

# Relation between hypertension and systolic and diastolic left ventricular function including segmental strain and strain rate

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## Abstract

**Background** Left ventricular (LV) systolic and diastolic functions are important cardiovascular risk predictors in patients with hypertension. However, data on segmental, layer-specific strain, and diastolic strain rates in these patients are limited. The aim of this study was to investigate segmental two-dimensional strain rate imaging (SRI)-derived parameters to characterize LV systolic and diastolic function in hypertensive individuals compared with that in normotensive individuals. **Methods** The study sample comprised 1194 participants from population studies in Arkhangelsk and Novosibirsk, Russia, and 1013 individuals from the Seventh Tromsø Study in Norway. The study population was divided into four subgroups: A. healthy individuals with normal blood pressure (BP), B. individuals on antihypertensive medication with normal BP, C. individuals with systolic BP 140–159 mmHg and/or diastolic BP >90 mm HG, and D. individuals with systolic BP [?]160 mmHg. In addition to conventional echocardiographic parameters, global and segmental layer-specific strains and strain rates in early diastole and atrial contraction (SR E, SR A) were extracted. The strain and SR (S/SR) analysis included only segments without strain curve artifacts. **Results** With increasing BP, the systolic and diastolic global and segmental S/SR gradually decreased. SR E, a marker of impaired relaxation, showed the most distinctive differences between the groups. In normotensive controls and the three hypertension groups, all segmental parameters displayed apico-basal gradients, with the lowest S/SR in the basal septal and highest in apical segments. Only SR A did not differ between the segmental groups but increased gradually with increasing BP. End-systolic strain showed incremental epi-towards endocardial gradients, irrespective of the study group. **Conclusion** Arterial hypertension reduces global and segmental systolic and diastolic left ventricular S/SR parameters. Impaired relaxation determined by SR E is the dominant factor of diastolic dysfunction, whereas end-diastolic compliance (by SR A) does not seem to be influenced by different degrees of hypertension. Segmental strain, SR E and SR A provide new insights into the LV cardiomechanics in hypertensive hearts.

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Data Availability Statement

The data that support the findings of this study are available from the Know Your Heart and the Tromsø Study, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data from the Know Your Heart Study and this study are, however, available from the authors upon reasonable request with permission from the Know Your Heart Steering Group and the corresponding author of this manuscript.

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Conflict of Interest Disclosure

HS has received lecture fees from Amgen and Novartis.

Ethics Approval Statement

This study complied with the principles of the Declaration of Helsinki. The Know Your Heart study was approved by the ethics committees of the London School of Hygiene & Tropical Medicine (approval number 8808 received 24.02.2015), Novosibirsk State Medical University (approval number 75 received 21/05/2015),

the Institute of Preventative Medicine, Novosibirsk (no number; approval received 26/12/2014), and the Northern State Medical University, Arkhangelsk (approval number 01/01–15 received 27/01/2015). All patients gave written informed consent.

### *Key words*

Speckle tracking imaging

Segmental strain and strain rate

Layer strain

Arterial hypertension

Blood pressure

### *Abbreviations*

S/SR: strain and strain rate

GLS: global longitudinal strain

AVC: aortic valve closure

CCTA: coronary computed tomography angiography

CVD: cardiovascular disease

SR S: strain rate at peak systole

SR E: strain rate in early diastole

SR A: strain rate in atrial contraction

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Left ventricular (LV) systolic and diastolic functions are important cardiovascular risk predictors in patients with hypertension. However, data on segmental, layer-specific strain, and diastolic strain rates in these patients are limited. The aim of this study was to investigate segmental two-dimensional strain rate imaging (SRI)-derived parameters to characterize LV systolic and diastolic function in hypertensive individuals compared with that in normotensive individuals.

#### Methods

The study sample comprised 1194 participants from population studies in Arkhangelsk and Novosibirsk, Russia, and 1013 individuals from the Seventh Tromsø Study in Norway. The study population was divided into four subgroups: A. healthy individuals with normal blood pressure (BP), B. individuals on antihypertensive medication with normal BP, C. individuals with systolic BP 140–159 mmHg and/or diastolic BP >90 mm HG, and D. individuals with systolic BP  $\geq$  160 mmHg. In addition to conventional echocardiographic parameters, global and segmental layer-specific strains and strain rates in early diastole and atrial contraction (SR E, SR A) were extracted. The strain and SR (S/SR) analysis included only segments without strain curve artifacts.

#### Results

With increasing BP, the systolic and diastolic global and segmental S/SR gradually decreased. SR E, a marker of impaired relaxation, showed the most distinctive differences between the groups. In normotensive controls and the three hypertension groups, all segmental parameters displayed apico-basal gradients, with the lowest S/SR in the basal septal and highest in apical segments. Only SR A did not differ between

the segmental groups but increased gradually with increasing BP. End-systolic strain showed incremental epi-towards endocardial gradients, irrespective of the study group.

## Conclusion

Arterial hypertension reduces global and segmental systolic and diastolic left ventricular S/SR parameters. Impaired relaxation determined by SR E is the dominant factor of diastolic dysfunction, whereas end-diastolic compliance (by SR A) does not seem to be influenced by different degrees of hypertension. Segmental strain, SR E and SR A provide new insights into the LV cardiomechanics in hypertensive hearts.

## INTRODUCTION

Among several risk factors, hypertension remains the leading cause of cardiovascular mortality among several risk factors (1). Myocardial structural and geometrical changes (i.e., left ventricular concentric remodeling and eccentric and concentric left ventricular hypertrophy) are accompanied by altered systolic and diastolic function (2). Thus, current guidelines have primarily implemented geometrical measurements of the left ventricle (LV) for cardiovascular risk management in the hypertensive population. However, previous studies on systolic and diastolic functional markers of the LV have indicated an even higher potential for risk stratification (Kuznetsova 2016).

Speckle-tracking echocardiography provides a comprehensive assessment of the global and segmental myocardial mechanics. Global longitudinal strain (GLS) is more sensitive than LV ejection fraction in detecting subtle systolic dysfunction even in the absence of overt heart failure (3). In addition, GLS is a more sensitive marker and robust predictor of cardiovascular events (4, 5). Segmental strain and strain rate (S/SR) reflect altered global and regional functions owing to geometrical changes in hypertensive hearts (6). However, only a limited number of studies have focused on segmental strain in hypertensive populations, and only a few studies have compared global longitudinal or regional myocardial function between patients with hypertension and those with normal cardiac function (7-10). The strain values of different myocardial layers have been reported to be of potential clinical interest (4, 5, 11) but have not been specifically described in subjects with hypertension. Segmental diastolic strain rates in early diastole and atrial contraction (SR E and SR A) have not been previously described in hypertensive populations.

The aim of this study was to investigate the S/SR-based characteristics of the LV in hypertensive subjects and to compare segmental layer S/SR with normal subjects. Patients with hypertension vary from those with accidentally measured high blood pressure to those with well or insufficiently regulated blood pressure under medication. To gain more knowledge about the effect of high blood pressure or well-regulated hypertension on cardiac global and segmental function, this study also aimed to investigate functional differences between groups graded by antihypertensive treatment and the degree of BP elevation. Higher basal-apical gradients due to high afterload in the healthy hypertensive population may be confused with pathological changes. Therefore, this study further aimed to determine the expected segmental S/SR values in an otherwise healthy hypertensive population.

## METHODS

### Study population

The study population consisted of participants of the Seventh Tromso Study (Tromso7) in Norway and the Know Your Heart (KYH) study in Russia. Both studies were cross-sectional and population-based. Tromso7 was conducted in the Tromso municipality between March 2015 and October 2016, and KYH from 2015 to 2018 in Arkhangelsk and Novosibirsk. The two studies were conducted in parallel and included questionnaires, health examinations, and biological sample collection. During the development phases, several aspects of data collection between the studies were harmonized, including the echocardiography protocols. Echocardiograms were performed in 2340 participants from Tromso7 and 4521 from Russia.

In Tromsø7, the inclusion age range was 40 years and older, without an upper limit, whereas KYH included participants aged 35–69 years. For the present study, a stratified random selection of participants was made, giving three equal-sized age groups (40–49, 50–59, and 60–69 years old). As shown in Figure 1, the sample comprised participants from Tromsø7 (50%), Arkhangelsk (25%) and Novosibirsk (25%). A total of 1194 participants from KYH (594 women and 600 men) and 1013 participants from Tromsø 7 (553 women and 460 men), aged 40–69 years, were selected.

### Definition of study groups

Figure 1 displays a flow chart of in- and exclusion of study participants. Individuals with cardiac disease that could impact myocardial function were excluded from the study population. Therefore, we excluded subjects with valvular heart disease (aortic insufficiency grade 3 and 4); aortic valve mean pressure gradient  $>25$  mmHg; mitral insufficiency degree 3 and 4; moderate and high-grade mitral stenosis; history, or objective indicators of previous coronary artery disease (classes 1.1 – 1.2.7. of Minnesota Code) or myocardial diseases; ECG with QRS  $>130$  ms, EF  $<45\%$ .

Hypertension was defined as either increased systolic or diastolic BP during the visit or the current use of antihypertensive medication. The study population was divided into groups using the following criteria: systolic BP  $\geq 140$  mmHg and diastolic BP  $\geq 90$  mmHg without antihypertensive medication (group A, normotensive); systolic BP  $\geq 140$  mmHg and diastolic BP  $\geq 90$  mmHg with antihypertensive medication (group B, controlled hypertension); systolic BP 140–159 mmHg and/or diastolic BP  $>90$  mmHg (group C), and systolic BP  $\geq 160$  mmHg (group D). Groups C and D were defined as hypertensive irrespective of the antihypertensive medication.

Participants were classified as taking antihypertensive medications when self-reported to be currently taking renin-angiotensin system drugs, beta-blockers, calcium antagonists, or diuretics.

### Data collection and echocardiography in KYH and Tromsø7

The transthoracic echocardiography was performed in the left lateral decubitus position using commercially available GE Healthcare systems: Vivid q equipped with a 1.5–3.6 MHz sector matrix transducer in KYH study and high-end machine E9 with single crystal matrix sector probe of 1.5–4.6 MHz in Tromsø7. From parasternal and apical views, two-dimensional (2D) grayscale images and pulsed, continuous, and color Doppler data were acquired. Both studies included apical four-chamber (4CH) and two-chamber (2CH) views, while apical long-axis views (APLAX) were only acquired in Tromsø7. 2D-images were obtained at a frame rate of at least 50 fps. The commercial software EchoPAC (v.203, GE-Vingmed AS, Horten, Norway) was used for strain analyses. Intra- and inter-observer variability for conventional echocardiographic measures were regularly assessed within both KYH and Tromsø7 reading laboratories and compared between laboratories. Conventional echocardiography included left ventricular systolic and diastolic volume (LV ESV; LV EDV), stroke volume (SV), ejection fraction (EF), and left atrial volume (LAV) measurements using the Simpson biplane method. Doppler-derived measurements included mitral valve (MV) E, A, E/A ratio, and deceleration time (MV DT). The M-mode was used to estimate the septal wall thickness and myocardial mass. SV, myocardial mass, and left atrial (LA) volume were indexed by body surface area (BSA).

### Strain and strain-rate analysis

A single reader (M.K.) analyzed all strain data using the Q-analysis function of EchoPAC. For all analyses, the peak R was set as the endpoint of end-diastole. Aortic valve closure was defined as a transaortic CW Doppler signal. The region of interest (ROI) was defined by manual definition of the subendocardial border and adjustment of the ROI width. Automated tracking was visually controlled, and suboptimal tracking results were repeated a maximum of three times. From the 12 (or 18) segments, the following segmental values were extracted from the strain analysis: segmental end-systolic (ES) subendocardial (endo), mid-myocardial (myo), and epicardial strain (epi). Furthermore, the peak systolic SR (SR S), peak SR E and SR A, and respective peak global S/SR values for two or three apical views were extracted using the software. Post-systolic stretching (PSS) was calculated as the difference between the ES strain and peak diastolic

strain. Segments were classified as PSS present or absent by defining cutoff values (-1 to -3% and > -3%).

S/SR from APLAX views was analyzed in 176 Tromsø7 participants. Based on previous analyses of this study population, we assigned segmental groups with similar values, that is basal septal, basal, mid, and apical segments.

#### Artefact reading

Artifact detection was used to identify distorted echocardiographic records that were to be excluded from analysis. The identification of strain-curve artifacts was based on artifact detection by visual assessment of the strain curves and was described in detail in a previous publication (12) on the same study population. Strain curve artifacts were subjectively assessed using these previously described features and classified as (1) “blunted curves” (a reduced or even positive strain in the start of the cycle, mirrored by a similar curve-formation at the end of systole), (2) “diastolic mismatch” (late diastolic strain curve significantly deviating towards 0 or positive values compared to the late diastolic strain-curves of other segments), and (3) “floating” (segmental strain curves with several negative and positive peaks without correspondence with timing or configuration of other segments). Segments with curve artifacts or apical foreshortening were discarded. As shown in Figure 2, apical foreshortening and curve artifacts reduced the number of echocardiograms included in the final analysis.

#### Blood pressure (BP) measurements

In KYH and Tromsø7, blood pressure was measured in the sitting position in a quiet room, either before or after the echocardiogram, but not on the same day. The measurements were performed three times at 1-minute intervals after an initial 2-minute seated rest. The results of the second and third measurements were averaged and used for the analysis. All study participants were asked about the medications they were currently taking, and the data were coded using the Anatomical Therapeutic Chemical (ATC) classification system. Any medications within ATC classes C02, C03, C07, C08, or C09 were regarded as antihypertensives.

#### Statistical analyses

If not stated otherwise, continuous variables are presented as mean  $\pm$  standard deviation (SD). Variables with skewed distributions are presented as medians with quartiles (Q1–Q3). Categorical characteristics are presented as absolute numbers and proportions (%). Between-group differences in continuous variables were tested using one-way analysis of variance (ANOVA) with Bonferroni post hoc tests, and a  $\chi^2$  test was used for group comparisons of categorical variables. Multiple linear regressions were used to assess associations between hypertension status and echocardiographic parameters with adjustments for potential confounders (age, sex, height, body mass index (BMI), heart rate (HR), atrial fibrillation (AF), and KYH/Tromsø study population). All multiple regression models were run on the sample with complete data for all covariates ( $n = 1707$ ). Statistical significance was set at  $p < 0.05$ . SPSS v28.0 (IBM Corp.) was used for statistical analyses.

#### Intra- and interobserver-variability

The intra- and inter-observer variabilities have been previously reported (12). For intra- and inter-observer variability in strain and SR measurements, the same observer repeatedly analyzed 135 randomly selected echocardiographic records comprising 1620 segments within 6–12 months from the initial analysis. The same data were reanalyzed by a second experienced observer. Intra- and inter-observer values were calculated as Bland–Altman limits of agreement for segments and discarding segments with curve-artifacts.

## RESULTS

### *Characteristic of study-subjects and groups*

After excluding subjects with previous coronary artery disease, myocardial or valvular heart disease, the final study sample included 1707 out of 2207 participants, of which 852 were defined as subjects with normal heart structure and function. As shown in Table 1, the groups of hypertensive and normotensive individuals were of

approximately equal size. Among hypertensive patients, the majority had moderately increased BP (140–159 mmHg) during the visit. BP during the visit was significantly higher in men than in women, and more women received antihypertensive medication. Participants with moderately increased systolic BP and with systolic BP > 160 mmHg were largely from the KYH study (56% and 65%, respectively). Normal subjects were the youngest, and their BP values increased with age. All groups with hypertension had significantly higher BMI, higher prevalence of diabetes, and higher creatinine and NT-proBNP levels, indicating the presence of subclinical heart failure.

### LV geometrical and functional parameters

Table 2 shows the LV geometrical and functional parameters comparing groups A-D. Adjustments of the mean values using multiple linear regression for factors known to affect cardiac function created only minor differences between the unadjusted and adjusted mean values. The unadjusted mean values with their respective standard deviations (SD) are displayed in the supplemental material (Table S1-S3). In general, there may be a gradual change in most of the parameters from normal subjects over the hypertensives with normalized, moderate and high BPs. Thus, individuals with the highest BP displayed the lowest ejection fractions and LV stroke volumes; and the highest LV masses, LV ES diameters, and heart rates. Compared with the normal control group, all hypertensive patients had higher LV ED and ES volumes and septal thickness, without significant differences between the hypertensive groups.

As shown in Table 3, all diastolic functional parameters were significantly different from those of the normotensive controls, with a gradual change towards the group with the highest BP. Reduced septal and lateral systolic (TD s') and septal early diastolic tissue Doppler (TD e'), lower E-velocity, lower E/A ratio, higher A velocity, longer MV E DT, and increasing LA size indicate gradually decreasing relaxation properties in parallel with higher BP. Indicators of increased filling pressures, such as an E/A ratio >1.5 or low MV DT, were not higher in the hypertensive groups.

Table 4 demonstrates the effect of hypertension on myocardial functional strain and SR parameters. With increasing BP, the global strain of all layers, SR S, and SR E gradually decreased. Interestingly, hypertension had no significant effect on the percentage of segments with post systolic strain.

Figure 2 shows significant basal-to-apical strain gradients in all layers and hypertensive groups. In the presence of hypertension, the strain was significantly reduced in all basal septal and medial segments and had little effect on the apical segments. This renders a slightly higher basal-apical gradient for all segmental layer strains. Figure 3 demonstrates the apico-basal gradients for systolic and diastolic SR comparing the different hypertensive groups. Interestingly, systolic SR did not seem to be significantly affected by hypertension, while SR E decreased in all segments as a sign of reduced relaxation properties. While the reduction of systolic strain and SR only affects basal and medial segments, SR E was the only parameter that showed a significant difference between normal and hypertensive apical segments. SR A, an indicator of LV compliance, increases in parallel with increasing blood pressure, and SR A was the only S/SR parameter without a basal-to-apical gradient. As BP has a significant effect on global and segmental S/SR values, we generated global and segmental reference values for the S/SR parameter in individuals with elevated BP, as shown in Table 5.

## DISCUSSION

### Main findings:

To our knowledge, this is the largest study to describe the influence of treated or untreated hypertension on global and segmental S/SR, and the first study describing segmental SR E and SR A in hypertensive patients.

The main findings of the study are:

1. Segmental basal-to-apical and endo- to epicardial gradients of S/SR are similar in normal individuals and individuals with hypertension.

2. All segmental systolic S/SR and SR E were reduced in hypertension compared to individuals with normal blood pressure. The reduction of systolic S/SR only affected the medial and basal segments, while SR E was also significantly reduced in the apical segments.
3. We demonstrated the dependency of S/SR values on increasing blood pressure, while individuals with normal BP on antihypertensive medication displayed a significant but less pronounced reduction.
4. SR A was the only segmental parameter without basal-to-apical gradients. SR A increased with antihypertensive treatment and increasing BP.

#### LV geometry, systolic and diastolic function

The combination of lowered longitudinal systolic contraction and abnormal diastolic LV filling may play a key role in the development of acute and chronic heart failure in hypertensive patients.

LV systolic function is commonly considered normal in the presence of a normal EF and fractional shortening, despite the fact that neither index reflects all aspects of LV contractile function (13). However, numerous population studies have demonstrated the detrimental impact of a chronically increased afterload in hypertension on both LV global and segmental function (14-18). In accordance with previous studies, the present results showed increasing septal hypertrophy and ventricular mass in participants with hypertension, both in those well-controlled with antihypertensive treatment and more so in the uncontrolled group with increased blood pressure. Similar to previous reports (18), the ventricular cavity was slightly enlarged, and the EF was slightly but significantly reduced. Thus, the extreme form of hypertensive remodeling with a smaller LV cavity does not seem to constitute the majority of hypertension.

Changes in the diastolic properties of hypertensive individuals are well known, and several mechanisms have been discussed. First, impaired relaxation is caused by prolonged systolic contractions followed by delayed relaxation (19). Micro-scarring may also cause weakened or delayed relaxation (19). Second, diastolic LV filling pressures might increase due to low ventricular compliance with stiffened scarred myocardium or a small ventricular cavity.

In the hypertensive population of our present study, the predominant diastolic dysfunction was impaired relaxation, which gradually increased with BP. Thus, hypertensives showed prolonged MV E DT and reduced MV E velocity and septal and lateral  $e'$ . In 10% of all hypertensives, NT-proBNP levels were pathologically elevated, indicating increased filling pressures, while remaining normal in all healthy controls. This observation is congruent with the close connection between heart failure, preserved EF, and hypertensive hearts (20). However, echocardiographic parameters for elevated filling pressures such as MV E-velocity, E/A ratio, and shortened DT were lower in the hypertensive group. As Prinzen et al. showed, delayed relaxation is an acute response to prolonged contractions at elevated blood pressure (20). We assume that impaired relaxation was a response to elevated blood pressure and hypertrophy was present in the majority of hypertensive patients, while higher filling pressures (indicated by increased NT-proBNP) were only present in 10% of the hypertensive population.

#### Strain and Strain Rate

Global systolic longitudinal S/SR showed lower values depending on higher BP, while no significant S/SR difference was registered between normal BP without antihypertensive treatment and controlled BP with treatment. These findings are in line with a recent population study reporting a significant reduction in global GLS/SR among “ineffectively treated” hypertensives but not in those with BP control (21). It is known, that decreased GLS occurs before LV hypertrophy in hypertensive patients (22, 23). Moreover, it was shown that GLS remained reduced in hypertensives compared to normotensives, even after the reduction of myocardial mass (21).

However, SR E was the only parameter that showed significant functional differences between all groups (A-D). Thus, early relaxation, measured as longitudinal SR E, appears to be the most sensitive parameter for subtle functional changes in the hypertensive population. Impaired relaxation as a key to the early detection of hypertensive heart disease has been previously described by the use of TDI  $e'$  (24), and GLS has been



suggested as a marker for early myocardial dysfunction in hypertensive heart disease (25), while SR E has not been previously described in a hypertensive population.

Strain-rate imaging provides new information regarding segmental systolic and diastolic function. Smaller studies on hypertensive hearts have suggested decreasing apico-basal gradients as pathognomonic of hypertension (19, 26). However, the present data suggest that normotensive controls and hypertensives in the investigated age group (40–70 years old) have similar apico-basal gradients, while apical, mid, and basal segmental S/SR values in hypertensive hearts are equally reduced. Kuznetsova et al. described two segmental groups with basal-mid strain at  $-20.7 \pm 1.98\%$  vs.  $-20.0 \pm 2.35\%$  and apical strain at  $-24.3 \pm 3.41$  vs  $-23.2 \pm 2.61\%$  in hypertensive and normotensive individuals, respectively. These results are similar to the present findings, although the division into four segmental groups in the present study delivers even more distinct basal septal to apical gradients.

To the best of our knowledge, this study is the first to compare segmental SR E and SR A in hypertensive and normotensive populations. Segmental SR E is not implemented in commercialized bulls-eye plots, and only a few studies have focused on SR E as a possible clinical marker (27). However, our results suggest that SR E might be the most sensitive S/SR marker for subclinical functional deterioration, and that differences between the three BP groups, especially in the apical segments, were best shown by this specific marker.

Higher BP was accompanied by a higher SR A, indicating reduced relaxation but normal end-diastolic filling pressure (28). Thus, a ventricle with poor filling after the relaxation phase is compensated for by atrial contraction when ventricular compliance is preserved. SR A showed no intersegmental gradient between segment groups. This can be explained by atrial contraction towards a fully relaxed ventricle in a state of uniform segmental compliance.

#### Study limitations

This study used conventional echocardiographic measurements by different readers from the three study locations. Inter-investigator variabilities of these measurements have been performed and showed a significant bias for all M-mode-based dimensional measurements. We applied linear regression analysis by integrating possible confounders, which were corrected for reader-specific differences. This problem did not affect the strain measurements, because they were performed by a single reader. Doppler and volume measurements are robust to inter-observer variability and are not affected by inter-reader variability (29). Furthermore, BP measurements were not taken at the same time as echocardiograms. Therefore, the influence of BP on myocardial function may be underestimated.

#### Clinical applications

The assessment of segmental LV longitudinal S/SR provides new insights into the myocardial function in hypertension. Kuznetsova et al. demonstrated a higher risk of cardiovascular events in individuals with low longitudinal strain and number of abnormal conventional echocardiographic measures (18). According to the present results, segmental SR E seems to be the most promising S/SR parameter, which should be investigated in future risk-stratification studies.

In hypertensive hearts, assessment of increased filling pressure is challenging. The combination of impaired relaxation with high filling pressures results in mitral flow patterns known as “pseudonormalization,” which typically hampers accurate estimation of diastolic filling pressures.

We also showed that basal-to-apical gradients are present in the normal population and should not be interpreted as an indicator of hypertensive heart disease. Typically, hypertension is characterized by reduced segmental systolic S/SR values and SR E values with a preserved basal to apical gradient. Elevated BP results in different S/SR values, without overt myocardial disease. To accurately identify myocardial pathology in the presence of high BP, we defined segmental S/SR in hypertensive individuals without features of structural cardiac disease.

#### Conclusion

This study describes in detail the influence of hypertension on global and segmental systolic function. Although all longitudinal functional parameters are reduced in hypertensive hearts, impaired relaxation appears to be the predominant cause of cardiac dysfunction in these patients. Accordingly, of all systolic and diastolic LV functional parameters, global and segmental SR E as a measure of LV relaxation is potentially the best indicator of reduced LV function in chronic and acutely elevated BP.

## Contributorship

MK: data collection, strain analysis, statistical analysis, and writing of the manuscript; HAC: artifact analysis, strain analysis for inter-observer-variability; AVK: critical revision of the manuscript for important intellectual content; SM and AR funding and conduction of the data collection in Russia; critical revision of the manuscript for important intellectual content; HS: design funding and conduction of the Tromsø7 study and critical revision of the manuscript; AR: study design, funding of the PhD project, statistical analyses, and writing

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Table 1: Group characteristics

	Healthy Normotensives	Controlled hypertension	Hypertension with systolic BP 140–159 mmHg	Hypertension with systolic BP [?] 160 mmHg	All withhypertension	
	Group A	Group B	Group C	Group D	Groups B-D combined	
Group <i>n</i>	852	206	501	148	855	
	Mean ± SD or <i>n</i> (%)	Mean ± SD or <i>n</i> (%)	Mean ± SD or <i>n</i> (%)	Mean ± SD or <i>n</i> (%)	Mean ± SD or <i>n</i> (%)	ANOVA / $\chi^2$ test <i>p</i> -value
Women	520 (61)	115 (56)	220 (44)*+	70 (47)*	405 (47)	<0.001
Men	332 (39)	91 (44)	280 (56)*+	78 (53)*	449 (53)	
Russian	358 (42)	144 (70)*	280 (56)*+	96 (65)*	520 (61)	<0.001
Norwegian	494 (58)	62 (30)*	221 (44)*	52 (35)*	335 (39)	
Age (years)	53±8	59±8*	57±8*	60±8*++	58±8	<0.001
BMI (kg/m <sup>2</sup> )	26.0±4.4	29.3±5.2*	28.9±5.2*+	29.3±5*	29.0±5.2	<0.001
Systolic BP (mmHg)	119±12	123±10*	146±7*+	171±11*+++	145±18	<0.001
Diastolic BP (mmHg)	73±9	76±8*	88±9*+	97±10*+++	87±11	<0.001
LDL Cholesterol (mmol/l)	3,7±0,9	3,7±1,0	3,7±1,0	3,7±0,9	3.7±9.3	0.400
HbA1C (%)	5,6±0,7	5,6±0,5	5,7±0,8	5,6±0,7	5.6±0.7	0.466
Diabetes diagnosis (n)	9 (1)	35 (17)*	25 (5)*+	9 (6)*+	69 (8)	<0.001
Smoking** (n)	170 (20)	23 (11)*	95 (19)	34 (23)+	152 (18)	0.018
Atrial fibrillation history (n)	26 (3)	10 (5)	15 (3)	7 (5)	32 (4)	0.242
Creatinin (mmol/l)	78±15	84±18*	81±30*	82±16	82±25	<0.001

Anti-hypertensive medication (n)	0	206(100)	175 (34) +	75 (51)+++	470 (53)	<0.001
RAS Drugs (n)	0	159 (77)	140 (28) +	65 (44) +++	15 (39)	<0.001
Diuretics (n)	0	35 (17)	40 (8) +	16 (11)	54 (8)	<0.001
Betablockers (n)	0	68 (33)	60 (12) +	30 (20) +	154 (18)	<0.001
Ca-Antagonists (n)	0	33 (16)	40 (8) +	179 (11)	86 (10)	0.005
NT-proBNP (pmol/l)	51 (30-89)	74 (42-126)	66 (32-123)	78 (34-132)	70 (36-127)	0.180
NT-proBNP high	(0)	16 (8)*	55 (11)*	16 (11)*	87 (10)*	<0.001

BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C	BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C	BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C	BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C	BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C	BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C	BMI: body mass index; BP: blood pressure; LDL: low density lipoproteins; HDL: high density lipoproteins; LV EF: left ventricle ejection fraction; RAS: renin-angiotensin system; Ca: Calcium; HbA1C: glycosylated hemoglobin. NT-proBNP: median with quartiles. Antihypertensive medication was per definition absent in healthy controls and comparisons to this group were not made. **Refers to the active current smoking Bonferroni post-hoc analysis or $\chi^2$ test! * $p < 0.05$ for difference towards group A + $p < 0.05$ for difference towards group B ++ $p < 0.05$ for difference towards group C
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Table 2: LV geometrical and systolic functional parameters

Group	<i>n</i>
LV ED volume (ml)	
LV ES volume (ml)	
EF biplane (%)	
LV stroke Volume (biplane) (ml)	
LV ED diameter (mm)	
LV ES diameter (mm)	
LV mass (g)	
LV mass Index (g/m <sup>2</sup> )	
Septal thickness (mm)	
Heart rate (bpm)	
Means derived from multiple linear regression analysis adjusted for age, sex, height, body mass index, heart rate, atrial fibrillation	

Table 3: LV diastolic functional parameters

Group	<i>n</i>
TD septal s' (cm/s)	
TD lateral s' (cm/s)	
TD septal e' (cm/s)	
MV velocity E (cm/s)	
MV E DT (ms)	
MV A velocity (cm/s)	
E/A ratio ()	
LA diameter (cm)	
LA volume Index (ml/m <sup>2</sup> )	
TR max peak gradient (mmHg)	
Means derived from multiple linear regression analysis adjusted for age, sex, height, body mass index, heart rate, atrial fibrillation	

Table 4: Systolic and diastolic Strain and Strain Rate

Group	<i>n</i>
ES LS epi(%)	
ES LS myo(%)	
ES LS endo(%)	
Global SR S (1/s)	
Global SR E (1/s)	
Global SR A (1/s)	
PSS (-1 to -3% mbn) percentage of segments (%)	
PSS (-3 to -5%) percentage of segments (%)	
Means derived from multiple linear regression analysis adjusted for age, sex, height, body mass index, heart rate, atrial fibrillation	

Table 5: Inter- and intraobserver variability

N=884	N=884	Mean	SD	Lower limit	Upper limit
Interobserver	ES LS epi (%)	-0.4	2.94	-6.16	5.36
	ES LS myo (%)	-0.42	3.11	-6.52	5.68
	ES LS endo (%)	-0.38	3.75	-7.73	6.97
	Global SR S (1/s)	-0.02	0.24	-0.49	0.45
	Global SR E (1/s)	0.04	0.36	-0.67	0.75
	Global SR A (1/s)	0.03	0.3	-0.56	0.62
	ES LS epi (%)	-0.18	3.28	-6.61	6.25
	ES LS myo (%)	-0.09	3.53	-7.01	6.83
Intraobserver	ES LS endo (%)	0.002	4.34	-8.50	8.51
	Global SR S (1/s)	-0.04	0.28	-0.59	0.51
	Global SR E (1/s)	0.005	0.41	-0.80	0.81
	Global SR A (1/s)	0.04	0.32	-0.059	0.67
	ES LS epi (%)	-0.18	3.28	-6.61	6.25
	ES LS myo (%)	-0.09	3.53	-7.01	6.83
	ES LS endo (%)	0.002	4.34	-8.50	8.51
	Global SR S (1/s)	-0.04	0.28	-0.59	0.51
SR: strain rate; epi: epicardial; myo: myocardial; endo: endocardial; ES: end-systolic; LS: longitudinal strain; SR S: strain rate at peak systole; SR E: strain rate in early diastole; SR A: strain rate in atrial contraction	SR: strain rate; epi: epicardial; myo: myocardial; endo: endocardial; ES: end-systolic; LS: longitudinal strain; SR S: strain rate at peak systole; SR E: strain rate in early diastole; SR A: strain rate in atrial contraction	SR: strain rate; epi: epicardial; myo: myocardial; endo: endocardial; ES: end-systolic; LS: longitudinal strain; SR S: strain rate at peak systole; SR E: strain rate in early diastole; SR A: strain rate in atrial contraction	SR: strain rate; epi: epicardial; myo: myocardial; endo: endocardial; ES: end-systolic; LS: longitudinal strain; SR S: strain rate at peak systole; SR E: strain rate in early diastole; SR A: strain rate in atrial contraction	SR: strain rate; epi: epicardial; myo: myocardial; endo: endocardial; ES: end-systolic; LS: longitudinal strain; SR S: strain rate at peak systole; SR E: strain rate in early diastole; SR A: strain rate in atrial contraction	SR: strain rate; epi: epicardial; myo: myocardial; endo: endocardial; ES: end-systolic; LS: longitudinal strain; SR S: strain rate at peak systole; SR E: strain rate in early diastole; SR A: strain rate in atrial contraction

#### Figure legends

Figure 1: Flow chart showing inclusion and exclusion of study participants. BP: blood pressure; EF: ejection fraction

Figure 2: Strain of the different segmental groups in different myocardial layers comparing normal and hyper-



tensive groups: A: systolic blood pressure (BP) <140 and diastolic BP <90 mmHg, but on antihypertensive medication; B: systolic blood pressure 140–159 mmHg; C: systolic blood pressure >160 mmHg.

Figure 3: Systolic and diastolic segmental strain-rate (SR) comparing normal individuals with the different hypertensive groups.







