

Implications of persistent prehypertension for ageing-related changes in left ventricular geometry and function: The MONICA/KORA Augsburg study

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Background It is unclear whether persistent prehypertension causes structural or functional alterations of the heart.

Methods We examined echocardiographic data of 1005 adults from a population-based survey at baseline in 1994/1995 and at follow-up in 2004/2005. We compared individuals who had either persistently normal (<120 mmHg systolic and <80 mmHg diastolic, $n = 142$) or prehypertensive blood pressure (120–139 mmHg or 80–89 mmHg, $n = 119$) at both examinations using multivariate regression modeling.

Results Over 10 years, left ventricular end-diastolic diameters were stable and did not differ between the two groups. However, the prehypertensive blood pressure group displayed more pronounced ageing-related increases of left ventricular wall thickness (+4.7 versus +11.9%, $P < 0.001$) and left ventricular mass (+8.6 versus +15.7%, $P = 0.006$). Prehypertension was associated with a raised incidence of left ventricular concentric remodeling (adjusted odds ratio 10.7, 95% confidence interval 2.82–40.4) and left ventricular hypertrophy (adjusted odds ratio 5.33, 1.58–17.9). The ratio of early and late diastolic peak transmitral flow velocities (E/A) decreased by 7.7% in the normal blood pressure versus 15.7% in the prehypertensive blood pressure group ($P = 0.003$) and at follow-up the ratio of early diastolic peak transmitral flow and early diastolic peak myocardial relaxation velocities (E/EM) was higher (9.1 versus 8.5, $P = 0.031$) and left atrial size was larger (36.5 versus 35.3 mm, $P = 0.024$) in the prehypertensive blood pressure group. Finally, the adjusted odds ratio for

incident diastolic dysfunction was 2.52 (1.01–6.31) for the prehypertensive blood pressure group.

Conclusions Persistent prehypertension accelerates the development of hypertrophy and diastolic dysfunction of the heart. *J Hypertens* 26:2040–2049 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Abbreviations: E/A, ratio of early and late diastolic peak transmitral flow velocities; E/EM, ratio of early diastolic peak transmitral flow and myocardial relaxation velocities; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVMI, left ventricular mass indexed for body height in meters, normalized to the allometric power of 2.7; nBP, persistently normotensive group; preBP, the persistently prehypertensive group; PWT, posterior wall thicknesses; RWT, relative wall thickness; SWT, septal wall thickness

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Introduction

The geometry and function of the heart change during adult life. Most notably, the left ventricular mass (LVM) increases due to a progressive thickening of the cardiac walls [1–6]. Moreover, the filling pattern of the left

ventricle undergoes characteristic alterations during the ageing process, suggesting a slowly evolving diastolic impairment [7–9]. By contrast, systolic function remains rather constant in most subjects over time [2]. Aside from ageing itself, it is unclear which mechanisms account for these structural and functional changes of the heart. Interestingly, many aspects of this process resemble those of chronic pressure overload [3,4] and, indeed, already young adults with prehypertension were shown to display an elevated wall thickness and an impaired relaxation of the left ventricle [6].

For the MONICA/KORA investigators. The MONICA Augsburg Study was initiated and conducted by Ulrich Keil and coworkers. The KORA Group consists of H.E. Wichmann (speaker), H. Löwel, C. Meisinger, T. Illig, R. Holle, J. John and their coworkers who are responsible for the design and conduct of the KORA studies.

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The definition of what is a normal blood pressure and thus a normal pressure load of the heart is difficult because in Western societies blood pressure (BP) tends to increase in most individuals during the ageing process. For the grey zone between clearly normal and undoubtedly elevated BP, that is, the range of 120–139 mmHg systolic or 80–89 mmHg diastolic BP, The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (The JNC 7 Report) coined the term ‘prehypertension’ [10]. The pathophysiological implications of prehypertension are difficult to define, given that it represents more than 30% of the overall healthy adult population [11]. However, the condition may herald arterial hypertension and has been associated with an increased long-term risk for cardiovascular events [12–14]. Indeed, prehypertension may be considered as a starting point in the cardiovascular disease continuum [15].

In the present study, we investigated whether changes in left ventricular (LV) geometry and function that occur with 10 years of ageing differ between individuals who remain normotensive and those who have persistent prehypertension over that period.

Methods

Study population

Between October 1994 and June 1995, baseline data were derived from the third survey (S3) of the population-based MONICA (Monitoring of Trends and Determinations in Cardiovascular Disease) – Augsburg/KORA (Cooperative Research in the Region of Augsburg) study. Only participants who displayed echocardiographic M-mode tracings with sufficient quality for quantitative measurements at baseline were also eligible for an echocardiographic investigation at follow-up (F3) that was conducted between March 2004 and May 2005. The MONICA Augsburg project was part of the international collaborative WHO MONICA project [16] and investigated the cardiovascular risk factor profile of randomly selected subjects of the resident population in cross-sectional surveys [17,18]. The study design, sampling frame and data collection have been described in detail before [16,18].

A number of S3 baseline participants were not eligible for the F3 follow-up for the following conditions: death (58 subjects), interdiction of contact (63 subjects), migration (41 subjects), and heavy illness (seven subjects). From 1248 eligible individuals, 1005 participated in the follow-up study (net response 80.5%). From 1005 subjects, 80 (7.96%) were excluded because of poor echocardiographic images.

On both occasions, all participants underwent an interview related to personal and family medical history, lifestyle and nutrition, health behavior and psychosocial factors. Body height and weight were measured in light clothing.

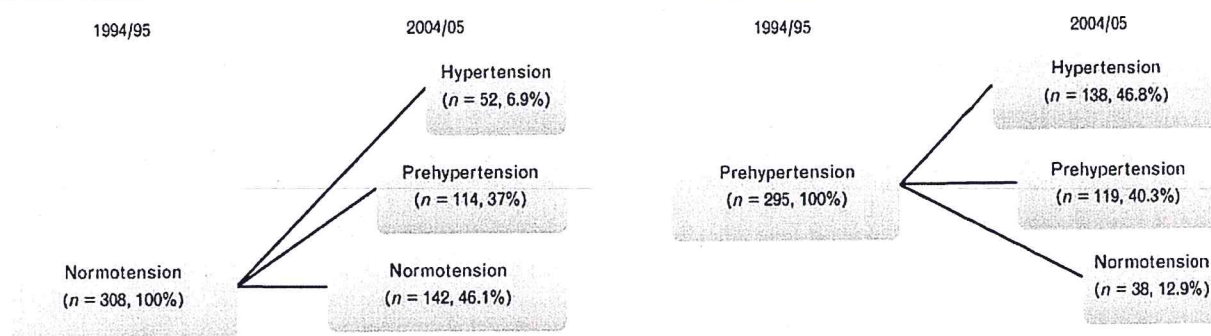
Resting BP was measured, under strictly standardized conditions, at the right arm after participants had been in a sitting position for a minimum of 30 min, using a random zero sphygmomanometer (Hawksley–Germann, Lancing, UK; zero range 0–60 mmHg) at baseline and an oscillometric automatic blood pressure monitor (HEM-705CP; Omron Corporation, Tokyo, Japan) at follow-up. BP values were corrected for differences of observers and devices between the two examinations (see statistical analysis, below). The mean of the second and third BP measurement was used for the present analyses. The BP categories were defined on the basis of the criteria of The JNC 7 Report [10]. Normal BP was defined as a systolic BP of less than 120 mmHg and a diastolic BP of less than 80 mmHg. Prehypertension was defined as either a systolic BP of 120–139 mmHg or a diastolic BP of 80–89 mmHg. Arterial hypertension was considered as either a minimum systolic BP of 140 mmHg or a minimum diastolic BP of 90 mmHg or both or a current intake of antihypertensive medication. If the systolic and diastolic pressure readings belonged to different categories, the higher of the two readings was used to assign the BP category. Diabetes mellitus was defined as disease known to the patient as reported by standard questionnaire.

From the 925 subjects with adequate echocardiographic images, who participated in the follow-up study, we extracted two groups: one with participants who presented with normal BP levels in the baseline and again with normal BP in the follow-up examination (142 individuals), which we called the persistently normotensive (nBP) group. The second group consisted of individuals who presented with prehypertensive BP levels in the baseline study and again with prehypertensive BP in the follow-up study (119 individuals), which we called the persistently prehypertensive (preBP) group. Individuals taking antihypertensive medications at either of the two examinations and those who changed their BP status from baseline to follow-up were excluded from the analyses. Analyses in this report are restricted to the nBP and preBP group only. Figure 1 displays the changes in BP category occurring over time among individuals that initially presented with normal and with prehypertensive BP levels.

Echocardiography

Echocardiograms were performed using commercially available echocardiographs (in 1994/1995: Sonos 1500 with 2.5 or 3.5 MHz transducer; in 2004/2005: Sonos 4500 with 2.0–4.0 MHz transducer; Philips Electronics, Eindhoven, Netherlands). Two-dimensionally guided M-mode echocardiograms were performed on each subject by one of two expert sonographers and M-mode and Doppler tracings were recorded on strip chart paper in the baseline study. In the follow-up study, all echocardiographic investigations including M-mode and Doppler tracings, as well as two-dimensional loops, were digitally stored. To reduce

Fig. 1



Changes of blood pressure categories over time. Left: persistently normotensive group (nBP); right: persistently prehypertensive group (preBP).

observer variability, all tracings were analyzed by a single cardiologist in each study. Echocardiographic measurements were corrected for observer-related differences and device-related differences between the two examinations (see statistical analysis, below).

All M-mode tracings were obtained at 50 mm/s. Measurements of left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameter, septal (SWT) and posterior wall thicknesses (PWT), as well as left atrial diameter, were performed according to the guidelines of the American Society of Echocardiography and the European Association of Echocardiography [19,20]. Wall thickness was calculated as the sum of SWT and PWT and relative wall thickness (RWT) as the ratio (SWT + PWT)/LVEDD. Left ventricular mass (LVM) was calculated according to the formula $LVM [g] = 0.8 \times \{1.04 \times [(LVEDD + SWT + PWT)^3 - (LVEDD)^3] (g)\} + 0.6$ as described by Reichek and Devereux [21,22]. LVM was indexed (LVMI) for body height in metres, normalized to the allometric power of 2.7, which linearizes the relations between LVM and height and identifies the impact of obesity [23]. LV hypertrophy was defined as a LVMI greater than $44 \text{ g/m}^{2.7}$ for women and $48 \text{ g/m}^{2.7}$ for men [20]. LV concentric remodeling was defined as a relative wall thickness more than 0.43 and a LVMI or less $44 \text{ g/m}^{2.7}$ for women and $48 \text{ g/m}^{2.7}$ for men [20]. The left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were determined using the Teichholz equations: $[24] \text{ LVEDV (ml)} = [7/(2.4 + LVEDD)] \times LVEDD^3$ and $\text{LVESV (ml)} = [7/(2.4 + LVESD)] \times LVESD^3$. Using LVEDV and LVESV, the left ventricular ejection fraction $[EF = (LVEDV - LVESV)/LVEDV]$ was calculated. A systolic cardiac dysfunction was defined by an ejection fraction minor than 45%.

All Doppler echocardiographic recordings were registered with 100 mm/s and performed in expiration. Examinations of mitral inflow were performed by pulsed wave Doppler with the sample volume at the tips of the mitral

valve in the apical four-chamber view and early (E wave) and late (A wave) diastolic peak transmitral flow velocities and ratio of early and late velocities (E/A) were determined. Doppler tissue imaging of the mitral annulus was obtained from the apical four-chamber view, using a 1–2 mm sample volume placed in the septal mitral valve annulus. Early (EM wave) and late (AM wave) diastolic peak myocardial relaxation velocities and the ratio of early transmitral flow and early myocardial relaxation velocities (E/EM) were determined according to Nagueh *et al.* [25]. Diastolic dysfunction was defined as E/A less than one. The individuals who presented pseudonormalization, defined as E/A at least one in conjunction with a left atrial end-systolic diameter, in parasternal long axis view, more than 38 mm for women and 40 mm for men, were also considered as having diastolic dysfunction.

All echocardiographic investigations and reading procedures were performed following a standardized protocol. The rank correlation for 144 duplicate LVM measurements by the two sonographers at baseline was 0.91 and there was a mean difference (systematic bias) between observers of 0.9 g with a standard deviation of 10.8 g [26]. In the follow-up study, the quality of the echocardiographic investigations was assessed as previously described by the Study of Health in Pomerania (SHIP) study group [27].

Body fat

Body fat was calculated as body weight minus fat-free mass. Fat-free mass was determined by measurement of bioelectrical impedance analysis with a Body Composition Analyzer TVI-10 (Danziger Medical Technology, Heidelberg, Germany) as previously reported in great detail [26].

Statistical analysis

BP measurements and echocardiography were carried out with different methods in MONICA baseline survey and in KORA follow-up study. The observers had changed after 10 years, as did the devices reflecting technological

progress or lack of appropriate maintenance options, for example, for the mercury sphygmomanometer and the strip paper echocardiograph. Systematic differences between surveys likely to occur due to different measurement methods were assessed by using data from all 1005 individuals examined on both occasions using a mixed regression model that estimated the effect of the measurement methods while adjusting for the confounding factors age, sex, BMI and antihypertensive medication. An interaction term between sex and study was included to allow for statistically significant effects of measurement devices in men and women. We specified a linear model with a common correlation between the two measurements from a single participant, with correlation being the same for all individuals, by introducing individual random intercepts. Systematic differences estimated from these models were used to derive correction values, which were applied to all values recorded in the baseline survey of 1994/1995.

The subjects were compared with regard to their baseline characteristics using frequencies, mean values and standard deviations. Statistical significances were tested with unpaired *t* tests for continuous and chi-squared tests for categorical variables. In the persistent nBP and persistent preBP groups we considered the absolute differences between the two groups at baseline and at follow-up as well as the relative changes, for each group, from baseline, that is (follow-up – baseline)/baseline, expressed in percent. Adjusted mean values in the cross-sectional analysis of baseline and follow-up for clinical, laboratory and echocardiographic measurements were calculated with a linear regression model that included age, gender, height^{2.7} and body fat. For the analyses of the relative changes over the 10-year period, the model included age, gender, height^{2.7}, plus the baseline value of body fat and its relative changes over the 10-year period. To account for regression to the mean effects, in the variable for

which the relative changes were studied, we additionally adjusted for the overall baseline mean. Incidence odds ratios (ORs) for left ventricular (LV) concentric remodeling, LV hypertrophy and diastolic dysfunction, comparing the persistent preBP group with the persistent nBP group, were calculated with a logistic regression model that included age, gender, height^{2.7}, the baseline value of body fat and its relative changes over the 10-year period. For diastolic dysfunction, the model also included the presence of diabetes (at baseline and at follow-up). All analyses were performed using SPSS version 14.0.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Clinical and laboratorial characteristics of the study

The characteristics of the study participants are shown in Table 1. We identified 142 individuals with persistent normotension and 119 individuals with persistent prehypertension. More than two-thirds of individuals in the persistent nBP group were women. Individuals in the persistent preBP group had, on average, higher weights and more unfavorable cholesterol levels. There were no individuals, in both groups, with severe aortic or mitral regurgitation or systolic heart failure. One individual (0.8%), in the preBP group (*P* = 0.454) presented a history of myocardial infarct.

Left ventricular mass and geometry

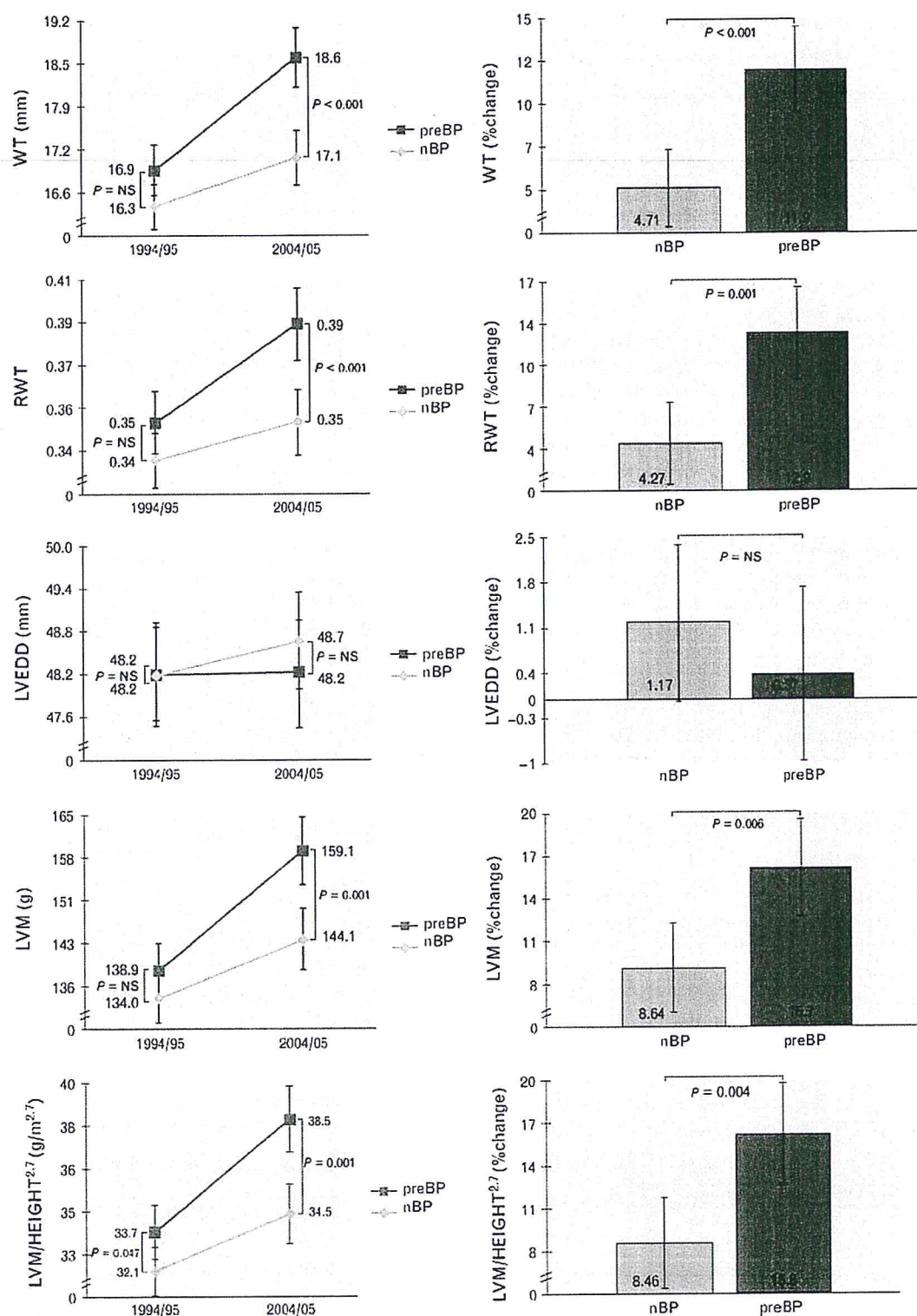
In cross-sectional comparisons of the baseline study, LV wall thickness, relative wall thickness, LV end-diastolic diameter and LV mass were similar in the persistently normal and prehypertensive groups (Fig. 2). LV mass indexed to height^{2.7} was slightly higher in the preBP group. At the follow-up examination, the persistent preBP group had significantly higher adjusted mean values for absolute as well as for relative wall thickness, LV mass and LV mass^{2.7} as compared with the persistent nBP group, whereas LV end-diastolic diameter was not

Table 1 Characteristics of the persistently normotensive and persistently prehypertensive individuals at the baseline (1994/1995) and the follow-up examination (2004/2005) of the MONICA-KORA cohort study

	1994/1995			2004/2005		
	nBP (n = 142)	preBP (n = 119)	<i>P</i>	nBP (n = 142)	nBP (n = 142)	<i>P</i>
Systolic blood pressure (mmHg)	103.6 ± 8.34	122.6 ± 8.49	<0.001	107.2 ± 7.51	127.8 ± 6.57	<0.001
Diastolic blood pressure (mmHg)	69.9 ± 6.16	80.1 ± 6.65	<0.001	71.3 ± 4.7	81.1 ± 5.29	0.001
Body weight (kg)	65.5 ± 11.5	76 ± 12.7	<0.001	67.4 ± 12.2	78.2 ± 12.8	<0.001
Fat-free mass (kg)	46.9 ± 8.11	54.7 ± 9.44	<0.001	46.9 ± 8.24	55 ± 9.81	<0.001
Body fat (kg)	18.6 ± 6.08	21.3 ± 7.95	0.002	20.5 ± 6.9	23.2 ± 7.6	0.003
Total cholesterol (mg/dl)	211.2 ± 39.5	226.7 ± 40.6	0.002	207.8 ± 36.7	219.8 ± 35.2	0.008
LDL cholesterol (mg/dl)	120.9 ± 41.2	138.2 ± 42.3	0.001	117.6 ± 30.5	130 ± 30	0.001
HDL cholesterol (mg/dl)	59.8 ± 17.4	54.5 ± 15.8	0.011	63.4 ± 16.4	57.9 ± 15.1	0.006
Diabetes (%)	0 (0)	1 (0.8)	NS	1 (0.7)	3 (2.5)	NS
Current smoker (%)	44 (31)	35 (29.4)	NS	34 (23.9)	34 (28.8)	NS
Men (%)	28 (19.7)			75 (63)		
Women (%)	114 (80.3)			44 (37)		<0.001
Age at baseline (years)	39.7 ± 10.3			42.2 ± 11		NS

Values are presented as means ± standard deviation. *P* values are given for the comparison between nBP and preBP. HDL, high density lipoproteins; LDL, low density lipoproteins; MONICA-KORA, monitoring of trends and determinations in cardiovascular disease; nBP, normal blood pressure; NS, not significant; preBP, prehypertensive blood pressure.

Fig. 2



Left-hand panels show the mean values and the 95% confidence interval in 1994/1995 and 2004/2005 (adjusted for age, gender, height^{2.7} and body fat) for the groups with persistent normotension (nBP) and prehypertension (preBP). Right-hand panels show the relative changes and the 95% confidence interval over the 10-year period (adjusted for age, gender, height^{2.7}, the baseline value of the respective variable under study plus the baseline value of body fat and its relative changes over the 10-year period). Left ventricular mass (LVM) was indexed and not adjusted for height^{2.7}. LVEDD, left ventricular end-diastolic diameter; RWT, relative wall thickness; WT, wall thickness.

Table 2 Crude incidences and prevalences for left ventricular concentric remodeling, left ventricular hypertrophy and diastolic dysfunction comparing the groups with persistent normotension and prehypertension

	Incidence (%)			Prevalence (%)		
	nBP	preBP	<i>P</i>	nBP	preBP	<i>P</i>
LV concentric remodeling ^a	2.33	24.1	<0.001	4.38	25.5	<0.001
Left ventricular hypertrophy ^b	2.86	17.1	<0.001	3.52	21.0	<0.001
Diastolic dysfunction ^c	12.6	42.1	<0.001	21.3	55.1	<0.001

LV, left ventricular; LVMI, left ventricular mass indexed; nBP, normal blood pressure; preBP, prehypertensive blood pressure. ^a Defined by relative wall thickness greater than 0.43 and a LVMI or less 44 g/m^{2.7} for women and 48 g/m^{2.7} for men [20]. ^b Defined by LVMI greater than 44 g/m^{2.7} for women and 48 g/m^{2.7} for men [20]. ^c Defined by *E/A* less than one or, to include pseudonormalization, by *E/A* at least one in conjunction with a left atrial end-systolic diameter, in parasternal long axis view, greater than 38 mm for women and 40 mm for men.

different between the two groups (Fig. 2). Consequently, when assessing the temporal changes in terms of relative changes from baseline, the persistent preBP group displayed significantly more pronounced relative changes of absolute and of relative wall thickness as well as of LV mass and LV mass^{2.7} than the nBP group (Fig. 2). Stratified analyses in both men and women confirmed that the greater relative increase of wall thickness found in the preBP group was statistically significant and of similar magnitude in both genders (men: +11.6 versus +4.48%, *P*=0.006; women: +11.7 versus +4.99%, *P*=0.018). By contrast, relative changes over time in LV end-diastolic diameter were nonsignificant in the nBP and preBP groups.

The 10-year crude incidences and prevalences of LV concentric remodeling and LV hypertrophy were substantially higher in the preBP group as compared with the nBP group (Table 2). The crude OR was only slightly attenuated by the adjustment for confounders (Table 3).

Left ventricular function

No marked differences were found crosssectionally between the nBP and preBP group for left atrial diameter as well as functional parameters of systole and diastole in the baseline study in 1994/1995. Likewise, the relative changes of ejection fraction were small (+0.7% in the persistent nBP versus +2.5% in the persistent preBP group) and not significantly different as compared with baseline measurements within the respective group or in between groups. In the follow-up study, the ejection fraction was 67.7% in the persistent nBP versus 69.6%

in the persistent preBP. By contrast, echocardiographic parameters reflecting diastolic function showed differential relative changes. Particularly, the *E/A* ratio, which was 1.56 in the persistent nBP versus 1.52 in the persistent preBP group (not significantly different) in the baseline study, decreased (*P*=0.003) more profoundly in the preBP than in the nBP group (Fig. 3). In addition, the left atrial size increased significantly more during the 10-years interval (Fig. 3) and was larger by the time of the follow-up study (36.5 versus 35.3 mm, *P*=0.024) in the preBP group. Moreover, in a cross-section analysis of the follow-up study, individuals in the preBP group showed a significantly less favorable *E/EM* ratio as compared with the nBP group (Fig. 3). Other indicators of diastolic dysfunction (deceleration time and left atrial area) didn't show significant differences between the two groups. Finally, the crude incidence and prevalence of diastolic dysfunction was higher in the preBP group as compared with the nBP group (Table 2) and the crude OR was only slightly attenuated after the adjustment for confounders (Table 3).

Discussion

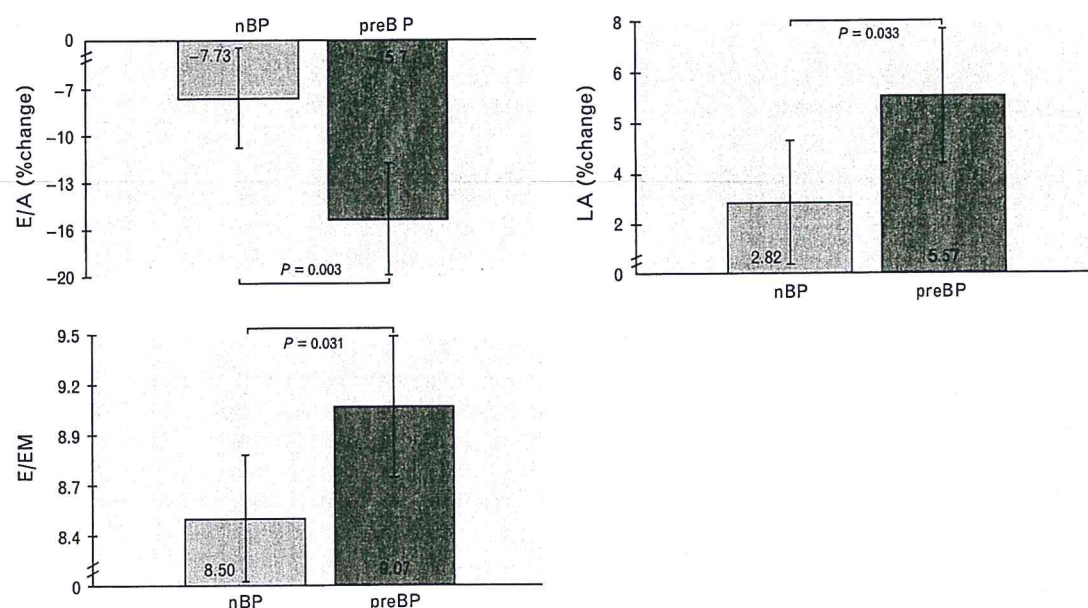
In agreement with cross-sectional patient samples [28,29] we confirmed that age-related adaptations in cardiac geometry and function might occur already to a moderate degree in healthy individuals with a normal BP. This adaptation, however, was significantly more pronounced in individuals in whom the BP persisted in the prehypertensive range (i.e., between 120 and 139 mmHg systolic or between 80 and 89 mmHg diastolic without medication for 10 years). Our observations were made

Table 3 Odds ratio for left ventricular concentric remodeling, left ventricular hypertrophy and diastolic dysfunction comparing the groups with persistent normotension and prehypertension

Groups (nBP)	Odds ratio (95% confidence interval, <i>P</i>)	
	Unadjusted (1.00)	Adjusted* (1.00)
preBP		
LV concentric remodeling ^a	13.4 (3.85 to 46.5, <i>P</i> <0.001)	10.7 (2.82 to 40.4, <i>P</i> <0.001)
Left ventricular hypertrophy ^b	7.02 (2.31 to 21.3, <i>P</i> =0.001)	5.33 (1.58 to 17.9, <i>P</i> =0.007)
Diastolic dysfunction ^c	5.04 (2.41 to 10.5, <i>P</i> <0.001)	2.52 (1.01 to 6.31, <i>P</i> =0.048)

LV, left ventricular; LVMI, left ventricular mass indexed; nBP, normal blood pressure; preBP, prehypertensive blood pressure. * Adjusted for age, gender, height^{2.7}, the baseline value of body fat and its relative changes over the 10-year period. For diastolic dysfunction further adjustment was made for the presence of diabetes (either at baseline or at follow-up or both). ^a Defined by relative wall thickness greater than 0.43 and a LVMI or less 44 g/m^{2.7} for women and 48 g/m^{2.7} for men [20]. ^b Defined by LVMI greater than 44 g/m^{2.7} for women and 48 g/m^{2.7} for men [20]. ^c Defined by *E/A* less than one or, to include pseudonormalization, by *E/A* at least one in conjunction with a left atrial end-systolic diameter, in parasternal long axis view, greater than 38 mm for women and 40 mm for men.

Fig. 3



Panels above show the relative changes and the 95% confidence interval over the 10-year period (adjusted for age, gender, height^{2.7}, the baseline value of the respective variable under study plus the baseline value of body fat and its relative changes over the 10-year period) of the *E/A* ratio (left) and of the left atrial (LA) size (right) for the groups with persistent normotension (nBP) and prehypertension (preBP). Panel below shows the mean values and the 95% confidence interval at the follow-up study in 2004/2005 (adjusted for age, gender, height^{2.7} and body fat) for the *E/EM* ratio.

in a middle-aged, population-based sample after adjustment for multiple confounders including changes in body composition. Therefore, prehypertension seems sufficient to induce substantial cardiac remodeling processes in such subjects involving an increase in LV wall thickness and mass, an impairment of LV filling pattern, and a progressive enlargement of the left atrium.

Progressive hypertrophy and diastolic impairment are characteristic for chronic cardiac pressure overload and already well established phenomena in patients with hypertension [30]. The present study adds to this evidence in that it focused on individuals who constantly had either normal or prehypertensive BP thereby deliberately avoiding contamination of the observed cardiac effects secondary to hypertension. The results demonstrate rather clearly that such alterations of the heart can already occur with increased frequency at BP levels with an average of 127/81 mmHg if they persist over a period of 10 years.

We excluded close to 50% of individuals with prehypertension at baseline because they left the prehypertensive BP range and became hypertensive during the follow-up period. Actually, the changes of LV wall thickness and diastolic function were even more pronounced in this group (data not shown) such that the long-term cardiac implications associated with prehypertension, at a given point in time, may be even underestimated by

the present analyses of our restricted study sample. Nevertheless, our prospective observations provide etiological support to cross-sectional analyses that documented a linear relationship between BP and LVM even at systolic BP levels below 140 mmHg [6,31].

End-diastolic diameters did neither differ between the normotensive and prehypertensive groups nor did they change on average over time. Thus, the progressive increase in LV mass found in prehypertensive individuals results predominantly from the increase in wall thickness in this group. Such pattern characterizes LV concentric remodeling of the heart, which is implicated as a disadvantageous adaption [3,4] and appears to be a characteristic of the ageing heart [28,29]. Indeed, LV concentric remodeling has been shown to result in diastolic filling abnormalities, increased oxygen requirement of myocardium, as well as a greater risk for arrhythmias and sudden death [9,32].

In the literature, there is some variability in the prevalence of LV concentric remodeling and LV hypertrophy [33–38]. Our data are consistent in the sense that a sizable proportion of normotensives individuals exhibits the echocardiographic criteria of LV hypertrophy, with our study being in the upper range of what has been reported [33–38]. In the Framingham Heart Study, normotensive, nonobese individuals, free of cardiopulmonary disease, showed a prevalence of LV hypertrophy

of 16 and 19% in men and women, respectively [38]. The prevalence of LV concentric remodeling in Framingham study [34] was 8% for men and women, that is lower than in our sample, but the relative wall thickness cut-off was higher than ours (0.45 against 0.43). Besides that, a cross-sectional Italian population-based study [36] showed a lower prevalence than our study for LV concentric remodeling (9.5%) and for LV hypertrophy (14%) in individuals with mild untreated hypertension (mean systolic BP was 148 mmHg). However, these individuals were less obese than in our sample. Besides that, definition of LV hypertrophy is extremely variable and based on as many 19 different echocardiographic criteria [39], which may partly explain the different prevalences in LV hypertrophy and LV concentric remodeling in previous studies. Actually, as far we know, our study is the first one to use the lower cut-off that has been suggested by the American Society of Echocardiography/European Association of Echocardiography [20]. Moreover, there is little data on the incidence of these conditions. One important point is that our population was exposed to 10 or more years of prehypertensive BP levels. It is, therefore, possible that the prevalences of cardiac structural abnormalities depend on a time factor, that is, that the prehypertensive BP levels need to be maintained for some time until echocardiographic abnormalities occur.

Systolic function did not display any substantial changes in the two BP groups in the 10-year interval. This may indicate that persistent prehypertensive BP, at least in the time frame of our study, does not affect contractility. Alternatively, our methods might not have been sensitive enough to discover a subtle deterioration of systolic function. By contrast, measures of diastolic function showed significant impairments. Specifically, measurements of relaxation velocities, mitral inflow pattern and left atrial size were all significantly more markedly altered in the prehypertensive group. Recently, a cross-sectional study on young adults with early stages of hypertension concluded that the first cardiac alterations are LV geometric abnormalities, whereas, LV diastolic function seemed only marginally affected, even when multiple parameters of LV filling were taken into account [40]. Our results are clearly more marked, probably due to the fact that our population was older and, in particular, that it was chronically exposed to prehypertensive BP levels.

Our data highlight the pathophysiological implications of prehypertension, which seems to amplify the cardiac responses during the ageing process. In fact, LV concentric remodeling of the heart and subsequent development of diastolic dysfunction are important intermediate steps towards the clinical manifestation of diastolic heart failure that is now a predominant type of symptomatic heart failure and cause of morbidity and mortality in the ageing populations of the industrialized nations [9,41,42].

An important issue is the translation of the present findings into the management of individuals with prehypertension. Evolving evidence suggest that prehypertensive persons carry an increased cardiovascular risk [12–15]. Indeed, the risk of cardiovascular events appears to double for every increment by 20 mmHg systolic or 10 mmHg diastolic BP, starting at levels as low as 115 mmHg systolic and 75 mmHg diastolic [43]. The present study suggests that prehypertension is causally associated with LV concentric remodeling and impaired diastolic function of the heart. This may explain some of the cardiovascular risks already found at BP levels well below the range of established hypertension. Interestingly, we show that these adaptations occur in the absence of progression to hypertension and after adjustment to potentially confounding factors. Thus, a more aggressive monitoring of individuals with persistent prehypertension including echocardiographic assessment of LV geometry and diastolic dysfunction might be considered [44]. In this regard, it is important to realize that nonpharmacological treatment options may have profound effects on both prehypertension and on cardiac remodeling [45,46].

Study limitations

This study was conducted in white individuals, so the results cannot be extended to other ethnic groups. The study sample was derived from a population-based sampling frame but loss to follow-up may have introduced some imbalances in our participants. BP measurements and echocardiography were carried out with different methods in MONICA baseline survey and in KORA follow-up study. The observers had changed after 10 years, as did the devices reflecting technological progress or lack of appropriate maintenance options, for example, for the mercury sphygmomanometer and the strip paper echocardiograph. Systematic differences between surveys likely to occur due to different measurement methods were assessed by using data from all 1005 individuals examined on both occasions using a mixed regression model that estimated the effect of the measurement methods as adjusting for the confounding factors age, sex, BMI and antihypertensive medication. An interaction term between sex and study was included to allow for statistically significant effects of measurement devices in men and women. We specified a linear model with a common correlation between the two measurements from a single participant, with correlation being the same for all individuals, by introducing individual random intercepts. Systematic differences estimated from these models were used to derive correction values that were applied to all values recorded in the baseline survey of 1994/1995. However, as the groups included in this analysis were mostly middle-aged and healthy we do not consider the quantitative impact of this selection as highly relevant. In addition, despite extensive efforts to standardize measurements, the inevitable employment of different observers and the use of novel echocardiographic and

BP measurement devices affected the comparisons. On the contrary, we accounted for these differences through stringent statistical methods of correction. More importantly, we cannot conceive of methodological differences arising from these corrections that would lead to systematically biased cardiac results between the persistent nBP and preBP groups. Additionally, determination of diastolic function with noninvasive techniques has its limitations. In the baseline study, only the mitral inflow pattern and atrial size were evaluated and available for comparisons with the follow-up findings. However, the consistency of the findings, including Doppler tissue at follow-up and changes in atrial size, strongly supports our conclusion of differentially altered diastolic function in the persistent prehypertensive group. Finally, exclusion of individuals who changed their BP category during long-term follow-up certainly affected our observations. Indeed, at the baseline survey BP levels of the preBP group were only mildly into the prehypertensive range (because many individuals with higher BP readings left the prehypertensive range, became hypertensive and thus were excluded). This may explain why at baseline most structural and functional parameters of the heart were rather similar in the normotensive and, at that time, mildly prehypertensive group. In addition to that, this definition may explain some differences with cross-sectional studies that reflect the entire spectrum of prevalent prehypertension. Nevertheless, contamination of our findings by individuals who subsequently had developed hypertension during follow-up would have counteracted our intention to study the effects of persistent prehypertension. Moreover, the relative change in systolic BP was used as a cofounder in a model comparing changes in LV mass, in the two groups, and has no influence on the results. Thus, we accepted the fact that our data may indeed underestimate the implications of prehypertension for ageing-related adaptations of the heart.

In conclusion, long-standing prehypertension appears to be associated with a significantly increased occurrence of LV concentric remodeling as well as a deterioration of diastolic ventricular function. These changes were significantly stronger than those observed during the ageing process of individuals with normotension. Thus, our data suggest that persistent prehypertension amplifies the typical age-related adaptations of the heart. Future studies need to assess whether lifestyle modifications or medications can effectively reduce cardiac remodeling and, subsequently, the risk of diastolic heart failure in individuals with prehypertension.

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