Directionality of Blood Pressure Response to Standing May Determine Development of Heart Failure: Prospective Cohort Study

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Abstract

Aims: To study the prospective relationship of blood pressure response during orthostatic challenge with incidence of heart failure (HF).

Methods and Results: In a Swedish prospective cohort study (the Malmö Preventive Project) we followed up 32,669 individuals (68.2% men; mean age, 46 yrs) over a period of 24 yrs. Incidence of first hospitalization due to new-onset HF was related to early (60-120 sec) postural changes in systolic and diastolic blood pressure (ΔSBP and ΔDBP), and mean arterial pressure (ΔMAP), using Cox proportional hazards models. Hazard ratio of incident HF increased across descending quartiles of ΔSBP from the first (and reference) quartile (+8.5±4.9 mmHg), through the second (neutral response), to the third and fourth quartiles (-5.0±0.1 and -13.7±6.1 mmHg, respectively; *p* for linear trend = 0.009). A pronounced hypotensive SBP response (fourth quartile) conferred the highest risk of new-onset HF (hazard ratio [HR], 1.31; 95% confidence interval [CI], 1.11-1.53). A similar pattern was observed in regard to ΔMAP, where the first (and reference) quartile with a marked positive MAP response (+7.7±3.1 mmHg) had the lowest, and the fourth quartile with a hypotensive MAP response (-5.2±3.4 mmHg) had the highest HF risk (HR for fourth vs. first quartile: 1.37; 95%CI, 1.17-1.62). In a continuous model, the risk of incident HF conferred by negative ΔSBP matched that of resting SBP (HR per 10 mmHg difference: 1.17; 95%CI, 1.11-1.23, and 1.17, 1.14-1.20, respectively), whereas MAP drop was the strongest individual predictor of HF development (HR 1.26, 95%CI, 1.21-1.31).

Conclusion: Early increase of blood pressure in response to orthostatic challenge signals reduced risk of HF development.

Keywords: blood pressure, cardiovascular reactivity, baroreflex, heart failure, epidemiology

Introduction

The haemodynamic response to the change of body position from supine to standing is based on a complex reflex controlled by the autonomic nervous system. Normally, while standing, systolic blood pressure (SBP) stabilizes on a level corresponding to that of the supine position, whereas diastolic blood pressure (DBP) increases by approximately 10 to 15%(1). As previously shown, measurement of the BP response to postural change may serve as a quantitative marker of susceptibility to cardiovascular morbidity (2). Moreover, extreme values of BP response, defined as either orthostatic hypertension (OHT, increase of SBP≥20 mmHg)(3), or orthostatic hypotension (OH, decrease of SBP≥20 mmHg and/or decrease of DBP≥10 mmHg)(4), have been linked to increased risk of cerebrovascular(5) and peripheral artery disease(6). Interestingly, OH but not OHT has also been associated with prevalent coronary artery disease, and left ventricular hypertrophy (LVH) in hypertensive patients(6). In parallel, as previously demonstrated by us, the orthostatic BP drop predicts in a linear way higher mortality and incidence of coronary events among middle-aged individuals(7), suggesting that the increase in SBP on standing may involve some protective mechanisms.

Consequently, there are contradictory reports on the variability of postural BP response and risk of cardiovascular disease (CVD). Although OH has been consistently shown to confer higher mortality and CVD risk (8-10), the role of an increased BP on standing is still controversial. In particular, we recently reported that incidence of heart failure (HF) is doubled in younger adults with OH(11) but there is no previous study exploring the prospective risk of HF across the whole spectrum of orthostatic response.

Thus, the aim of this work was to investigate relationship between directionality of BP response during orthostasis and the long-term incidence of HF.

Methods

Study population

The Malmö Preventive Project, a population-based prospective cohort study, was aimed to screen large strata of the urban population for CVD(12). Between 1974 and 1992, a total of 33 346 inhabitants of Malmö (22 444 men and 10 902 women; mean age, 45 yrs; range, 26-61 yrs), born between 1921 and 1948, were examined. The overall attendance rate for the examined age cohorts was 71% (range, 64-78%)(13)

In the present study, we excluded 549 participants (1.6%) because of missing information on BP measurements, seven individuals who before baseline examination had been hospitalized due to HF according to the Swedish National Hospital Discharge Register (SNHDR, code 428 for the *9th Revision of ICD*), and 121 individuals with history of myocardial infarction. Thus, the study population consisted of 32,669 subjects.

Baseline examination

The mailed invitation to attend for the baseline examination contained instructions to abstain from food, alcoholic or stimulating beverages and tobacco for 12 h prior to the examination, which was performed by trained nurses during the morning (8-12 a.m.). Participants were only allowed to drink water *ad libitum*. Blood pressure was measured using the auscultatory method with a mercury sphygmomanometer and an appropriately sized cuff placed around the right arm. The arm was situated parallel to the torso,

supported at the level of the heart in the supine position and hanging down in the standing position. First, BP was taken twice within one min after 10 min rest in the supine position. Then, the participants were asked to stand up and BP was taken twice between 60 and 120 seconds of standing. The mean values of the two readings were recorded for each position.

Body-mass index (BMI) was calculated as weight in kg divided by height squared in meters. Blood samples were collected and analyzed by standard methods at the Department of Clinical Chemistry, Malmö University Hospital. The participants were also asked to fill in a self-administered questionnaire about personal and family history of CVD, hypertension, diabetes, smoking habits, and lifestyle patterns. A positive answer to the following question was considered relevant to the history of myocardial infarction: "*Have you ever been hospitalized for myocardial infarction?"* Data on particular types of antihypertensive agents were not collected and current antihypertensive treatment was defined as a positive answer to the question: "*Do you take medication for high blood pressure?*" Those who confirmed regular or occasional current smoking were classified as smokers. A detailed description of recruitment and screening procedures has been published previously (12, 14). The health service authority of Malmö approved and funded the screening programme. All participants gave informed consent.

Definition of clinical characteristics

Hypertension was defined according to the current guidelines as supine SBP ≥ 140 mmHg and/or supine DBP ≥ 90mmHg, or use of antihypertensive treatment (15). Diabetes was defined as fasting plasma glucose ≥ 7.0 mmol/L, or current

pharmacological treatment for diabetes, or self-reported history of diabetes (16). Orthostatic SBP response (ΔSBP) was defined as standing SBP – supine SBP, and orthostatic DBP response (ΔDBP) as standing DBP – supine DBP Mean arterial pressure (MAP) was defined as DBP + 1/3 (SBP – DBP). Orthostatic MAP response (ΔMAP) was calculated as standing MAP – supine MAP.

Retrieval of end-points

All study participants were followed from the baseline examination until the first hospitalization due to HF, death, emigration from Sweden, or December 31, 2006, whichever came first. We applied linkage of each subject's unique 10-digit personal identification number with the SNHDR, and the Swedish National Cause of Death Register, both of which are characterized by high case validity (17, 18). The mean follow-up time was 24.1±6.5 years.

Statistical analysis

In the primary analysis, we divided the study population into quartiles corresponding to ΔSBP values. Group-wise differences in continuous variables between quartiles were compared using one-way ANOVA test, and dichotomous variables were compared using Pearson's Chi-square test.

To evaluate the association between quartiles of ΔSBP and the risk of the first incident HF event, we applied crude and adjusted Cox proportional hazards models. The proportional hazards assumption was assessed graphically in a univariate model and found to be met during the whole follow-up period. In the adjusted model the following

potential confounders were entered: age, gender, body-mass index, supine SBP, antihypertensive treatment, diabetes, current smoking and total cholesterol.

In the alternative Cox regression models, we employed quartiles of ΔDBP and ΔMAP instead of ΔSBP as diastolic compared with systolic response is a better predictor of coronary events(7), whereas MAP is a better indicator of tissue perfusion and its variability during orthostatic stress is directly involved in the baroreflex(19). For resting BP adjustment in a model employing ΔDBP and ΔMAP, we entered supine DBP and MAP instead of SBP, respectively. To compare relative risk if incident HF conferred by quartiles of postural BP response with that related to ascending quartiles of resting supine BP we applied matched models of Cox regression analysis, entering quartiles of SBP, DBP, and MAP as a categorical variable, and ΔSBP, ΔDBP and ΔMAP as a corresponding covariate, respectively.

Moreover, to study whether arterial stiffness, which is commonly associated with increased risk of HF development(20), may play a mediating role between orthostatic BP change and incidence of HF, supine pulse pressure (SBP-DBP) was related to ΔSBP, ΔDBP and ΔMAP using multivariate-adjusted linear regression with corresponding covariate panel as in the Cox regression models.

Finally, resting (SBP, DBP, and MAP) and postural (ΔSBP, ΔDBP and ΔMAP) haemodynamic parameters were modelled as continuous variables in a univariate and multivariate Cox regression analysis. We then applied the bootstrap method, performed on 1,000 samples, to obtain confidence intervals for regression coefficients. In the multivariate-adjusted model we entered age, gender, body-mass index, antihypertensive treatment, diabetes, current smoking and total cholesterol as covariates. Hazard ratios

were reported for 10 mmHg difference in the analyzed haemodynamic parameters in order to make them directly comparable.

All analyses were performed using SPSS statistical software version 17.0 for Windows (SPSS Inc., Chicago, IL). All tests were two-sided and a p-value <0.05 was considered statistically significant.

Results

Baseline characteristics according to orthostatic blood pressure response

As can be seen in Fig. 1, orthostatic SBP response was normally distributed. However, the number of individuals in quartiles was unequal because in 10,307 cases (31.5%, second quartile) there was no difference between supine and standing SBP. There were more participants with negative ΔSBP (n=12,685) than with positive ΔSBP (n=9,677). Participants with positive ΔSBP were younger and more likely to be male, had lower supine SBP, lower total cholesterol, and a lower proportion were on antihypertensive treatment or had diabetes as compared to those with negative ΔSBP (Table 1).

Prospective association between orthostatic blood pressure response and heart failure

During follow-up a total of 1,293 (4.0%) study participants were hospitalized due to new-onset HF. As shown in Table 2, the event rate almost doubled across the quartiles, from 1.2 events/ 1,000 person-yrs in the first quartile ($Q1_{\Delta SBP}$, with hypertensive orthostatic SBP response) to 2.3 events/ 1,000 person-yrs in the fourth quartile ($Q4_{\Delta SBP}$, with the most pronounced hypotensive orthostatic SBP response). In both crude and adjusted Cox proportional hazards models, as can be seen in Figure 2, the relative risk of incident HF increased significantly across the quartiles from hypertensive (a reference

quartile) to hypotensive response (*p* for linear trend <0.001, and 0.009, respectively). Consequently, in the crude model the hazard ratio of incident HF was highest in $Q4_{\Delta SBP}$ (hazard ratio [95% confidence interval]: 2.01 [1.72-2.34]). After adjustment for traditional risk factors the relative HF risk conferred by the most pronounced hypotensive SBP response was attenuated but still significantly increased by about 30% (Fig.2).

In a supplementary analysis, we excluded all HF events which occurred concomitantly with or after the first incident myocardial infarction (n=381). We then followed up the study participants until the first myocardial infarction episode and censored them thereafter, or until the first HF episode, death, emigration, or December 31, 2006, whichever occurred first. The hazard ratio for $Q4_{\Delta SBP}$ vs. $Q1_{\Delta SBP}$ was similar to that obtained in the basic Cox regression model: crude, 2.03 [1.70-2.44], and adjusted, 1.35 [1.12-1.63].

Diastolic BP response to orthostasis (Table 3) was more "hypertensive" as nearly 42% of all individuals increased their DBP after standing ($Q3_{\Delta DBP}$ and $Q4_{\Delta DBP,}$ n=13,696). Risk of incident HF followed the same trend as for ΔSBP, the main difference was a marked attenuation of HF risk in the multivariate-adjusted Cox regression model for ΔDBP ($Q4_{\Delta DBP}$ vs. $Q1_{\Delta DBP}$: 1.17 [0.94-1.45]).

As can be further seen in Table 4, the orthostatic MAP response showed a similar pattern of association as SBP change and incident HF. The reference quartile with a pronounced positive MAP response ($Q1_{\Delta MAP}$, +7.7±3.1 mmHg) was associated with the lowest HF risk, whereas the quartile with a hypotensive MAP response ($Q4_{\Delta MAP}$, -5.2±3.4 mmHg) was associated with the highest HF risk (hazard ratio for $Q4_{\Delta MAP}$ vs. $Q1_{\Delta MAP}$: 1.42 [1.21-1.67]). The main differences between postural changes in SBP and

MAP were a slightly positive mean ΔMAP (+1.1±5.9 mmHg), a higher overall number of individuals with positive ΔMAP (n=16,330; quartiles $Q1_{\Delta MAP}$ and $Q2_{\Delta MAP}$), and interestingly, a more U-shaped hazard ratio profile with a nadir in the third quartile characterized by a neutral MAP response (hazard ratio for $Q3_{\Delta MAP}$ vs. $Q1_{\Delta MAP}$: 1.19 [1.01-1.41]).

Increased pulse pressure was independently associated with orthostatic SBP drop (ΔSBP, β= - 0.15 [per 1 mmHg increase of pulse pressure], SE=0.007, $p<0.001$), and in contrast, with a slightly higher DBP and MAP during orthostasis (ΔDBP, β= 0.03, SE=0.003, $p<0.001$, and ΔMAP, β=0.08, SE=0.003, $p<0.001$, respectively).

Finally, as presented in Table 5, both decrease in MAP during orthostatic challenge and increased supine MAP were the strongest predictors of new-onset HF on a continuous scale (hazard ratio per 10 mmHg difference in a multivariate-adjusted model: 1.26 [1.21-1.31], and 1.30 [1.27-1.33], respectively). Moreover, HF risk related to postural decrease in SBP was comparable with that of resting supine SBP (same model: 1.17 [1.11-1.23], and 1.17 [1.14-1.20], respectively).

Discussion

Main findings

To our knowledge, this is the first study to describe a prospective relationship between directionality of postural BP response and hospitalization due to new-onset HF in middle-aged adults. Although the causal association still remains uncertain, we observed that those individuals who demonstrated a hypertensive (positive) postural response had a lower risk of HF development. This is interesting in light of previous

studies, which suggested the existence of a U-curve relationship between orthostatic BP change and CVD (in particular, stroke and peripheral artery disease)(5, 6). Our results appear to contradict these reports, but it is important to note that the cross-sectional association between LVH and extreme deviations in the orthostatic BP response (OH and OHT) in hypertensive individuals was observed in regard to OH alone, and not to OHT(6). This could partially explain why the hypertensive orthostatic response, which logically should increase "afterload", and thus predispose to LVH, did not predict HF in "real life".

Potential pathomechanisms

We currently have strong evidence for the epidemiological link between hypertension and HF development.(21, 22) So why do individuals who demonstrate a hypertensive orthostatic response, seem to paradoxically benefit from it in terms of reduced HF risk? According to our previous work, a pronounced BP fall, which meets the diagnostic criteria of OH, predicts incident HF(11). Interestingly, we found here that not only extreme but also moderate hypotensive response was associated with increased HF incidence, and that the hazard ratio was proportional to the magnitude of SBP fall. The linear relationship between ΔSBP and HF throughout the whole spectrum of postural BP response suggests that the "elasticity" of the autonomic nervous system can be the main factor behind this association. Theoretically, a rise in BP during early orthostasis may indicate well-functioning circulatory reflexes, a greater capacity to manage the orthostatic stress, and consequently, an optimal cardiac load. However, in this study we lack additional data, such as continuous BP monitoring under orthostatic challenge, BP measurements taken after 3 minutes, cardiovascular biomarkers (e.g. natriuretic peptides)

and echocardiographic examination at baseline to test this hypothesis. Sine BP was measured between the first and third minute of standing, we cannot exclude that the hypertensive phase was temporary and BP successively stabilized to a lower level. Furthermore, only an increase of MAP by at least 5 mmHg indicated the presence of hypothetical protective mechanisms, as there was only a minor difference in the relative HF risk between a slightly increased MAP ($Q2_{\Delta MAP}$) and a neutral MAP response ($Q3_{\Delta MAP}$). A corresponding magnitude of MAP change during orthostasis is what one would expect of properly working baroreceptor reflexes(19). In contrast, even a less pronounced orthostatic BP fall might be an early sign of autonomic dysfunction leading in turn to left ventricular hypertrophy and alterations in left ventricular diastolic filling(23), disorders of circadian BP rhythm (especially non-dipping) (24, 25), diurnal BP swings (i.e. supine or sitting vs. standing), and a reflex increase in heart rate during orthostasis, all of which are implicated in HF development (26-28). A higher resting BP and resting heart rate, as observed in the fourth and most hypotensive quartile of ΔSBP, might additionally strengthen these effects (28). The association between postural BP variability and incident HF seems not to be primarily mediated by an increased risk of coronary artery disease, since exclusion of HF cases relative to the prevalent or concurrent myocardial infarction did not alter our results. Moreover, arterial stiffness does not seem to be primarily involved in this process: although increased pulse pressure predicts hypotensive SBP response, orthostatic decrease of MAP demonstrates the opposite relationship, both of which are associated with comparable HF hazards. Interestingly, on a continuous scale, decrease in MAP was a better predictor of new-onset HF than was a decrease in SBP of the same magnitude. On the other hand, it is much

more practical to study postural SBP response, because all physicians are trained to determine resting SBP in order to diagnose and treat a possible hypertension. Postural SBP values can be directly obtained during such a procedure and changes in SBP are in general larger than changes in MAP.

Implications for future studies

The neurohumoral characteristics of the different types of postural haemodynamic response have not been sufficiently studied, and neither have the various biomarkers predictive of increased CVD risk, such as mid-regional pro-atrial natriuretic peptide, N-terminal pro-B-type natriuretic peptide, mid-regional pro-adrenomedullin, cystatin C, C-reactive protein and copeptin (29). Future studies should thus concentrate on evaluating associations between the circulatory responsiveness of the autonomic nervous system, in particular with regard to orthostatic BP autoregulation, and these biomarkers, in order to provide more insights into the underlying long-acting pathomechanisms. Moreover, BP adjustments within the first few minutes of standing are mainly governed by autonomic neural pathways. It would therefore be interesting to study peripheral sympathetic nerve activity in relation to postural BP responses as an inverse relationship between the former and cardiac output has previously been demonstrated(30).

Strengths and limitations of the study

The strengths of this study are the large number (over 30,000) and similar ethnic background of the included individuals, the high participation rate, long follow-up (over 20 years), and access to end-point registers with a high case ascertainment. The main limitation of the study is a potential underestimation of HF incidence as the case ascertainment was based on in-hospital HF diagnoses only. Furthermore, orthostatic BP

response was measured during the baseline examination and thus we cannot draw conclusions about the persistence of autonomic dysfunction among included individuals.

In summary, throughout the whole spectrum of postural BP response, a more positive value of BP response signals a lower risk of HF development. Further studies to explore underlying pathomechanisms, especially associations between peripheral sympathetic nerve activity, cardiovascular biomarkers and directionality of postural circulatory responses are needed.

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Conflict(s) of Interest

None declared

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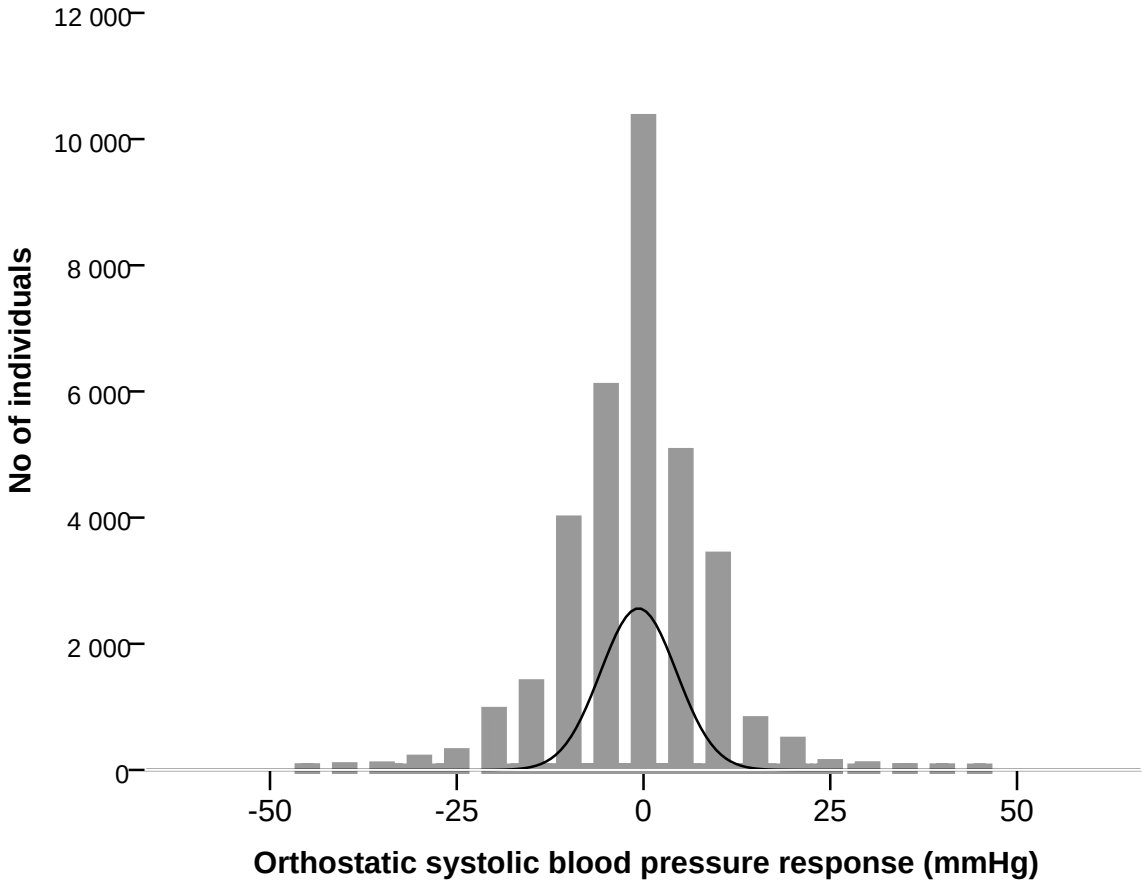
Figure legends

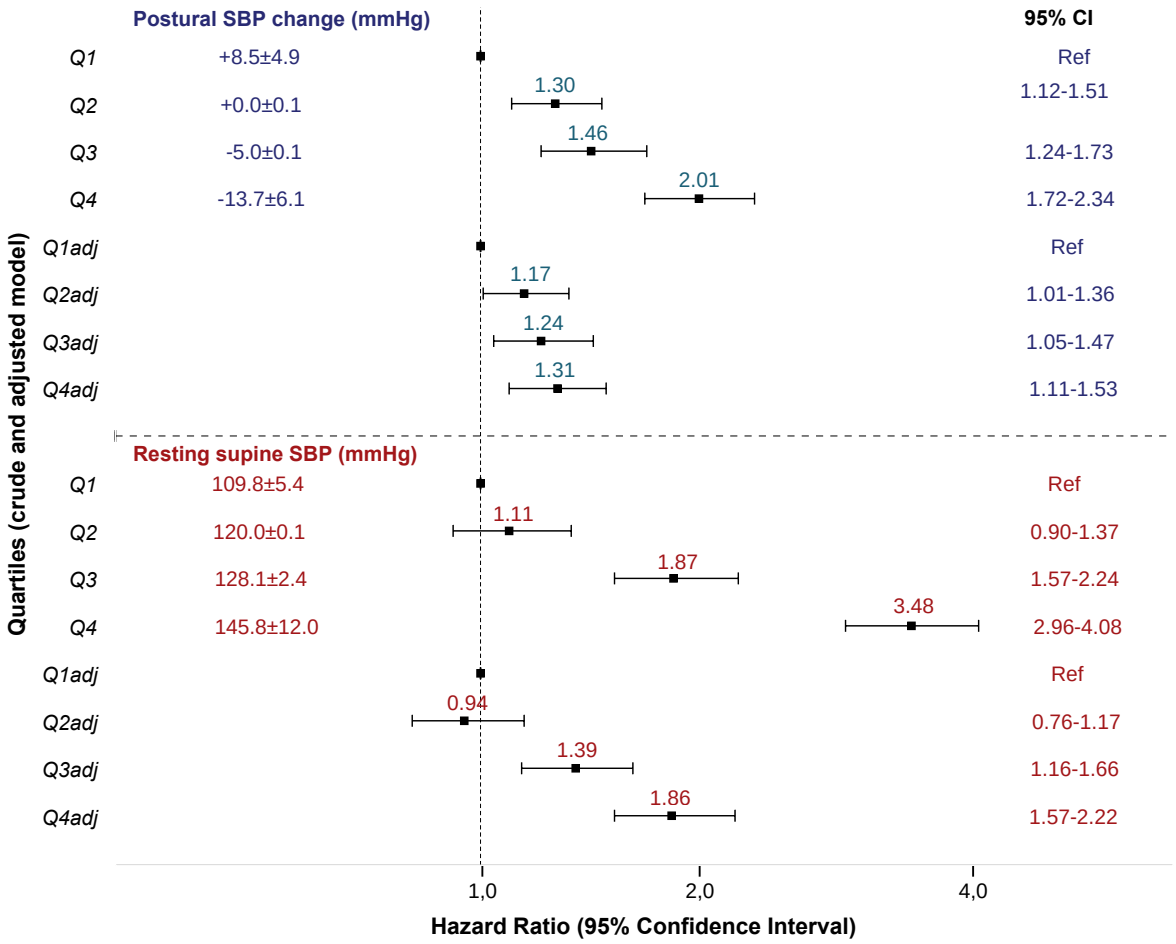
Fig.1

Distribution of postural systolic blood pressure response among participants of the Malmö Preventive Project (n=32,699).

Fig. 2

Hazard ratio for the first hospitalization due to new-onset heart failure among participants of the Malmö Preventive Project (n=32,699) according to the crude and adjusted Cox regression models by quartiles of postural systolic blood pressure response (postural SBP change) and resting systolic blood pressure (SBP). Covariates used in the adjusted model: age, gender, body-mass index, resting SBP (for quartiles of postural SBP response) or postural SBP response (for quartiles of resting SBP), antihypertensive treatment, diabetes, current smoking and total cholesterol. Quartiles of resting SBP: *1st quartile*, n=9,169; *2nd quartile*, n=6,379; *3rd quartile*, n=7,997; *4th quartile*, n=9,124.


12 000
10 000
8 000
6 000
4 000
2 000
0
No of individuals
-50
-25
0
25
50
Orthostatic systolic blood pressure response (mmHg)


Postural SBP change (mmHg)
95% CI
Q1
+8.5±4.9
Ref
Q2
+0.0±0.1
1.30
1.12-1.51
Q3
-5.0±0.1
1.46
1.24-1.73
Q4
-13.7±6.1
2.01
1.72-2.34
Q1adj
Ref
Q2adj
1.17
1.01-1.36
Q3adj
1.24
1.05-1.47
Q4adj
1.31
1.11-1.53
Resting supine SBP (mmHg)
Q1
109.8±5.4
Ref
Q2
120.0±0.1
1.11
0.90-1.37
Q3
128.1±2.4
1.87
1.57-2.24
Q4
145.8±12.0
3.48
2.96-4.08
Q1adj
Ref
Q2adj
0.94
0.76-1.17
Q3adj
1.39
1.16-1.66
Q4adj
1.86
1.57-2.22
Quartiles (crude and adjusted model)
1,0
2,0
4,0
Hazard Ratio (95% Confidence Interval)

Tables

Table 1. Baseline characteristics of the study participants according to quartiles of postural systolic blood pressure response.

Characteristics	**All n=32,669**	**1st Quartile ($Q1_{\Delta SBP}$) n= 9,677**	**2nd Quartile ($Q2_{\Delta SBP}$) n=10,307**	**3rd Quartile ($Q3_{\Delta SBP}$) n= 6,043**	**4th Quartile ($Q4_{\Delta SBP}$) n= 6,642**	***P* linear trend**
Postural SBP response (mmHg)	-1.2±8.8	8.5±4.9	0.0±0.1	-5.0±0.1	-13.7±6.1	
Age (yrs)	45.6±7.4	44.1±7.4	45.2±7.5	46.2±7.1	47.9±7.0	<0.001
Gender (male, %)	68.2	75.3	69.1	63.9	60.3	<0.001
BMI (kg/m^2)	24.6±3.6	24.5±3.4	24.6±3.6	24.6±3.7	24.6±3.8	0.64
Current smoker (%)	44.7	45.0	44.5	45.0	44.5	0.81
Hypertension (%)	40.2	35.0	39.5	37.9	51.2	<0.001
Antihypertensive treatment (%)	5.3	3.7	4.8	4.8	9.0	<0.001
Supine SBP (mmHg)	126.3 ±15.5	122.6 ±14.4	125.4 ±14.6	126.2 ±14.4	133.2 ±17.2	<0.001
Supine DBP (mmHg)	84.3±9.6	83.6±9.6	84.1±9.1	83.9±9.3	85.9±10.1	<0.001
Supine heart rate	67.5±9.7	66.9±9.7	67.2±9.7	67.8±9.5	68.6±10.0	<0.001

(beats/min)						
Diabetes (%)	4.7	4.0	4.5	4.6	6.1	<0.001
Total cholesterol (mmol/L)	5.7±1.1	5.6±1.1	5.7±1.1	5.7±1.1	5.8±1.1	<0.001

Data are presented as proportions or mean ± standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body-mass index.

$Q1_{\Delta SBP}$ = hypertensive orthostatic SBP response; $Q4_{\Delta SBP}$ = the most pronounced hypotensive orthostatic SBP response

Table 2. Total number of hospitalizations due to first incident heart failure event and event rate according to quartiles of postural systolic blood pressure response.

Quartiles	**All**	**$Q1_{\Delta SBP}$**	**$Q2_{\Delta SBP}$**	**$Q3_{\Delta SBP}$**	**$Q4_{\Delta SBP}$**
	n=32,669	**n= 9,677**	**n=10,307**	**n= 6,043**	**n= 6,642**
No of events	1,293 (4.0%)	298 (3.1%)	390 (3.8%)	255 (4.2%)	350 (5.3%)
Event rate (per 1,000 person-yrs)	1.6	1.2	1.6	1.7	2.3

$Q1_{\Delta SBP}$ = hypertensive orthostatic SBP response; $Q4_{\Delta SBP}$ = the most pronounced hypotensive orthostatic SBP response

Table 3. Quartiles of postural diastolic blood pressure response (ΔDBP) and resting diastolic blood pressure (DBP) for prediction of first hospitalization due to incident heart failure according to crude and adjusted Cox regression models.

Quartiles	1st Quartile (ref)	2nd Quartile	3rd Quartile	4th Quartile
ΔDBP (mmHg)*	n=4,796	n=8,900	n=14,510	n=4,463
	11.6±10.8	5.0±0.1	0.0±0.0	-5.2±3.4
Hazard ratio†	1.00	1.22	1.50	1.79
[95%CI]	*p*<0.001**	[1.01-1.49]	[1.25-1.79]	[1.45-2.21]
Hazard ratio ‡	1.00	1.08	1.19	1.17
[95%CI]	*p*=0.19**	[0.88-1.31]	[0.99-1.43]	[0.94-1.45]
DBP (mmHg)*	n=6,867	n=8,231	n=12,380	n=5,191
	71.9±4.1	80.0±0.1	87.5±2.5	100.0±6.6
Hazard ratio†	1.00	1.52	2.30	4.16
[95%CI]	*p*<0.001**	[1.22-1.88]	[1.90-2.78]	[3.41-5.07]
Hazard ratio ‡	1.00	1.23	1.52	2.05
[95%CI]	*p*<0.001**	[0.99-1.50]	[1.24-1.85]	[1.65-2.54]

*mean ± standard deviation; ** test for linear trend; † crude; ‡ adjusted for age, gender, body-mass index, supine diastolic blood pressure (for quartiles of ΔDBP) or orthostatic diastolic blood pressure response (for quartiles of DBP), antihypertensive treatment, diabetes, current smoking and total cholesterol.

Table 4. Quartiles of postural mean arterial pressure response (ΔMAP) and resting mean arterial pressure (MAP) for prediction of first hospitalization due to incident heart failure according to crude and adjusted Cox regression models.

Quartiles	1st Quartile (ref)	2nd Quartile	3rd Quartile	4th Quartile
ΔMAP (mmHg)*	n=8,051	n=8,279	n=8,275	n=8,064
	7.7±3.1	2.4±1.0	-0.5±0.8	-5.2±3.4
Hazard ratio†	1.00	1.43	1.38	2.07
[95%CI]	*p*<0.001**	[1.21-1.68]	[1.16-1.63]	[1.76-2.42]
Hazard ratio ‡	1.00	1.27	1.17	1.37
[95%CI]	*p*=0.001**	[1.07-1.50]	[0.98-1.38]	[1.17-1.62]
MAP (mmHg)*	n=7,918	n=9,123	n=7,660	n=7,968
	85.9±4.2	94.3±1.8	100.1±1.8	112.7±8.0
Hazard ratio†	1.00	1.39	2.30	4.07
[95%CI]	*p*<0.001**	[1.13-1.70]	[1.90-2.79]	[3.40-4.88]
Hazard ratio ‡	1.00	1.13	1.57	2.03
[95%CI]	*p*<0.001**	[0.92-1.38]	[1.29-1.91]	[1.67-2.47]

*mean ± standard deviation; ** test for linear trend; † crude; ‡ adjusted for age, gender, body-mass index, supine mean arterial pressure (for quartiles of ΔMAP) or orthostatic mean arterial pressure response (for quartiles of MAP), antihypertensive treatment, diabetes, current smoking and total cholesterol.

Table 5. Comparison of resting and postural haemodynamic parameters modelled as continuous variables for prediction of first hospitalization due to incident heart failure using univariate and multivariate Cox regression analysis.

Haemodynamic parameter	Mean±SD (mmHg)	Hazard ratio [95% CI] (per each 10 mmHg difference)	
		Univariate	Multivariate*
Resting SBP ↑	126.3±15.5	1.30 [1.27-1.33] *p*<0.001	1.17 [1.14-1.20] *p*<0.001
Resting DBP ↑	84.3±9.6	1.46 [1.41-1.51] *p*<0.001	1.26 [1.21-1.32] *p*<0.001
Resting MAP ↑	98.3±10.7	1.44 [1.40-1.48] *p*<0.001	1.30 [1.27-1.33] *p*<0.001
Postural Δ SBP ↓	-1.2±8.8	1.29 [1.24-1.35] *p*<0.001	1.17 [1.11-1.23] *p*<0.001
Postural Δ DBP ↓	2.2±5.4	1.33 [1.24-1.43] *p*<0.001	1.21 [1.11-1.32] *p*<0.001

Postural Δ MAP ↓	1.1±5.2	1.49 [1.40-1.57] p<0.001	1.26 [1.21-1.31] p<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; * adjusted for age, gender, body-mass index, antihypertensive treatment, diabetes, current smoking and total cholesterol.