Word count of manuscript: 3033

Word count of abstract: 250

Number of references: 37

Number of figures: 4

Number of tables: 3

Title: High home blood pressure variability associates with exaggerated blood pressure response to cold stress

Running head: Home BP variability and reactivity to stress

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Conflicts of Interest/Disclosures

The authors declared no conflict of interest.

Keywords: blood pressure monitoring, home; blood pressure; physiological stress reactivity; essential hypertension; environmental health; cold temperature

Public trials registry number

www.clinicaltrials.gov, ID:NCT02007031

Abstract

BACKGROUND. Exaggerated sympathetic cardiovascular (CV) reactivity to stress associates with elevated risk for clinical and preclinical endpoints of CV disease. It would be useful to identify these individuals, preferably from feasible measurements commonly used in healthcare. Our study examined the association between home blood pressure (BP) variability and cardiac workload response to whole-body cold exposure.

METHODS. 75 men (55-65 years, 46 hypertensive) measured BP at home twice in the morning and evening for a week. We computed systolic home BP variability as standard deviation of daily means and divided the subjects to groups demonstrating either high or low BP variability. They were exposed to whole-body cold exposure (-10°C, wind 3m/s, 15min, winter clothes, standing). BP and heart rate (HR) were measured at three-minute intervals during, and 15 minutes before and after the exposure. Rate-pressure product (RPP) was calculated to represent cardiac workload.

RESULTS. Subjects with high systolic home BP variability demonstrated a greater RPP increase in cold conditions compared to those with low BP variability [mean change from baseline (95%CI): 1850 (1450, 2250) bpm*mmHg vs. 930 (610, 1250) bpm*mmHg, $p<0.01$]. This was related to the augmented systolic BP change [31(28, 35) mmHg vs. 23(20, 26) mmHg, $p<0.01$]. Home BP variability correlated with cold-related RPP ($r_S=0.34$, $p=0.003$) and systolic BP ($r_S=0.38$, $p<0.001$) responses.

CONCLUSIONS. Moderate whole-body cold exposure increased BP and cardiac workload more among those with higher systolic home BP variability, independently of home BP level. Elevated home BP variability may indicate augmented sympathetically mediated vascular reactivity for environmental stressors.

Public trials registry number: www.clinicaltrials.gov, ID:NCT02007031

Introduction

Blood pressure (BP) exhibits physiological variation to maintain homeostasis, such as circadian variation, and changes related to e.g. hormonal regulation, respiration, emotions, or physical exercise. However, sustained augmentation in BP variability may also reflect undesirable changes in BP regulation and arterial structure, such as excessive sympathetic activity and reduced arterial compliance.[1-5] In fact, BP variability has been suggested as an independent determinant of cardiovascular (CV) diseases and adverse health events beyond the average BP level[2]. This association was also confirmed in a few recent studies involving assessment of home BP variability, and further suggesting a role for BP variability in the progression of cardiac, arterial, and renal damage.[4,6-8]

Increased BP variability could associate with exaggerated sympathetic CV reactivity to physical and/or psychological stressors. There is evidence, that individuals who exhibit greater stressor evoked CV reactions have elevated risk for clinical and preclinical endpoints of CV disease.[9,10] The exaggerated sympathetic responses could also act as a trigger for CV events, especially in people with predisposing conditions, and provide one possible pathophysiological mechanism to explain the association between BP variability and CV morbidity. However, the studies assessing the relation between CV reactivity (often defined as BP or heart rate (HR) increase during stress exposure) and either 24 h ambulatory or home BP variability, or changes in BP occurring during daily tasks towards laboratory stressors have yielded diverse results.[11-15] This could relate to possible confounding from habitual activities in commonly applied 24 h measurements compared with those obtained from home measurements.

Cold exposure represents a stressor causing sympathetic activation that increases BP[16,17] and is therefore relevant for examining the association between BP variability and

CV reactivity, which both associate with excessive sympathetic activity[5,9]. Experimental studies simulating habitual exposure to cold, have reported usually a 10 - 30 mmHg increase in BP [18,19]. It appears that irrespective of having hypertension or not [18,19], there is considerable individual variation in CV reactivity to cold. It is not known whether home BP variability is associated with CV reactivity towards habitual cold exposure. This information could be applied to estimate CV reactivity to everyday stressors and help prediction of CV endpoints.

In the present study we investigated the relationship of daily systolic home BP variability and CV responses to whole-body cold air exposure among untreated hypertensive and normotensive middle-aged subjects under controlled conditions. We hypothesized that individuals having higher home BP variability have an exaggerated cardiac workload response to simulated habitual cold exposure.

Methods

Participants of the study

We conducted recruitment of participants (Fig 1) in 2011 from a population based random sample of 1000 men aged 55-65 years and residing in the City of Oulu, Finland, which has been previously been described in detail [19]. Of those, the final study population consisted of 75 men having home BP level between optimal and moderately high (mean systolic and diastolic home BP <175 mmHg and <105 mmHg). The study was approved by the ethics committee of Northern Ostrobothnia Hospital District (EETTMK:111/2010) and all participants of the study gave written informed consent. The study has been registered in the Clinical Trials registry (www.clinicaltrials.gov, ID:NCT02007031).

PLACE FIGURE 1 APPROXIMATELY HERE.

Home blood pressure variability

We trained the participants to measure their home BP with validated [20] automatic oscillometric brachial BP meters (HEM-7200-E; Omron Healthcare, Kyoto, Japan) according to the guidelines of European Society of Hypertension [21]. The participants were advised to abstain from exercise, eating, caffeine, and smoking for 30 minutes before each measurement. The participants measured their BP at home twice (two minutes apart) in the morning and evening during seven consecutive days, after 5 minutes of rest in sitting position, and with the cuff (HEM-CR24 or HEM-CL24) at the level of the heart. Hypertensive subjects identified in the screening were referred to their health-care center for further evaluation and possible treatment of hypertension.

Measurements with irregular heartbeats (deviation of two or more RR-intervals > 25% from an average RR-interval during the measurement), movement, or cuff misplacement were automatically detected by the BP monitor and then excluded from further analysis of the data. Then we defined the mean values of all remaining systolic and diastolic BP and HR home measurements for each individual. For daily variability analyses, days of measurements including either only morning or evening values were excluded and, thereafter, minimum of four days of successful measurements was required for calculations. Systolic home BP variability was computed as within-subject SD of daily mean values [22]. The participants were divided to groups of high or low systolic home BP variability (above or below original group median). We applied median as cut-off value for high/low BP variability as there is no consensus thresholds for definition of high home BP variability, and the reproducibility of this classification with other data cannot be confirmed. Analyses were confirmed by applying coefficient of

variation (cv) (within-subject SD of daily mean values divided by the mean of systolic BP [22]) in addition to absolute variability (SD) (Supplement 2).

Experimental protocol

The experiments were performed in autumn 2011 (August till early November) by trained professionals during office hours. The participants were told to abstain from vigorous exercise, smoking more than usual, and consumption of alcohol a day before the measurements and to abstain from eating, consuming caffeine, smoking, and exercising 2 hours before the measurements. First, the participants were introduced to the protocol and familiarized with the climatic chambers. Following this, their height and weight were measured, body composition assessed with bioelectrical impedance analysis (InBody 720 Biospace Ltd, Korea), and physical fitness estimated from resting HR and HR variability [23] (PolarS610; Polar Electro, Kempele, Finland). The participants were equipped with skin temperature thermistors, electrocardiogram electrodes, an arm BP cuff (for arm circumference of 25−35 cm), and dressed with three-layer winter clothing (insulation value of approx. 2 clo during cold exposure, including hat and gloves, and approx. 1.6 clo during baseline measurements [24]. The exposure protocol consisted of three consecutive 15 min phases (baseline, cold exposure, and recovery follow-up) during which the participants were standing with their arms supported at the level of the heart. During baseline measurements, central hemodynamics were measured with applanation tonometry [25] (SPC-301; Millar Instruments, Houston, TX, USA and SphygmoCor Px; AtCor Medical, Sydney, Australia). This provided an augmentation index, an index of wave reflection and a surrogate measure of arterial stiffness [26], which was adjusted for HR. Baseline and recovery follow-up measurements were performed in

a climatic chamber (air temperature of 18 °C, air velocity < 0.2 m/s; relative humidity of 30%) and cold exposure in an adjacent wind tunnel (−10 °C, 3 m/s, 50%).

Cardiovascular responses to experimental cold stress

We measured BP and HR with oscillometric brachial BP meter (Schiller BP 200 Plus; Schiller, Baar, Switzerland) at three-minute intervals 15 minutes before, during, and after the cold exposure (a total of 15 measurements). The first BP measurement was initiated one minute after starting each phase. Cardiac workload was estimated noninvasively with rate-pressure product (RPP) computed as product of systolic BP (mmHg) and HR (bpm) for each measurement and for each participant.

CV reactivity to cold stress was defined as changes in RPP, systolic BP and HR from baseline to cold exposure. We also computed this as area under curve (AUC) in cold conditions - AUC baseline for the same parameters.

Skin temperature and thermal sensations

We measured skin temperature with thermistors (NTC DC95; Digi-Key, Thief River Falls, MN, USA) placed on the calf, shoulder blade, chest, arm, back of the hand, middle finger, and cheek, and recorded the data at 12-second intervals with an eight-channel temperature data logger (Smart Reader Plus; Acr Systems, Surrey, Canada) throughout the experimental measurements. Thermal perception for the face and whole body was assessed at five-minute intervals using subjective judgment scale [27].

Statistical methods

The characteristics of the study subjects were compared between the study groups (high/low home BP variability) and the statistical significance for the differences between the groups was assessed by independent t-test (parameters with Gaussian distribution) or independent samples Mann-Whitney U-test for continuous variables, and chi-square test for categorical variables.

Statistical analyses for the experimental data were conducted for RPP, systolic BP, and HR. Variables with a non-Gaussian distribution were transformed into natural logarithm for parametric statistical tests. The differences in the means between baseline (mean value), exposure (five measurements) and recovery (five measurements) as well as study groups were compared by two-way repeated measures analysis of variance (ANOVA) and contrast tests (simple). BP level in cold conditions (mean value) was also compared between those having high/ low home BP variability and hypertension/ no hypertension (four groups) with one-way ANOVA and Tukeys' post hoc tests.

The association between home BP variability and CV reactivity (AUC in cold conditions – AUC in baseline) was estimated with Spearman correlation. Linear regression models were applied to estimate the percentage of variation in CV reactivity and RPP and BP levels in cold conditions (AUC) explained by home BP level and variability. Regression models were adjusted for body fat, age, augmentation index, and smoking. Statistical analyses were performed with IBM SPSS for Windows version 23 (IBM Corp. Released 2015, Armonk, NY, USA) and significance was set at $p < 0.05$.

Results

Home blood pressure

The characteristics of the study subjects are presented in Table 1. Men with elevated systolic home BP variability had a higher amount of body fat, and three of them had type 2 diabetes, but otherwise there were no differences between the groups. According to our sensitivity analyses, those with diabetes did not differ in their responses from the reminder of the subjects. Systolic and diastolic BP, HR, and systolic BP variability (SD, cv) from home BP measurements among study groups are presented in Table 2. The study groups included comparable amounts of hypertensive and non-hypertensive men. Systolic BP levels were slightly higher among those with higher systolic home BP variability except not in evening measurements. Diastolic BP and HR at home did not differ between the study groups.

PLACE TABLES 1 AND 2 APPROXIMATELY HERE.

Experimental cold stress

The applied cold exposure induced a rapid (10°C decrease within 5 minutes) and substantial (from ca. 30°C in baseline to ca. 13°C at the end of the exposure) facial cooling. Superficial cooling was otherwise limited due to the used winter clothing, as demonstrated by only a small change in skin temperature at the shoulder blade (from ca. 34°C in baseline to ca. 31°C at the end of the exposure). Thermal perceptions (median) of face and body were reported to be neutral at the baseline and recovery. While exposed to cold, thermal perceptions ranged from slightly cool to cold for the face and slightly cool to cool for the whole body. Skin temperature and thermal sensations did not differ between the study groups.

Cardiac workload

Exposure to cold increased RPP via increased systolic BP in both study groups, despite of reduced HR (Fig. 2). The changes in RPP and systolic BP, but not HR, were greater among those with high home BP variability, compared to those with low home BP variability (Fig. 2). The group difference in the responses was detectable already at the beginning of the exposure and remained similar thereafter. No group difference was observed after 5 to 10 minutes of the exposure. RPP recovered almost immediately after the exposure and remained at a slightly lower level compared with baseline at the end of the follow-up period. Systolic BP returned to baseline by the end of the follow up, but HR remained lower than during the baseline. Table 3 presents AUC for RPP, systolic BP, and HR during baseline and exposure to cold, as well as cold-related AUC changes for same parameters for participants with high and low home BP variability.

PLACE FIGURE 2 AND TABLE 3 APPROXIMATELY HERE.

Systolic BP was comparable in cold conditions among hypertensive subjects with low home BP variability and normotensive subjects with high home BP variability ($p=0.18$) (Fig. 3). Among hypertensive with high home BP variability, systolic BP in cold conditions was higher than among the other groups ($p<0.05$).

PLACE FIGURE 3 APPROXIMATELY HERE.

Estimated regression models for RPP and systolic BP change from baseline to cold, and mean levels while exposed to cold are presented in Supplement table 1. Home BP variability contributed 11% and 14% of the variation in the cold related changes in RPP and systolic BP (Fig 4), correspondingly, and this change was independent of the home BP level. In the fully adjusted model, home BP variability and body fat together contributed 16% to the cold related changes in systolic BP while contribution to RPP responses was insignificant. Systolic home BP and home HR levels contributed together

ca. 50% (adjusted) of the variation in RPP level while exposed to cold, while home BP variability did not contribute to this. Systolic home BP level, variability and fat percentage contributed together ca. 60% (adjusted) to the systolic BP level while exposed to cold.

PLACE FIGURE 4 APPROXIMATELY HERE.

The results with cv (SD/mean) were comparable to the absolute home BP variability (SD) (Supplement 2). Those with cv above median had exaggerated RPP and SBP, but not HR response to cold compared to those with lower cv (Supplement 2C). Cv correlated with RPP (r_S=0.30, p=0.009) and SBP (r_S=0.33, p=0.005) responses to cold, and contributed 9.7% (adjusted ns) and 14.7% (adjusted 16.9%) to the RPP and SBP responses, correspondingly (Supplement 2D).

Discussion

Our results suggest that people with higher daily systolic BP variability at home have an augmented cardiac workload response to a laboratory stress test, involving exposure to cold. More specifically, the association related to an exaggerated systolic BP response to stress.

For the first time, we found that participants with elevated home BP variability demonstrated an exaggerated increase in cardiac workload during a cold exposure resembling everyday exposure to winter conditions. This likely relates to overall higher BP reactivity, and reflects exaggerated sympathetic responsiveness. Excessive sympathetic activity relates to higher BP variability[5] and the (cold) stress response is sympathetically mediated[9,16,17]. This provides a possible, and previously suggested[15], explanation to the detected association. Instead, we did not find any association between home BP variability and HR response that represents predominantly vagal activation

during facial cooling [28,29]. Increased arterial stiffness could also mediate the association between BP reactivity to stress and home BP variability. However, we observed that the measured augmentation index did not contribute to the cold-related responses and baseline levels were comparable between the test groups, which do not support the assumed association. A previous study of Kingma et al. [30] suggested higher body fat to associate with reduced heat production (thermogenesis) while exposed to cold in elderly subjects, and greater increases in post exposure systolic BP. Consistent with this, we observed an association between higher body fat and greater increases in systolic BP while exposed to cold, which was independent of the contribution of home BP variability to the responses. We observed, based on our regression analyses, that home BP variability contributed only moderately to the observed CV responses, explaining less than one fifth of the variation at its best. This is probably due to multiple mechanisms (e.g., humoral and behavioral) contributing to home BP variability, in addition to sympathetic reactivity and arterial stiffness [3,5].

We found that those subjects with both high home BP variability and hypertension have the highest BP level during experimental cold stress. Our previous study demonstrated that higher basal BP level elevates BP considerably during cold exposure, without affecting the magnitude of the response [19]. In the present study we observed that higher home BP variability was independently related to exaggerated BP response. Hence, hypertensive subjects with higher BP variability should receive special attention as a possible high-risk population for stress related exaggerated CV load.

Previous studies have found inconsistent associations between BP variability and CV reactivity to stress [12,13,15,31]. For example, the BP response to a cold pressor test (a sympathoexcitatory stimulus) did not to associate with daytime or 24 h ambulatory BP

variability among young people [12,13] but showed a modest correlation in a study involving both young and middle-aged subjects [32]. Instead, a strong correlation was detected between daily systolic home BP variability and cold pressor test responses among middle-aged population.[15] In addition, BP level during a stress test was independently related to ambulatory BP level measured at work or during perceived stress [33-35]. The observed inconsistent results can be due to lack of controlling for determinants of 24 h BP variability, such as physical activity, posture, and caffeine consumption [32,36]. Therefore, adjusting for important covariates have provided stronger associations [14].

These results highlight the importance of standardized or adjusted conditions when evaluating out-of-lab BP variability. Differences of the results may also relate to the varying stress tests applied (e.g. cold pressor test, psychological, handgrip), the definition of BP variability (measurement and calculation methods), and individual characteristics like age or underlying diseases. From a clinical perspective, home BP measurements could be considered ideal to assess daily BP variability [2], as they are easy to perform, inexpensive, and well accepted for long term monitoring by hypertensive patients. Albeit, there is diversity regarding the applied indexes [2] (e.g. morning, daily, how many days, handling of missing values), which, however, are currently assessed to be better standardized [8,37].

The strengths of our study include applying a population-based recruitment and habitual type of controlled exposure to cold. The population-based study design enables generalization of the results from our laboratory experiments to the source population. Home BP measurements were performed according the current guidelines and we used at least four days of measurements to compute the BP variability. The subjects of the present study were Caucasian middle-aged untreated men with BP varying from optimal

to moderately high, and the responses may differ from other populations, e.g. women or patients having severe hypertension or cardiac disease. In addition, multiple laboratory stress tests would have provided deeper insight to the generalizability of the results.

Conclusions

Our study provides further evidence on the association between home BP variability and response to stress. In this investigation whole-body cold exposure represented the stressor. We also observed that a combination of hypertension and elevated BP variability produced the highest BP during stress. Further studies with standardized or adjusted BP variability indexes and different stressors are suggested. The identification of subjects with exaggerated CV reactivity could result in the prevention of adverse health events.

Disclosure

The authors declared no conflict of interest.

Acknowledgments

We wish to thank Henna Hyrkäs-Palmu, Heta Helakari, Saana Rautakoski, Heikki Koivuranta, Arno Kandelberg, and Jaakko Takkunen for their help in the collection of the data.

Sources of funding

This work was funded through a grant from the National Institute for Health and Welfare (Finland), Yrjö Jahnsson Foundation (Finland), Ida Montin Foundation (Finland), Veritas

Säätiö (Finland), Aarne and Aili Turunen Foundation (Finland), The Finnish Foundation for Cardiovascular Research, (Finland) and the Paulo Foundation (Finland).

Supplementary information is available at http://www.oup.com/ajh.

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Figure legends

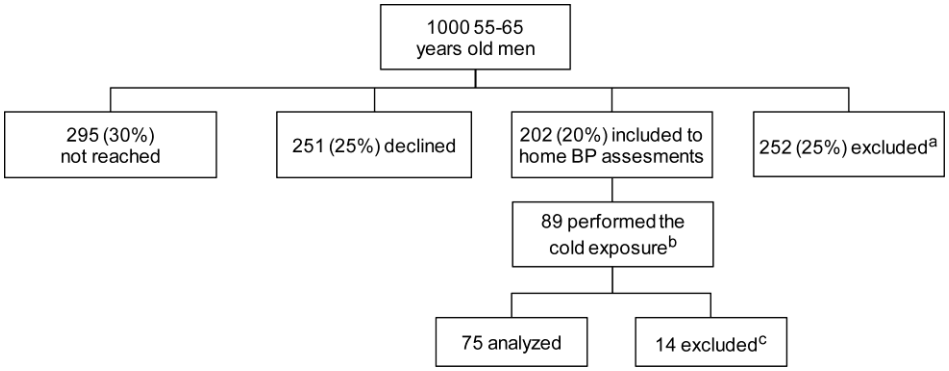


Figure 1. Recruitment procedure. a. Excluded were people with antihypertensive drugs, cardiac or respiratory disease, inadequate home blood pressure (BP) measurements to define hypertension status, mean home BP ≥ 175/105 mmHg (systolic/diastolic), or safety reasons (n=2). b. All eligible hypertensive and 34 men without hypertension were invited and attended to the experiments. c. Excluded were people with antihypertensive drugs (n=5) or inadequate home BP data for BP variability computation (n=7).

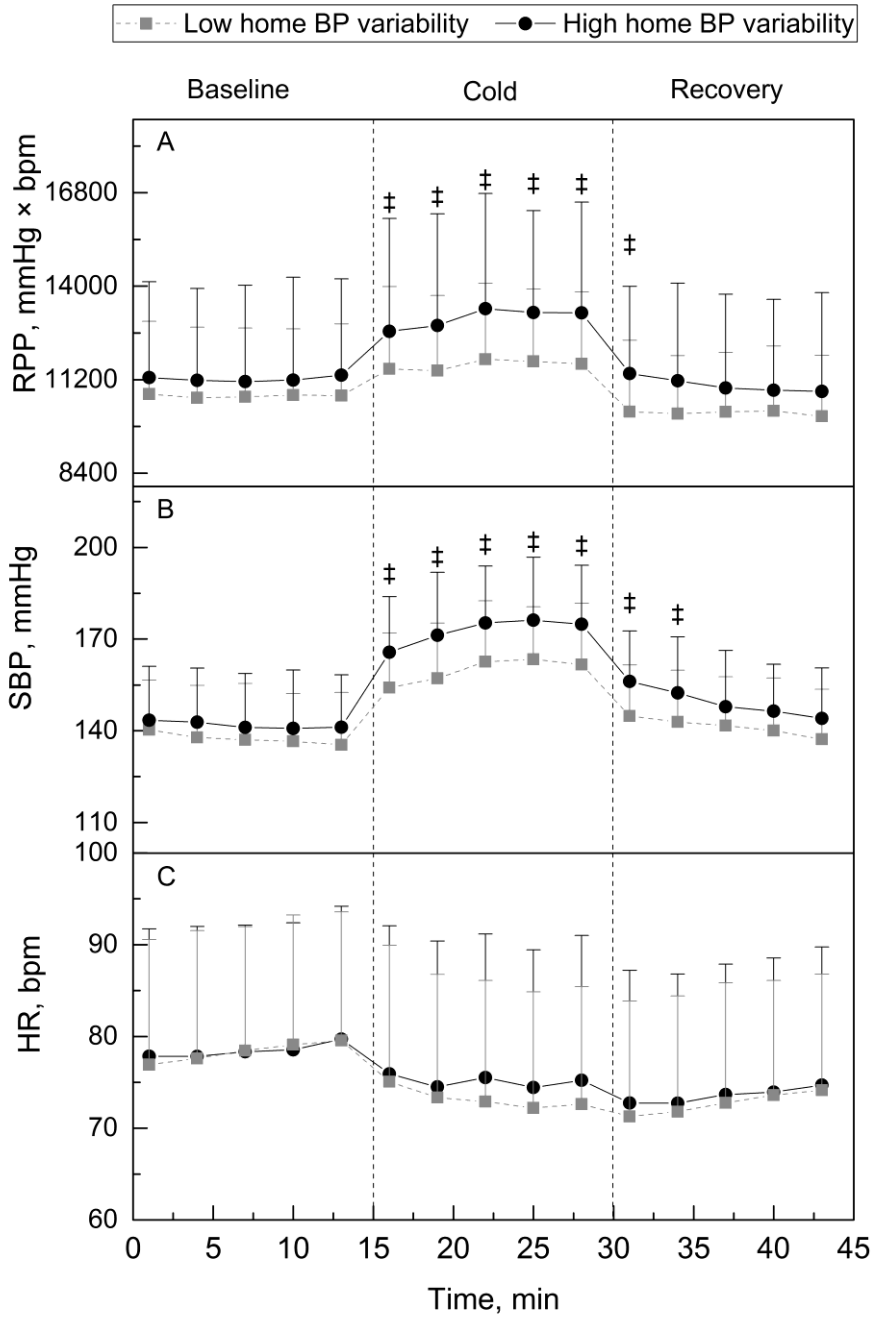


Figure 2. Cardiac workload in cold. Cold exposure increased rate-pressure product (RPP) more among those with higher than lower daily systolic blood pressure variability at home measurements (A). The difference related to augmented systolic blood pressure (SBP) response (B), changes in heart rate (HR) did not differ between the groups (C). ‡$p<0.05$ vs. changes from baseline in those with high home BP variability (time x group interaction), assessed with two-way repeated measures ANOVA and contrast tests.

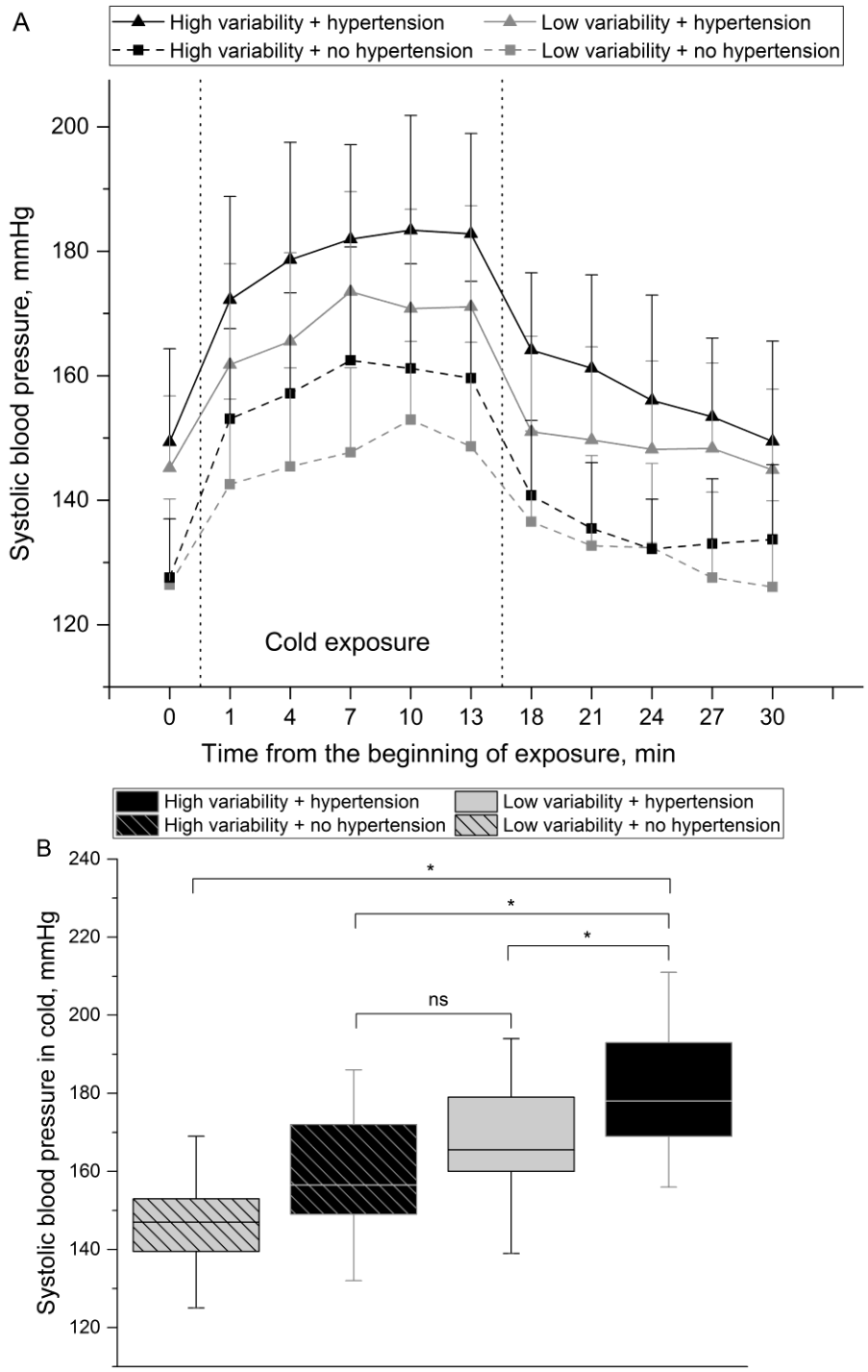
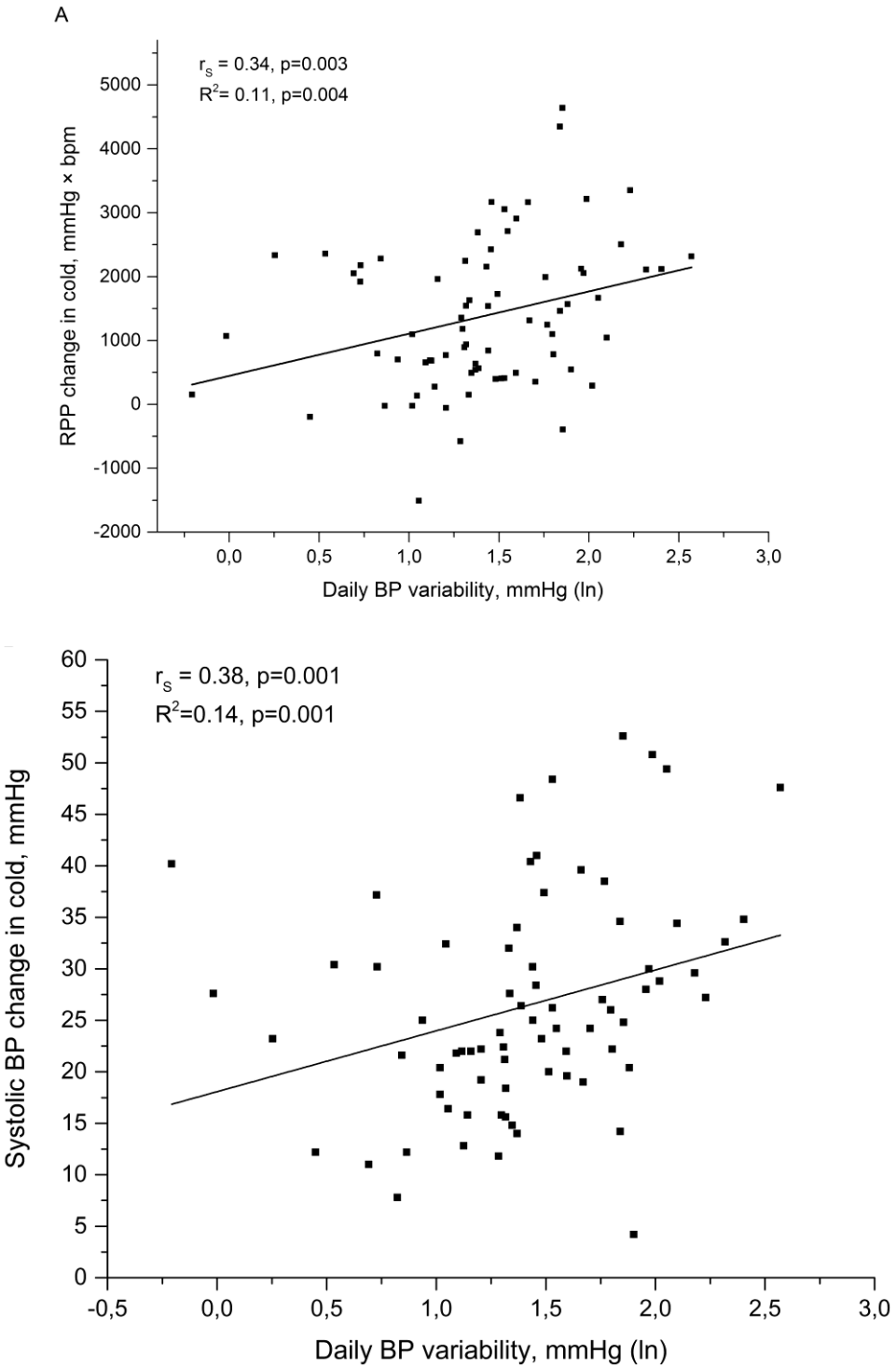


Figure 3. Systolic blood pressure in cold among those with high / low blood pressure variability at home and hypertension / no hypertension. Group means and standard deviation for baseline and each measurement point during and after exposure (A). Mean values of all measurements during cold exposure depicted as boxplot (B). *p<0.05 vs. BP among those with high variability and hypertension, assessed with one-way ANOVA and Tukeys' post hoc tests (B).



513 Figure 4. Scatter plot and regression line with Spearman correlation (rs) and crude R-
514 squared between daily home blood pressure variability and changes from baseline to cold
515 in (A) rate-pressure product (RPP) and (B) systolic blood pressure (BP).

Table 1, Characteristics of the study group.

Variable	**High variability, n=38**	**Low variability, n=37**	**P-values**
Age, years	61 (60 to 62)	60 (59 to 61)	0.19
BMI, kg/m²	27 (26 to 28)	26 (25 to 27)	0.24
BF, %	25 (23 to 27)	22 (21 to 24)	0.035*
Augmentation index, %	14 (11 to 17)	14 (10 to 17)	0.72
Estimated VO2max, ml/kg/min	36 (34 to 38)	38 (36 to 40)	0.24
Diabetes mellitus, n (%)	3 (8)	0 (0)	-
Ever smoker, n (%)	21 (55)	24 (65)	0.48
Alcohol consumption ≥ 1 time/month, n (%)	30 (81)	25 (68)	0.29

Continuous variables are presented as mean values and 95% confidence intervals, categorical variables as number of cases and percentages. BMI, body mass index; BF, body fat percentage; and estimated VO2max, indirectly estimated maximal oxygen uptake. *$p<0.05$ vs. high variability (group), assessed with independent t–tests and chi-square tests.

Table 2, Home blood pressure measurements

Variable	**High variability, n=38**	**Low variability, n=37**	**P-values**
Hypertension, n (%)	25 (66)	21 (57)	0.64
SBP, mmHg	139 (128, 147)	134 (119, 138)	0.04*
DBP, mmHg	83 (80 to 85)	79 (77 to 82)	0.12
HR, bpm	67 (65 to 70)	64 (62 to 66)	0.08
SBP morning, mmHg	138 (125, 146)	133 (117, 139)	0.04*
DBP morning, mmHg	83 (80 to 86)	79 (76 to 82)	0.08
SBP evening, mmHg	138 (128, 149)	136 (119, 141)	0.07
DBP evening, mmHg	82 (79 to 85)	79 (76 to 81)	0.10
Daily SBPV, mmHg	6.0 (4.6, 7.4)	3.1 (2.3, 3.7)	-
Daily SBP CV, %	4.6 (3.6, 5.6)	2.4 (1.8, 2.8)	-

Continuous variables are presented as mean values and 95% confidence intervals or medians and medians and interquartile range (Q1, Q3), and categorical variables as number of cases and percentages. SBP and DBP systolic and diastolic blood pressure; HR, heart rate; SBPV, systolic blood pressure variability; CV, coefficient of variation. Values are computed from home BP measurements of 4 to 7 days and consisting of two measurement both on morning and evening. * $p<0.05$ vs. high variability (group), assessed with independent t–tests, independent samples Mann-Whitney U-test, or chi-square tests.

Table 3, Rate-pressure product, systolic blood pressure, and heart rate in baseline and cold conditions.

	High variability (n=38)			**Low variability (n=37)**		
Variable	Baseline	Cold	Difference	Baseline	Cold	Difference
RPP, (mmHg x bpm)	11200 (10270 to 12140)	13060 (12000 to 14110)*	1850 (1450 to 2250)	10710 (10030 to 11380)	11640 (10920 to 12360)*	930 (610 to 1250)‡
SBP, mmHg	142 (136 to 147)	173 (167 to 179)*	31 (28 to 35)	137 (132 to 143)	160 (154 to 166)*†	23 (20 to 26)‡
HR, bpm	78 (74 to 83)	75 (70 to 80)*	-3 (-5 to -2)	78 (74 to 83)	73 (69 to 77)*	-5 (-7 to -3)

Values are AUC/min group means and 95% confidence intervals. Abbreviations: RPP, rate-pressure product; SBP, systolic blood pressure; HR, heart rate. * $p<0.01$ vs. baseline (time), † $p<0.05$ vs. high home systolic BP variability (group), ‡ $p<0.01$ vs. (cold-baseline) difference among high variability group (interaction), assessed with 2-way repeated measures analysis of variance and contrast tests.

Supplement 1. Regression models for rate-pressure product and systolic blood pressure.

Δ VALUES (COLD-BASELINE)									
	RPP, model 1 (n=74)			RPP, model 2 (n=74)			RPP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
HBPV	**170**	**60**	**0.33†**	**150**	**60**	**0.30***	**140**	**60**	**0.30***
Fat %				40	20	0.18	30	30	0.15
HSBP				0	10	0.06	0	10	0.06
Age							-10	50	-0.01
AI							0	20	0.01
Smoking							-160	300	-0.07
R^2	**0.109**			**0.111**			0.050		
F	**8.76†**			**4.05***			1.58		
	SBP, model 1 (n=74)			SBP, model 2 (n=74)			SBP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
HBPV	**1.8**	**0.5**	**0.38†**	**1.8**	**0.5**	**0.38†**	**1.7**	**0.6**	**0.37†**
Fat %				**0.4**	**0.2**	**0.20***	**0.6**	**0.3**	**0.30***
HSBP				-0.1	0.1	-0.07	-0.1	0.1	-0.11
Age							-0.5	0.4	-0.13
AI							0.1	0.2	0.09
Smoking							-3.8	2.7	-0.17
R^2	**0.143**			**0.148**			**0.162**		
F	**11.97†**			**5.23†**			**3.13†**		
MEAN LEVEL IN COLD									
	lnRPP, model 1 (n=74)			lnRPP, model 2 (n=74)			lnRPP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
HSBP	**0.008**	**0.002**	**0.54†**	**0.008**	**0.002**	**0.49†**	**0.006**	**0.002**	**0.34†**
HBPV				0.004	0.010	0.05	0.004	0.008	0.04
Fat %				**0.008**	**0.004**	**0.21***	0.001	0.004	0.03
Age							0.012	0.007	0.16
AI							-0.001	0.002	-0.02
Smoking							0.003	0.041	0.01
HR							**0.012**	**0.003**	**0.45†**
R^2	**0.289**			**0.306**			**0.497**		
F	**29.29†**			**11.74†**			**10.33†**		
	SBP, model 1 (n=74)			SBP, model 2 (n=74)			SBP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
HSBP	**0.85**	**0.11**	**0.67†**	**0.73**	**0.11**	**0.58†**	**0.78**	**0.12**	**0.63†**
HBPV				**1.81**	**0.65**	**0.24†**	**1.89**	**0.66**	**0.25†**
Fat %				**0.57**	**0.27**	**0.18***	**0.67**	**0.300**	**0.20***
Age							-0,48	0,52	-0,08
AI							0,300	0,19	0,13
Smoking							-3,59	3,21	-0,10
HR							-0,17	0,205	-0,08
R^2	**0.452**			**0.514**			**0.563**		
F	**59.27†**			**26.78†**			**13.15†**		

Estimated regression models for rate-pressure product (RPP) and systolic blood pressure (SBP) changes from baseline to cold conditions, and mean levels in cold conditions. Crude R^2 for one explanatory variable and adjusted R^2 for models including more explanatory variables. HBPV, daily home SBP variability (SD); HSBP, SBP at home; AI, augmentation index; F, F for change in R2; HR, heart rate. * p<0.05, † p<0.01 for contribution.

Supplement 2. Results by applying the coefficient of variation (cv).

Table S2A-B. Characteristics of the study groups and home blood pressure measurements.

A. Characteristic	**High cv, n=38**	**Low cv, n=37**	**P-values**
Age, years	61 (60 to 62)	60 (59 to 61)	0.19
BMI, kg/m²	26 (25 to 28)	26 (25 to 27)	0.76
BF, %	24 (22 to 26)	23 (22 to 25)	0.69
Augmentation index, %	15 (12 to 18)	13 (10 to 16)	0.38
Estimated VO2max, ml/kg/min	37 (35 to 39)	37 (35 to 39)	0.96
Diabetes mellitus, n (%)	2 (5)	1 (3)	-
Ever smoker, n (%)	20 (53)	25 (68)	0.24
Alcohol consumption ≥ 1 time/month, n (%)	29 (76)	26 (70)	0.60
B. Home BP	**High cv, n=38**	**Low cv, n=37**	**P-values**
Hypertension, n (%)	21 (55)	25 (68)	0.35
SBP, mmHg	134 (128 to 139)	135 (130 to 139)	0.80
DBP, mmHg	80 (77 to 84)	81 (78 to 84)	0.77
HR, bpm	66 (63 to 69)	65 (63 to 68)	0.61
SBP morning, mmHg	133 (127 to 139)	133 (129 to 138)	0.98
DBP morning, mmHg	81 (78 to 84)	81 (79 to 84)	0.77
SBP evening, mmHg	134 (129 to 140)	136 (132 to 140)	0.60
DBP evening, mmHg	80 (77 to 83)	81 (78 to 83)	0.68
Daily SBPV, mmHg	5.9 (4.6, 7.4)	3.1 (2.3, 3.8)	-
Daily SBP CV, %	4.6 (3.5, 5.6)	2.4 (1.8, 2.7)	-

Continuous variables are presented as mean values and 95% confidence intervals or medians and medians and interquartile range (Q1, Q3), and categorical variables as number of cases and percentages. cv, coefficient of variation (SD/mean); BMI, body mass index; BF, body fat percentage; estimated VO2max, indirectly estimated maximal oxygen uptake. SBP and DBP systolic and diastolic blood pressure; HR, heart rate; SBPV, systolic blood pressure variability (SD). Values for home BP are computed from measurements of 4 to 7 days and consisting of two measurement both on morning and evening. P-values were assessed with independent t–tests or chi-square tests.

Table S2C. Rate-pressure product, systolic blood pressure, and heart rate in baseline and cold conditions.

	High cv, n=38			**Low cv, n=37**		
Variable	Baseline	Cold	Difference	Baseline	Cold	Difference
RPP, (mmHg x bpm)	10910 (9950 to 11860)	12710 (11610 to 13810)*	1800 (1380 to 2220)	11010 (10350 to 11660)	11990 (11280 to 12700)*	980 (680 to 1290)‡
SBP, mmHg	140 (135 to 146)	171 (164 to 177)*	31 (27 to 34)	139 (134 to 144)	163 (157 to 168)*	24 (21 to 27)‡
HR, bpm	77 (72 to 82)	74 (69 to 79)*	-3 (-5 to -1)	80 (75 to 84)	74 (70 to 79)*	-6 (-8 to -3)

Values are AUC/min group means and 95% confidence intervals. Abbreviations: cv, coefficient of variation; RPP, rate-pressure product; SBP, systolic blood pressure; HR, heart rate. * $p<0.001$ vs. baseline (time), † $p<0.05$ vs. high home systolic BP variability (group), ‡ $p<0.01$ vs. (cold-baseline) difference among high variability group (interaction), assessed with 2-way repeated measures analysis of variance and contrast tests.

Table S2D. Regression models for rate-pressure product and systolic blood pressure.

Δ VALUES (COLD-BASELINE)									
	RPP, model 1 (n=74)			RPP, model 2 (n=74)			RPP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
cv_BPV	**220**	**80**	**0.31†**	**210**	**80**	**0.30†**	**200**	**80**	**0.29***
Fat %				40	20	0.18	30	30	0.14
HSBP				10	10	0.12	10	10	0.13
Age							-10	50	-0.02
AI							0	20	0.00
Smoking							-160	300	-0.07
R^2	**0.097**			**0.116**			0.054		
F	**7.73†**			**4.19†**			1.63		
	SBP, model 1 (n=74)			SBP, model 2 (n=74)			SBP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
cv_BPV	**2.5**	**0.7**	**0.38†**	**2.4**	**0.7**	**0.37†**	**2.4**	**0.8**	**0.36†**
Fat %				0.4	0.2	0.20	**0.6**	**0.3**	**0.28***
HSBP				0.0	0.1	0.01	0.0	0.1	-0.03
Age							-0.5	0.4	-0.14
AI							0.1	0.2	0.09
Smoking							-3.8	2.7	-0.17
R^2	**0.147**			**0.152**			**0.169**		
F	**12.40†**			**5.37†**			**3.23†**		
MEAN LEVEL IN COLD									
	lnRPP, model 1 (n=74)			lnRPP, model 2 (n=74)			lnRPP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
HSBP	**0.008**	**0.002**	**0.54†**	**0.008**	**0.002**	**0.49†**	**0.006**	**0.001**	**0.39†**
cv_BPV				0.005	0.013	0.04	0.004	0.011	0.03
Fat %				**0.008**	**0.004**	**0.21***	0.001	0.004	0.03
Age							0.012	0.007	0.16
AI							-0.001	0.002	-0.02
Smoking							0.002	0.041	0.01
HR							**0.012**	**0.003**	**0.45†**
R^2	**0.289**			**0.306**			**0.497**		
F	**29.29†**			**11.71†**			**10.30†**		
	SBP, model 1 (n=74)			SBP, model 2 (n=74)			SBP, model 3 (n=67)		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
HSBP	**0.85**	**0.11**	**0.67†**	**0.80**	**0.11**	**0.63†**	**0.85**	**0.11**	**0.68†**
cv_BPV				**2.53**	**0.88**	**0.24†**	**2.64**	**0.89**	**0.25†**
Fat %				**0.56**	**0.27**	**0.17***	**0.66**	**0.30**	**0.20***
Age							-0.49	0.52	-0.08
AI							0.29	0.19	0.13
Smoking							-3.60	3.19	-0.10
HR							-0.17	0.20	-0.08
R^2	**0.452**			**0.518**			**0.567**		
F	**59.27†**			**27.16†**			**13.33†**		

Estimated regression models for rate-pressure product (RPP) and systolic blood pressure (SBP) changes from baseline to cold conditions, and mean levels in cold conditions. Crude R^2 for one explanatory variable and adjusted R^2 for models including more explanatory variables. cv_BPV, daily home SBP variability (coefficient of variation i.e. SD/mean); HSBP, mean SBP at home; AI, augmentation index; F, F for change in R2; HR, heart rate. * p<0.05, † p<0.01 for contribution.