Interplay of cardiac remodelling and myocardial stiffness in hypertensive heart disease: A shear wave imaging study using high-frame rate echocardiography

Marta Cvijic, MD, PhD [1,2,*], Stéphanie Bézy, MSc [1,2], Aniela Petrescu, MD [1,2 #], Pedro Santos, PhD [1], Marta Orlowska, MSc [1], Bidisha Chakraborty, PhD [1], Jürgen Duchenne, PhD [1,2], João Pedrosa, PhD [1], Thomas Vanassche, MD, PhD [1,2], Jan D'hooge, PhD [1,2], Jens-Uwe Voigt, MD, PhD [1,2]

[1)] Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

[2)] Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium

Jan D'hooge and Jens-Uwe Voigt share senior authorship.

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Address for correspondence:

Prof. Dr. Jens-Uwe Voigt

University Hospitals Leuven

Herestraat 49, 3000 Leuven, Belgium

Tel.: +32 / 16 / 349016, Fax.: +32 / 16/ 344240

Email: jens-uwe.voigt@uzleuven.be

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*MC is permanently affiliated with the University Medical Centre Ljubljana, Department of Cardiology, Ljubljana, Slovenia

#AP is permanently affiliated with the University Medical Center of the Johannes Gutenberg University Mainz, Germany

Abstract

Aims: To determined myocardial stiffness by means of measuring the velocity of naturally occurring myocardial shear waves (SW) at mitral valve closure (MVC) and investigated their changes with myocardial remodelling in patients with hypertensive heart disease.

Methods and results: Thirty-three treated arterial hypertension (HT) patients with hypertrophic left ventricular (LV) remodelling (59±14 years, 55% male) and 26 aged matched healthy controls (55±15 years, 77% male) were included. HT patients were further divided into a concentric remodelling (HT1) group (13 patients) and a concentric hypertrophy (HT2) group (20 patients). LV parasternal long axis views were acquired with an experimental ultrasound scanner at 1266 ± 317 frames per seconds. The SW velocity induced by MVC was measured from myocardial acceleration maps**.** SW velocities differed significantly between HT patients and controls (5.83±1.20 m/s vs. 4.04±0.96 m/s; $p<0.001$). Additionally, the HT2 group had the highest SW velocities ($p<0.001$), whereas values between controls and the HT1 group were comparable ($p=0.075$). Significant positive correlations were found between SW velocity and LV remodelling (IVS thickness: $r=0.786$, $p<0.001$; LV mass index: $r=0.761$, $p<0.001$). SW velocity normalized for wall stress indicated that myocardial stiffness in the HT2 group was twice as high as in controls ($p<0.001$), whereas values of the HT1 group overlapped with the controls ($p=1.00$).

Conclusions: SW velocity as measure of myocardial stiffness is higher in HT patients compared to healthy controls, particularly in advanced hypertensive heart disease. Patients with concentric remodelling have still normal myocardial properties while patients with concentric hypertrophy show significant stiffening.

Keywords: high-frame rate echocardiography, myocardial stiffness, shear wave, arterial hypertension, cardiac remodelling

Abbreviations list

EDD = end-diastolic diameter

EDP = end-diastolic pressure

EDV = end-diastolic volume

HFpEF = heart failure with preserved ejection fraction

HFR = high-frame rate

HT = arterial hypertension

HT1 group = concentric remodelling group

HT2 group = concentric hypertrophy group

IVS = interventricular septum

LA = left atrium

LAV = left atrial volume

LV = left ventricle

MVC = mitral valve closure

ROC = receiver-operating characteristic

RWT = relative wall thickness

SW = shear wave

Introduction

Hypertensive heart disease is characterized by thickening of the myocardium as a response to elevated arterial pressure to reduce wall stress. Besides this, neurohormones, growth factors and cytokines induce numerous pathological alterations of the myocardium including interstitial fibrosis and increasing myocardial stiffness.[1,2] This myocardial remodelling in arterial hypertension (HT) is very heterogeneous, involving varying geometric patterns of left ventricular (LV) hypertrophy with increase in absolute LV mass and/or increase in relative wall thickness as well as different extents of fibrosis. Previous studies suggest that patients with a milder form of hypertension-induced myocardial remodelling ("concentric remodelling") have no interstitial fibrosis, while patients with more advanced hypertensive heart disease ("concentric hypertrophy") have.[3] Hearts with advanced hypertensive disease have also been shown to have significantly altered collagen content and increased passive myocardial stiffness.[2] We therefore hypothesized, that the quantification of myocardial stiffness by measuring shear wave (SW) velocities could help to identify fibrosis and may help to differentiate phenotypes of hypertensive heart disease.

Shear wave imaging is a new echocardiographic approach to characterize myocardial tissue properties noninvasively,[4–6] as the propagation velocity of SWs depends directly on the local myocardial stiffness.[7] As SWs propagate fast, high-frame rate (HFR) echocardiography is needed for an accurate assessment of their propagation velocity. SWs can be artificially induced by the acoustic radiation force of ultrasound,[7] but physiologic events, such as aortic and mitral valve closure, induce natural SWs, which can also be used to assess stiffness.[4,8] As myocardial stiffness increases with increasing with wall stress, differences in measured myocardial stiffness do not necessarily reflect differences in myocardial properties, but can also be caused by changing loading conditions or chamber geometry. Myocardial stiffness should therefore be compared at equivalent wall stress levels or should be normalized to wall stress.[9,10]

In this study, we measured the velocity of naturally occurring myocardial SWs in patients with HT and investigated the changes in myocardial stiffness with myocardial remodelling in hypertensive heart disease.

Methods

Study population

We prospectively enrolled patients with treated HT from the hypertension outpatient clinic of the University Hospitals Leuven, Belgium, between June and December 2018. Only patients in sinus rhythm, with an LV ejection fraction of more than 50% and LV hypertrophy due to HT were included. Patients with history of coronary artery disease, any cardiac pathology potentially causing hypertrophy (storage diseases, hypertrophic cardiomyopathy, more than mild valvular diseases) and patients with poor echogenicity were excluded. Age-matched healthy volunteers with normal ECG, normal blood pressure, normal resting echocardiogram and without history of cardiovascular disease were recruited as controls.

The study protocol was approved by the local Ethics Committees and written informed consent was obtained from all study participants before inclusion.

Standard echocardiographic data acquisition and analysis

In each participant, cuff blood pressure was acquired using standard automated sphygmomanometer at the time of echocardiography. Standard echocardiographic data were acquired using commercially available scanners (Vivid E9 and E95, GE Vingmed Ultrasound, Norway). Digitally stored data were analysed offline using an EchoPac workstation (Version 202, GE Vingmed Ultrasound). Relative wall thickness (RWT) and LV mass were determined and patients were grouped according to recent guidelines[11] as having concentric remodelling (normal LV mass, abnormal RWT) (HT1 group) and concentric hypertrophy (abnormal LV mass, abnormal RWT) (HT2 group). Our HT patient cohort comprised no individuals with eccentric hypertrophy (abnormal LV mass, normal RWT). LV and left atrial (LA) volumes and LV ejection fraction were measured with the biplane Simpson method in apical 2- and 4-chamber views. LV speckle tracking was performed from which the mid-wall tracking line was stored for calculating wall curvature.

Assessment of LV stress

End-diastolic wall stress (σ) was estimated according to the Laplace formula $\sigma = \frac{EDP \times R}{2 \times WT}$, where R is the radius of curvature, WT is wall thickness and EDP is end-diastolic pressure in the LV. The analysed myocardial region consisted of the basal and mid anteroseptal segments. Wall thickness was averaged over four measurements along the myocardial region. Its regional radius of curvature was averaged from the longitudinal curvature, determined from fitting a circle to the speckle-tracking-derived midline contour of the myocardial region, and the circumferential curvature, determined from the mid-wall diameter of the LV. Both wall thickness and radius of curvature were assessed at the end-diastole defined by mitral valve closure (MVC). EDP was estimated from echocardiographic Doppler measurements using the formula: $EDP = 11.96 + 0.596 \times E/e'$.[12] All post-processing for curvature assessment was performed using a dedicated, MATLAB-based (version 2018a, The MathWorks, Massachussetts, USA) research software (TVA version 22.02, JU Voigt, Leuven, Belgium).

Shear wave imaging

The principle of measuring natural SW velocity has been previously described.[4,6] Briefly, HFR ultrasound images (1266 ± 317 frames per second) of the parasternal long axis view were acquired with a fully programmable experimental scanner (HD-PULSE) equipped with a clinical phased array transducer (Samsung Medison P2-5AC). Data reconstruction and post-processing was performed using a Matlab-based, in-house developed software (SPEQLE, version 4.6.8, University Leuven). HFR data were processed to obtain myocardial Doppler velocities from which myocardial acceleration was calculated. Then, an anatomical M-mode line was drawn along the midline of the interventricular septum (IVS). In the M-mode display, SWs induced by MVC and propagating from base to apex, become visible as tilted colour bands (Figure 1). The SW propagation velocity was measured semi-automatically from the slope of the colour bands. Measurements were repeated three times and averaged SW propagation velocities at MVC were used as measure of myocardial stiffness. In order to

compare myocardial stiffness among hearts with differing geometry, SW velocities were normalized to end-diastolic wall stress.

Statistical analysis

Normality was assessed with the use of the Shapiro–Wilk test. Continuous variables were expressed as mean and standard deviation, if normally distributed, or otherwise by median and 25th and 75th percentiles (inter-quartile range). Categorical data were summarized as frequencies and percentages. The unpaired Student *t*-test or Mann-Whitney test was used for comparison between two groups depending on the distribution of the data. Comparisons of normal distributed data between more than two groups were performed using one-way analysis of variance (ANOVA). Bonferroni correction was applied to account for multiple comparisons. Comparison of categorical variables was assessed by a chi-square test. Correlations between variables were described by Pearson correlation coefficients. Multiple linear regression analysis, using the backwards method, was performed to identify the potential variable which was associated with SW velocity. Variables selected in the univariate analysis ($p<0.05$) and those considered clinically important were entered into multivariate analysis. Collinearity of variables was tested using variance inflation factors. IVS thickness, LV mass index, RWT and LA diameter were not included together in the multivariate analysis due to strong collinearity. The optimal value for the SW propagation velocity at MVC to differentiate subgroup of patients was determined by a receiver-operating characteristic (ROC) curve analysis.

Intraclass correlation coefficient (ICC) was used to test the reproducibility of the analysed methods, and the inter-observer agreement between two readers. A two-tailed p-value of ≤ 0.05 was considered statistically significant. Data were analysed using SPSS version 20 (IBM, Chicago, IL, USA).

Results

Study population

The study population consisted of 33 HT patients and 26 healthy control subjects (characteristics are summarized in Table 1). Patients with HT had higher in-office blood pressure than controls and had on echocardiography typical morphologic changes consistent with chronic increase in afterload caused by hypertension. Median treatment duration of HT was 11 (6-21) years and the average number of antihypertensive drug classes was 3±1, with blockers of the renin-angiotensin system being the most common prescribed medication (29 (88%) patients). Thirteen hypertensive patients were found to have a concentric remodelling pattern (HT1 group) and 20 had concentric hypertrophy (HT2 group).

Myocardial SW velocity in hypertension patients

Hypertensive patients had significantly higher SW velocities at MVC than the control group (5.83±1.20 m/s vs. 4.04±0.96 m/s; respectively, $p<0.001$). Age was associated with higher SW velocities (Figure 2A). The HT patients showed a wider range of values and overlapped those from the control group. The overlapping patients were all from the HT1 group so that SW velocity values in controls and patients of the HT1 group were not significantly different ($p=0.075$) (Figure 2B). Patients of the HT2 group had significantly higher SW velocities ($p<0.001$) compared to controls and HT1.

A ROC analysis showed that a SW velocity >4.99 m/s differentiated the phenotype of the HT2 group from controls with sensitivity 94.4%, specificity 90.5% and area under the curve 0.971 (95% CI: 0.860-0.999, $p<0.001$). Additionally, the optimal cut-off of SW velocity at MVC for detecting phenotype HT2 from controls and HT1 was >5.05 m/s [sensitivity 94.4%, specificity 84.9%, area under the curve 0.963 (95% CI: 0.869-0.996, $p<0.001$)].

Relationship of SW velocity and parameters of myocardial remodelling, diastolic function and clinical characteristics

More advanced LV remodelling was related with increased myocardial stiffness, as demonstrated by the significant positive correlations between SW velocities and parameters of LV geometry (IVS thickness: r=0.786, p<0.001; LV mass index: r=0.761, p<0.001; RWT: r=0.629, p<0.001 (Figure 3A-C). However, there was no correlation between SW velocity and LV diameter (LV EDD: r=0.075, p=0.601) or LV volume (LV EDV: r=0.166, p=0.254 (Figure 3D)).

SW propagation velocity was moderately correlated with diastolic parameters (septal e`: r=-0.609, p<0.001; average E/e`: r=0.567, p<0.001 (Figure 3E)). Higher SW velocity was strongly associated with larger LA dimension (LA diameter: r=0.800, p<0.001 (Figure 3F); left atrial volume (LAV): r=0.613, p<0.001, LAV index: r=0.642, p<0.001).

There was a weak correlation between SW velocity and in-office systolic blood pressure (r=0.468, p=0.001). Among patients with HT, no significant associations were found with the measurement of SW velocity and duration of HT treatment (r=-0.073, p=0.724) or numbers of antihypertensive drug classes (r=0.227, p=0.277). Furthermore, we found no association between SW velocities and the treatment with certain classes of antihypertensive drugs.

The univariate linear regression analysis between SW velocity and different clinical and echocardiographic parameters is presented in Table 2. The best multiple regression model explained 73.5% of the variability of SW velocity in our study group and consisted of LA diameter, age and study group (R^2 =0.735 for the model, p<0.001) (Table 2).

Estimated end-diastolic LV stress and SW velocity

The estimated end-diastolic septal wall stress was comparable in the HT patients and the control group (43±14 mmHg vs. 49±16 mmHg; respectively, p=0.150). HT2 patients had higher SW velocities at the same wall stress than HT1 patients or controls (Figure 4A). After normalizing for the confounding

effect of end-diastolic wall stress, SW velocity as measure of myocardial stiffness significantly differed between HT2 and the other groups (ANOVA $p<0.001$) (Figure 4B).

Reproducibility and feasibility

Successful measurements of SW velocity were obtained in 51 subjects (86%) after MVC. Intra- and inter-observer agreement was 0.96 (95% CI: 0.85-0.99) and 0.92 (95%: 0.74-0.98).

Discussion

In this study, we could demonstrate that SW velocity – as measure of myocardial stiffness – was higher in HT patients compared to healthy controls and that it was related to the severity of hypertensive heart disease. Patients with concentric remodelling (HT1) had still close-to-normal myocardial properties while patients with concentric hypertrophy (HT2) showed significant stiffening. This difference became even more pronounced when the measures of myocardial stiffness were normalized for the confounding effect of wall stress.

Myocardial stiffness in hypertensive heart disease

In our group of HT patients with hypertrophic LV remodelling, myocardial stiffness measured by echocardiographic SW elastography was significantly higher compared to controls. To the best of our knowledge, this is the first study that assessed myocardial stiffness non-invasively in HT patients. In a previous patient study analysing myocardial stiffness in HT, endomyocardial biopsies were analyzed[2] which has obvious limitations for a widespread clinical application.

Beside the hypertrophy as a compensatory mechanism to increased afterload, HT also induces numerous pathological modification in the composition of cardiac tissue, including unnecessary and excessive hypertrophy, alteration in the extracellular matrix and accumulation of interstitial and perivascular fibrosis.[13–15] Animal experiments suggest, that neither compensatory nor excessive LV hypertrophy alone can explain myocardial stiffening,[14] but that the deposition of collagen fibers and qualitative changes of the collagen are major determinants.[14–16] A recent study in humans found that also the passive stiffness of cardiomyocytes can change through alterations in the myofilament titin.[2] Zile et al. showed, that collagen-dependent stiffness was increased by 220% and titin-dependent stiffness was increased by 92% in HT patients with heart failure and preserved ejection fraction (HFpEF) compared to controls or HT patients without diastolic dysfunction. It is worth noting that HT patients studied by these investigators had very similar LV geometry and diastolic parameters as our HT2 group, however patients in their study also fulfilled the criteria for HFpEF. Although the order of

magnitude is comparable, it is difficult to directly compare the stiffness measurements of Zile et al. with our data as these ex vivo measurements were done in processed myocardial strips, separately for titin and for extracellular matrix, while the actual operating sarcomere length range was not taken into account.

Relationship of SW velocity to parameters of myocardial remodelling, diastolic function and clinical characteristics

The association of parameters of LV remodelling and SW velocity supports the concept that LV remodelling induced by HT causes an increase in myocardial stiffness. Similar to our results, a positive correlation of wall thickness with myocardial stiffness measured by MRI elastography was observed in hypertension animal models.[17] Furthermore, histological data from hypertensive hearts with increased cardiac mass show an association between the degree of hypertrophy and the increase in fibrosis content which can even exceed the increase in the myocyte compartment.[18,19]

Additionally, higher SW velocities were associated with more impaired diastolic function. This finding is in line with previous observations from different patient groups.[4,5] Interestingly, however, the strongest correlation between SW velocities and echocardiographic parameters was observed for LA size. This could be explained by the fact that LA size reflects elevated filling pressures on a long term, whereas E/e' can be normal at the time of echocardiography.

Besides parameters of cardiac remodelling, multivariate analysis showed that also age was independently correlated with SW velocity. Given that aging is known to be associated with increased myocardial fibrosis and thus myocardial stiffness,[4,5,20] our findings indicate that age-dependent myocardial stiffening might develop alongside with stiffening in response to arterial hypertension.

Phenotypic patterns of left ventricular geometry and myocardial stiffness

The LV adaptation to HT is a gradual and varying process. Commonly, HT patients are classified by the geometric phenotype of the LV to allow a localization within the spectrum of hypertensive heart

disease. We observed that SW velocity significantly varied across LV geometric phenotypes of hypertensive heart disease. Patients with HT2 showed significant increase in myocardial stiffness, while patients with HT1 had close-to-normal myocardial properties.

Our results are supported by previous observations from cardiovascular MRI in HT patients,[3] were patients comparable to our HT1 group had no extracellular myocardial expansion and therefore no increased myocardial interstitial fibrosis compared to controls. However, the phenotype of HT2 was associated with significant expansion of the myocardial cell component as well as the interstitium, indicating an increase in interstitial fibrosis[3,21] and, with this, higher LV stiffness. Estimating myocardial stiffness solely based on the extracellular volume fraction of the myocardium by cardiovascular MRI T1 mapping, however, may probably not truly represent the operating myocardial stiffness as both, changes in cardiomyocyte titin and qualitative changes in collagen are not considered.[2,15,22]

Additionally, we demonstrated that using a cut-off value of 5 m/s, SW velocity at MVC could differentiate HT2 from healthy volunteers with 94% sensitivity and 91% specificity. Therefore, applying this value as cut-off could potentially distinguish normal from diseased myocardium in hypertensive heart disease. We believe that our method can reveal structural and functional differences among HT patients and might become a new, non-invasive diagnostic tool for the assessment of the disease progression in hypertension.

Estimated end-diastolic LV stress and myocardial stiffness

End-diastolic myocardial stiffness is defined as the slope of the tangent on a curvilinear stress-strain relationship, indicating that the operative myocardial stiffness depends on the level of operating end-diastolic stress.[9] Thus, myocardial stiffness can change merely by virtue of a change in wall stress despite constant myocardial properties. Therefore, the observation of differing myocardial stiffness between two groups does not allow to draw conclusions regarding different myocardial characteristics

as long as the operating wall stress is unknown.[9,23] This is of particular importance if loading conditions and chamber geometry differ between the investigated groups.

After normalising for wall stress, our patients in the HT2 group still had higher SW velocities compared to patients of the HT1 group or controls. Interestingly, differences were even more pronounced after normalization. This confirms that the observed differences reflect intrinsic material properties rather than differences in wall thickness or filling pressure. However, in compensated heart disease the direct measure of SW velocities might be sufficiently accurate even without normalization for wall stress, as the myocardium in compensated disease is adapted to the altered loading conditions and therefore maintains wall stress within a narrow, physiological range.[24,25]

Limitations

With our current approach, measurements of SW velocities are best possible in the interventricular septum, and its local stiffness might not necessarily reflect global myocardial properties. We assume, however, that our findings are representative for the entire LV as adaptive remodelling in hypertension is a diffuse and global process.

We analysed SWs induced by MVC, which occurs at the transition from end-diastole to the onset of isovolumetric contraction. Myocardial stiffness at that moment may therefore not strictly represent end-diastolic myocardial properties.

The available temporal resolution of our acquisitions and the only semi- automated measurement process contribute to the intra-/inter-observer variability of SW velocity estimates. A 10 to 13% variability of the measurement can be expected by a SW velocity of 4m/s, a temporal resolution 1200 fps and a 3cm long M-mode. Our data show, however, that the measurement variability was sufficiently low to support our findings. Also the effects of myocardial anisotropy on the wave propagation velocity might not be neglected, as the sampling location and direction can influence the measurements.[5]

A number of assumptions were made in the calculation of LV wall stress which have the potential to limit the accuracy of our estimates. However, our wall stress estimates were in the range reported by other investigators,[24] so that we assume that they are sufficiently accurate for the purpose of this study.

Our study group comprised only hypertensive patients with hypertrophic LV remodelling and preserved ejection fraction, so that our results cannot be extrapolated to patients with HFpEF or reduced LV function or even patients with other aetiology of LV hypertrophy. Further studies are needed to explore the full potential of SW velocity measurements and to establish its clinical utility and its diagnostic and prognostic value in these populations.

Conclusion

In hypertensive heart disease, patients with concentric hypertrophy have higher SW velocities than patients with concentric remodelling or controls. Our data suggest an increased myocardial stiffness in this subgroup, due to maladaptation of the LV myocardium to excessive chronic loading. Echocardiographic SW elastography is a promising new technique for the non-invasive assessment of myocardial stiffness and might provide valuable new insights into myocardial function and the pathophysiology of myocardial disease.

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Table

Table 1. Study population.

	Control (n=26)	**Arterial hypertension**			**p-value**	
		All HT patients (n=33)	HT1 group (n=13)	HT2 group (n=20)	Control vs. All HT patients	Control vs. HT1 group vs. HT2 group
Clinical parameters						
Age (years)	55±15	59±14	57±14	58±15	0.329	0.596
Male (%)	20 (77)	18 (55)	3 (23) * †	15 (75)	0.075	**0.002**
BMI (kg/m^2)	24±3	27±5	25±3 †	28±5 *	**0.017**	**0.002**
Systolic BP (mmHg)	128±17	148±20	140±15	154±22 *	**<0.001**	**<0.001**
Diastolic BP (mmHg)	71±11	82±12	78±12	85±11 *	**<0.001**	**0.001**
Heart rate (bpm)	59±11	64±12	66±14	62±12	0.192	0.313
Echocardiographic parameters						
LV EDD (cm)	4.6±0.6	4.4±0.5	4.0±0.4 * †	4.6±0.5	0.193	**0.003**
IVS thickness (cm)	1.0±0.1	1.4±0.2	1.2±0.1 * †	1.5±0.2 *	**<0.001**	**<0.001**
RWT	0.44±0.07	0.61±0.11	0.56±0.08 * †	0.64±0.12 *	**<0.001**	**<0.001**
LV mass index (g/m^2)	80±14	119±32	86±10 †	140±20 *	**<0.001**	**<0.001**
LV EDV (ml)	110±26	104±24	87±18 * †	115±22	0.349	**0.006**
LV EF (%)	60±4	62±5	63±6	61±5	0.208	0.194
LA diameter (cm)	3.3±0.4	4.0±0.7	3.4±0.5 †	4.4±0.5 *	**<0.001**	**<0.001**
LAV index (ml)	31±6	38±10	32±6 †	43±10 *	**0.001**	**<0.001**
E (m/s)	0.66±0.11	0.70±0.17	0.70±0.17	0.69±0.17	0.334	0.656
A (m/s)	0.57±0.21	0.74±0.19	0.79±0.24 *	0.70±0.16	**<0.001**	**0.005**
Septal e' (cm/s)	9.1±2.0	7.4±1.2	8.0±1.1	7.1±1.2 *	**0.001**	**<0.001**
Average E/e'	6.8±1.5	8.8±2.7	8.0±1.6	10.1±2.3 *	**0.001**	**0.002**

Average regional radius of curvature (cm)	6.2±1.9	6.9±2.3	6.7±2.4	7.0±2.3	0.281	0.529
Regional wall stress (mmHg)	49±16	43±14	48±15	40±13	0.150	0.118
Antihypertensive therapy						
ACEi/ARB (%)	0 (0)	29 (88)	12 (92)	17 (85)	-	-
CCB (%)	0 (0)	26 (79)	10 (77)	16 (80)	-	-
Diuretics (%)	0 (0)	22 (67)	9 (69)	13 (65)	-	-
Beta blockers (%)	0 (0)	16 (48)	5 (38)	11 (55)	-	-
Spironolactone (%)	0 (0)	7 (21)	3 (23)	4 (20)	-	-
Central acting drug (%)	0 (0)	2 (6)	0 (0)	2 (10)	-	-
Alpha-blockers (%)	0 (0)	2 (6)	0 (0)	2 (10)	-	-
Direct vasodilators (%)	0 (0)	1 (3)	0 (0)	1 (5)	-	-

* $p<0.05$; post hoc test, significantly different from Control

† $p<0.05$; post hoc test, significant different between HT1 group and HT2 group

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, BP: blood pressure, BMI: body mass index, CCB: calcium channel blocker, HT: arterial hypertension, HT1 group: concentric remodelling, HT2 group: concentric hypertrophy, EDD: end-diastolic diameter, EDV: end-diastolic volume, EF: ejection fraction, IVS: interventricular septum, LA: left atrium, LAV: left atrium volume, LV: left ventricle, RWT: relative wall thickness.

Table 2. Linear regression analysis of determinants of shear wave velocity in study population

Parameters	Beta	95% CI		P-value
		Lower limit	Upper limit	
Univariate analysis				
Age	0.029	0.003	0.055	**0.030**
Systolic BP	0.034	0.016	0.053	**0.001**
LV EDD	0.193	-0.545	0.932	0.601
LV EDV	0.010	-0.007	0.027	0.254
IVS thickness	4.243	3.286	5.200	**<0.001**
LV mass index	0.033	0.025	0.041	**<0.001**
RWT	7.115	4.593	9.637	**<0.001**
Septal e'	-0.496	-0.681	-0.310	**<0.001**
Average E/e'	0.319	0.186	0.452	**<0.001**
LAV	0.044	0.027	0.061	**<0.001**
LA diameter	1.729	1,356	2,102	**<0.001**
Study group HT Control*	1.794	1.163	2.425	**<0.001**
Multivariate analysis: R^2=0.735				
Intercept	-1.369	-2.881	0.143	0.075
Age	0.015	0.000	0.030	**0.047**
Study group HT Control*	0.932	0.442	1.422	**<0.001**
LA diameter	1.353	0.962	1.744	**<0.001**

*Reference group

BP: blood pressure, CI: confidence intervals, EDD: end-diastolic diameter, EDV: end-diastolic volume, HT: arterial hypertension, IVS: interventricular septum, LA: left atrium, LAV: left atrium volume, LV: left ventricle, RWT: relative wall thickness.

Figure legends

Figure 1. M-Mode maps of the basal and mid segment of the interventricular septum showing the acceleration of the tissue.

All maps have the same scaling. Note the shear waves (SW) occurring after mitral valve closure which have different slopes in a healthy volunteer (control) and in a hypertensive patient with concentric remodelling (HT1) and concentric hypertrophy (HT2). The marked region on the ECG indicates the time interval covered by the M-mode map in the corresponding panel.

Figure 2. SW velocities at mitral valve closure in healthy controls and patients with arterial hypertension.

A. Correlation between SW velocity and age in controls and patients with arterial hypertension. The 95% confidence intervals of the mean are shaded.

B. Average SW velocities with standard deviations in controls, HT1 and HT2 patients.

Abbreviations as in Figure 1.

Figure 3. SW velocity and left heart function and remodelling.

Correlation of SW velocities with different echocardiographic parameters of left ventricular (LV) function and remodelling: septal thickness (A), LV mass index (B), relative wall thickness (C), LV end-diastolic volume (D), E/e` (E) and LA diameter (F). Correlation lines and coefficients refer to all patients.

IVS = interventricular septum; RWT = relative wall thickness; EDV = end-diastolic volume; LA = left atrium. Colour coding and other abbreviation as in Figure 2.

Figure 4. SW velocity and wall stress.

A. SW velocity at mitral valve closure versus regional wall stress. Dashed lines represent the mean values of the respective groups. Note the higher SW velocities in HT2 patients despite the comparable wall stress in all groups.

B. Comparison of SW velocity normalized for wall stress (mean and standard deviation). Colour coding and abbreviation as in Figure 2.

Cover illustration. Increasing of myocardial stiffness with a progression of left ventricular remodelling in hypertensive heart disease.

Mild hypertensive heart disease causes concentric remodelling. Advanced disease results in concentric hypertrophy. Myocardial stiffness in patients with concentric remodelling is close to normal while concentric hypertrophy is associated with increased end-diastolic myocardial stiffness and significant worsening of diastolic dysfunction.