjusted for age and sex (Model 1). Echocardiographic parameters associated with BP change upon 3 min of active standing with a P -value <0.1 in Model 1 were further adjusted for BMI, hypertension, LVEF, diabetes, smoking, HDL, LDL, FPG, and prevalent AF in Model 2. All analyses were performed using SPSS Windows version 23.0, and a two-tailed P -value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population are listed in *Table 1*. SBP decreased by 1.1 mmHg, and DBP increased by 1.1 mmHg, respectively, following 3 min of active standing. A total of 34 patients (22.8%; age 76.7 years) met conventional OH criteria (*Table 1*). Of the 149 HF patients, 142 could be classified according to whether HF was newly diagnosed or chronic. Of these, 53 subjects (37%) were newly diagnosed with HF, whereas 89 subjects (63%) were chronic HF patients. There was no difference in Δ SBP ($P = 0.366$) and Δ DBP ($P = 0.432$) between these two groups. In linear regression models adjusted for age and sex, SBP decrease upon standing (Δ SBP) was associated ($P < 0.1$) with greater left atrial volume [β per 10 mmHg: 2.27 (standard error = 1.22), $P = 0.065$], inter-ventricular systolic diameter at diastole (IVSDd) [β per 10 mmHg: 0.36 (0.19), $P = 0.055$], and greater left ventricular mass (LVM) [β per 10 mmHg: 6.11 (2.29), $P = 0.009$]. DBP increase upon standing was however not significantly associated with any of the echocardiographic measurements (*Table 2*).

In linear regression models adjusted for BMI, hypertension, LVEF, smoking, HDL, LDL, FPG, and prevalent AF, Δ SBP was associated with greater left atrial volume [β per 10 mmHg: 2.37 (1.16), $P = 0.043$] and greater LVM [β per 10 mmHg: 5.67 (2.24), $P = 0.012$], but not with IVSDd [β per 10 mmHg: 0.35 (0.20), $P = 0.074$] (*Table 3*). Other significant associations in the multivariable regression analysis were as follows: AF was associated with greater left atrial volume [β : 11.8 (3.58), $P = 0.001$] and LVEF, which was inversely associated with LVM [β : -0.73 (0.22), $P = 0.002$] (*Table 3*). Also, when adding loop diuretic medication on top of the risk

Table 1 Baseline characteristics of the study population ($n = 149$)

Characteristics	Value
Age (years)	74.0 (± 11.3)
Sex (female), n (%)	44 (30)
Smoking, n (%)	22 (14.8)
BMI (kg/m^2)	27.3 (± 5.4)
SBP (mmHg)	137.3 (± 28.8)
DBP (mmHg)	78.8 (± 14.1)
HT, n (%)	58 (38.9)
AHT, n (%)	149 (100%)
β -Blockers, n (%)	137 (92)
ACE-I or ARB, n (%)	115 (77)
Aldosterone antagonists, n (%)	10 (7)
Loop diuretics, n (%)	139 (93)
LVEF (%)	40.0 (± 16.1)
Diabetes, n (%)	56 (37.6)
HDL (mmol/L)	1.1 (0.87–1.50)
LDL (mmol/L)	2.1 (1.6–2.9)
FPG (mmol/L)	6.2 (5.4–7.6)
AF, n (%)	71 (47.7)
SBP (mmHg)	–1.1 (± 14.6)
DBP (mmHg)	1.0 (± 9.5)
Prevalent OH, n (%)	34 (23)
Newly diagnosed HF, n (%)	53 (37)

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AHT, antihypertensive treatment; ARB, angiotensin II receptor antagonists; BMI, body mass index; DBP, diastolic blood pressure; DBP, diastolic blood pressure reaction between supine diastolic blood pressure and diastolic blood pressure upon 3 min of standing; SBP, systolic blood pressure reaction between supine systolic blood pressure and systolic blood pressure upon 3 min of standing; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HF, heart failure; HT, hypertension; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction, OH, orthostatic hypotension; SBP, systolic blood pressure. Values are means (\pm standard deviation or medians, 25th–75th interquartile range).

Table 2 Associations of echocardiographic parameters with systolic and diastolic orthostatic blood pressure reactions

	SBP per 10 mmHg of change		DBP per 10 mmHg of change	
	β (SE)	P -value	β (SE)	P -value
EF%	–0.12 (0.91)	0.895	0.42 (1.38)	0.762
IVSDd (mm/mm^2)	0.36 (0.19)	0.055	0.13 (0.29)	0.651
LVIDd (mm/m^2)	0.59 (0.59)	0.322	–0.23 (0.91)	0.799
RVIDd (mm/m^2)	–0.48 (0.37)	0.194	–0.31 (0.56)	0.587
PWDd (mm/m^2)	0.04 (0.45)	0.933	–0.22 (0.69)	0.751
LA volume (mm/m^2)	2.27 (1.22)	0.065	–0.40 (1.88)	0.830
RA volume (mm/m^2)	–2.41 (1.50)	0.110	–1.92 (2.29)	0.405
LVMl (g/m^2)	6.11 (2.29)	0.009	0.10 (3.58)	0.977

EF, ejection fraction; IVSDd, interventricular septal diameter diastole; LA, left atrium; LVIDd, left ventricular inner-diameter diastole; LVMl, left ventricular mass index; PWDd, posterior wall diameter diastole; RA, right atrium; RVIDd, right ventricular inner diameter diastole. β are unstandardized coefficients. Linear regressions are adjusted for age and sex.

factors included in multivariable used in *Table 3*, we found that the use of loop diuretics had no significant impact on LA size [β : 5.88 (7.3), $P = 0.420$] or LVM [β : –14.4 (14.03), $P = 0.306$], nor did the addition of loop diuretic attenuate the associations of Δ SBP with LA size [β : 2.45 (1.17), $P = 0.037$] or LVM [β : 5.49 (2.25), $P = 0.016$].

In addition, we performed sensitivity analysis using an interaction term ‘age/sex/hypertension $\times \Delta$ SBP’ to test whether specific age/sex or hypertension groups contribute more to the observed risks, but no significant interaction was found for any of the tested variables.

Finally, we performed a subanalysis to investigate the prevalence of OH in the 78 patients with sinus rhythm and its relationship with diastolic dysfunction, and of these, 32 subjects had type 3 diastolic dysfunction (restrictive filling pattern) according to European Society of Cardiology/American Heart Association guidelines.¹⁷ Of these 32 subjects, 12 subjects had significant OH, giving a 38% prevalence of OH in subjects with type 3 diastolic dysfunction.

Discussion

In this cross-sectional study of patients with a diagnosis of congestive HF, we found that orthostatic SBP decline is significantly associated with increased left atrial volume and LVM, independently of left ventricular function and traditional CV risk factors. In contrast, no significant associations were observed between echocardiographic signs of cardiac remodelling and orthostatic DBP changes.

This is, to our knowledge, the first study to report significant associations of orthostatic BP decline with echocardiographic signs of cardiac remodelling among patients with HF. These data are well in line with our previous findings from a healthy population-based study⁹ where prevalent OH was predictive of LVH development, implicating that although HF patients may respond differently from healthy persons to change in posture from supine to upright,^{18,19} the ultimate consequences in terms of cardiac remodelling might be the same as for patients without manifest HF.

In two smaller studies ($n = 33$ and $n = 36$), it has been observed that OH is extremely frequent in HF (approximately 80% in both studies).^{20,21} In our larger study sample, only 23% of the HF patients met conventional OH criteria, i.e. SBP/DBP decrease $\geq 20/10$ mmHg. This proportion is similar to previously published data by Weiss *et al.* who reported 26% OH prevalence among 147 HF patients discharged from an acute geriatric ward.²² Interestingly, in a random sample of 480 subjects aged 65 years or older, the prevalence of OH was 28%, suggestive of increasing age and not HF per se, being the main predictor of OH occurrence.²³

The cross-sectional character of this study does not allow any conclusions about the causal role of autonomic dysfunction in the aetiology of cardiac changes. Although the presence of OH has been associated with increased risk of HF development, especially in younger subjects,⁵ the exact pathophysiological mechanisms are not clear and pleiotropic effects may be expected. For instance, one of possible interactions between OH and left ventricular changes might

Table 3 Associations between left atrial volume, left ventricular mass, and interventricular systolic diameter diastole with systolic orthostatic blood pressure reactions in multivariate linear regression analysis

Variables	LAV		LVM		IVSDd	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Age	-0.13 (0.18)	0.472	-0.38 (0.34)	0.271	-0.60 (0.67)	0.375
Sex	-2.87 (4.09)	0.483	-14.7 (7.92)	0.064	0.05 (0.03)	0.084
BMI	-0.48 (0.38)	0.202	0.09 (0.72)	0.897	0.12 (0.06)	0.060
HT	6.05 (3.54)	0.090	7.33 (6.83)	0.285	0.05 (0.58)	0.935
Smoking	3.49 (4.87)	0.475	6.13 (9.40)	0.515	0.67 (0.80)	0.405
LVEF	-0.03 (0.12)	0.804	-0.73 (0.22)	0.002	0.06 (0.02)	0.954
HDL	8.92 (5.13)	0.085	8.46 (9.91)	0.395	0.62 (0.85)	0.467
LDL	-6.64 (4.53)	0.145	1.97 (8.75)	0.822	-0.62 (0.75)	0.408
FPG	-11.4 (5.93)	0.058	4.44 (11.5)	0.699	-0.57 (0.98)	0.561
AF	11.8 (3.58)	0.001	-7.68 (6.92)	0.269	0.57 (0.59)	0.338
SBP	2.37 (1.16)	0.043	5.67 (2.24)	0.012	0.35 (0.20)	0.074

AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure reaction per 10 mmHg of change between supine systolic blood pressure and systolic blood pressure upon 3 min of standing; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HT, hypertension; IVSDd, interventricular systolic diameter diastole; LAV, indexed left atrial volume; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVM, indexed left ventricular mass. β are unstandardized coefficients.

be the prospective association of OH with ischaemic heart disease, observed in large population-based studies.³

Further, supine hypertension and increased BP variability are commonly present in OH patients and may result in chronic cardiac overload and subsequently in hypertrophy and increased stiffness of left ventricle.^{24,25} Interestingly, in neurogenic autonomic failure, the proportion of patients with LVH is comparable with that observed in hypertensive patients.²⁶ A recent study compared the grade of cardiac organ damage in subjects with autonomic failure and essential hypertension and healthy controls and found that those with autonomic failure and essential hypertension had similar LVM and carotid–femoral pulse wave velocity and that both parameters were significantly lower in healthy controls, implicating that subjects with autonomic failure develop hypertensive heart disease and increased arterial stiffness, similar to subjects with essential hypertension with comparable mean BP values.²⁷

At this point, it is important to emphasize that the association between impaired orthostatic SBP response and cardiac anomalies was independent of the global function and CV risk factors. Consequently, hypertrophy of the left ventricle might also be a direct result of chronic autonomic and neuroendocrine activation, usually present in patients with dysautonomia.²⁸

Finally, confirmatory of numerous earlier studies, we observed that prevalent AF was associated with increased left atrial volume,^{29,30} whereas LVEF was inversely associated with LVM, as previously reported.^{31,32} Thus, our patient series seems to be representative of a typical HF population.

Study limitations

Due to the fact that almost half of the study population (48%) had prevalent AF, we did not study the relation

between orthostatic BP and signs of diastolic dysfunction since the exclusion of subjects with AF would result in a significant selection bias and concomitant risk of false findings. As this is a cross-sectional study, it is vitiated with problems such as causality, common to all cross-sectional studies. Since orthostatic changes have been shown to be associated with the future development of HF and cardiac remodelling occurs as a part of the HF, process it is difficult to separate these from each other in this cross-sectionally designed study. The HARVEST study is conducted at a single regional centre, which usually limits the applicability to other populations. However, a multicentre study would probably result in a greater interobserver intraobserver bias in ultrasound cardiogram measurements. Also, the variation in left ventricular systolic function (EF variation 40% \pm 16%) in the study population is notably wide in range. This is most likely due to the fact that we included all patients admitted with the clinical diagnosis of HF without any exclusion criteria except severe cognitive impairment, and the variation in EF might therefore reflect a real-life hospitalized HF population. Finally, the study was undertaken in individuals of mainly Swedish descent, and the conclusions may not be generalizable to all ancestries.

Conclusions

Orthostatic decrease in SBP among older HF patients is associated with the presence of structural cardiac changes such as increased LVM and increased left atrial volume, independently of traditional risk factors and left ventricular systolic function. These findings suggest that autonomic dysfunction promotes cardiac remodelling in HF.

Acknowledgements

We thank the research nurses Hjördis Jernhed and Dina Chatziapostolou for valuable contributions, and we thank all the staff at the echocardiographic laboratory at Skåne University Hospital Malmö.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This work was supported by grants from the Medical Faculty of Lund University (ALFSKANE-432021 and ALFSKANE-436111), Skane University Hospital, the Crafoord Foundation, the Ernhold Lundstroms Research Foundation, the Region Skane, the Hulda and Conrad Mossfelt Foundation, the Southwest Skanes Diabetes Foundation, the Kockska Foundation, the Research Funds of Region Skåne, the Swedish Heart and Lung Foundation (2015-0322), and WCMM-Lund University (ALFSKANE-675271).

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