The mechanism of reduced longitudinal left ventricular systolic function in hypertensive patients with normal ejection fraction

Short title: Mechanism of LV systolic dysfunction vs. normal EF in HT

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Abstract

Background: MacIver and Townsend's hypothesis predicts, based on a mathematical model of left ventricular (LV) contraction, that preserved absolute radial wall thickening (radWT) due to LV hypertrophy is responsible for the normal ejection fraction (EF) in patients with heart failure with preserved ejection fraction (HFPEF). **Methods:** We tested the validity of this hypothesis by detailed echocardiography including evaluation of ventricular myocardial strain (S) using speckle tracking imaging in ≥60-year-old 18 controls and 94 hypertensive patients with normal EF. **Results:** Echocardiography revealed no LV diastolic dysfunction in 38/94(40%) patients with HT (HTDD- group), and 56/94(60%) patients had diastolic dysfunction (HTDD+ group). The absolute values of global longitudinal LV peak systolic S were significantly reduced in both patient groups ($p<0.05$ for HTDD-, $p<0.01$ for HTDD+ groups) versus the controls. There were no significant between-groups differences in circumferential and radial peak LV systolic Ss, radWT and EF. LV mass (LVM) ($p<0.001$), LVM/body mass index (BMI) ($p<0.01$) increased in the HTDD+ group and EF/LVM/BMI decreased in both patient groups ($p<0.01$ for HTDD-, $p<0.001$ for HTDD+ groups) versus the controls. LVM increased, EF/LVM/BMI decreased in the HTDD+ group versus the HTDD- group ($p<0.05$ and $p<0.01$ respectively). **Conclusions:** We demonstrated decreased longitudinal LV systolic function, and showed that preserved EF was due to preserved absolute radWT and not to increased radial or circumferential systolic function in patients with HT and normal EF, a potential HFPEF precursor condition. Instead of EF, rather EF/LVM/BMI might be used to detect subtle LV systolic dysfunction in hypertension and HFPEF.

Key words: heart failure with preserved ejection fraction, hypertension, left ventricular function

Condensed abstract

MacIver and Townsend's hypothesis predicts that preserved absolute radial wall thickening (radWT) due to left ventricular (LV) hypertrophy is responsible for the normal ejection fraction (EF) in heart failure patients with preserved ejection fraction (HFPEF). Detailed echocardiography was performed in ≥60-year-old normotensive and hypertensive patients with normal EF and with or without LV diastolic dysfunction. Global longitudinal LV peak systolic strain in both hypertensive groups was reduced versus the normotensive group but circumferential and radial peak LV systolic strains, radWT and EF did not change. In conclusion, we verified the validity of MacIver and Townsend's hypothesis demonstrating that normal EF was due to preserved absolute radWT and not to increased radial or circumferential systolic function in hypertensive patients with normal EF, a precursor condition of HFPEF.

Abbreviations

A'=mitral annulus peak late diastolic velocity
BMI=body mass index
BSA=body surface area
DT=deceleration time
E'=mitral annulus peak early diastolic filling velocity
EDV=end-diastolic volume
EF=ejection fraction
EF(S)=EF Simpson
ESV=end-systolic volume
GLS=global longitudinal left ventricular peak systolic strain
HFPEF=heart failure with preserved ejection fraction
IVA=isovolumic acceleration
IVRT=isovolumic relaxation time
IVV=isovolumic velocity
LA=left atrial
LAV=left atrial volume
LV=left ventricular
LVH=left ventricular hypertrophy
LVM=left ventricular mass
LVOT-TVI=left ventricular outflow tract time velocity integral
radWT=radial wall thickening
S=strain
SV=stroke volume
STI=speckle tracking imaging
TDI=tissue Doppler imaging

Introduction

Reduced left ventricular (LV) systolic function despite normal LV ejection fraction (LVEF) was reported in heart failure with preserved ejection fraction (HFPEF)[1-3] or in hypertension with normal EF[4-6], which is a precursor state of HFPEF.

Controversy exists concerning the mechanism of normal EF in HFPEF. Although decreased longitudinal LV systolic strain (S) was repeatedly demonstrated[2-6], there are conflicting reports about radial and circumferential S in HFPEF and in hypertension with normal EF. Some authors reported that reduced longitudinal LV systolic S and yet normal LVEF in HFPEF is due to a compensatory increase in circumferential and/or radial function[1,7-9]. Radial S was increased in asymptomatic mildly hypertensive patients, however, radial S decreased as symptoms appeared, LV hypertrophy (LVH) progressed, and the severity of heart failure increased.[10,11] In more advanced disease with concentric LVH and a normal EF the longitudinal S was reduced besides decreased circumferential and radial S.[12] MacIver and Townsend[13] suggested that the concept of commonly present diastolic dysfunction is unnecessary to describe the pathophysiology of HFPEF. LV thickening depends on both myocardial shortening and end-diastolic wall thickness. Because the myocardium is non-compressible, longitudinal and circumferential shortening results in radial thickening. Thus, reduced long-axis and circumferential shortening should reduce radial thickening (strain).[14] Since LVH is present in HFPEF, the paradox of reduced longitudinal, circumferential and radial S yet a normal EF is explained by the preserved absolute radial wall thickening (due to increased end-diastolic wall thickness).[14] Earlier studies[4,15] that measured myocardial shortening instead of S reported results consistent with this assumption. MacIver and Townsend[13] verified this hypothesis using a mathematical model of LV contraction. We tested the MacIver-Townsend's hypothesis in patients with hypertension and normal EF, the

most common precursor condition of HFPEF.

Methods

The study was conducted from December 2007 to July 2012 at the 3rd Department of Medicine, Semmelweis University, Budapest. The study complied with the Declaration of Helsinki, and was approved by the Institutional Committee on Human Research. All participants signed an informed consent. We designed to prospectively enroll 100 hypertensive patients with normal LVEF (> 50%) and 40 normotensive, healthy controls ≥ 60 years old over 3 years, but even during an extended period we could enroll only 94 hypertensive patients and 18 age-matched controls. Each patient was followed up for at least one year and 44 patients for 3 years (the average follow-up period was 23.3 ± 12.5 months). Each patient underwent a physical examination, an ECG, a detailed echocardiography, a carotid ultrasound and a chest X-ray at annual follow-up examinations. This study is a part of a multipurpose study conducted in the same patients with the objective to provide new insights into the pathogenesis of HFPEF by investigating its most common precursor state hypertension with normal EF. We conducted 3 studies: 1) investigating the role of oxidative stress, inflammation, prothrombotic state and neuroendocrine activation in the pathogenesis of HFPEF; 2) investigating the genetic predisposition to oxidative stress, 3) The testing of MacIver-Townsend hypothesis.

Eight patients quit the study, and nine patients fulfilled the exclusion criteria (HFPEF developed in two of them) during follow up. Hypertension was defined by a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg, or by antihypertensive pharmacotherapy. Blood pressure values are the average of three readings obtained using standard procedures.

Exclusion criteria included diabetes mellitus, more than a mild degree valvular or congenital heart disease, the presence of pacemakers or implantable cardiac defibrillators, prior cardiovascular surgery, coronary heart disease, prior or ongoing atrial tachyarrhythmias, prior or manifest heart failure, any malignant or immunological disease, anticoagulant or antioxidant treatment, or conditions associated with acute inflammation or stress.

Standard echocardiography

Echocardiography was performed using a Philips iE33 system (Philips Ultrasound, Bothell, WA, USA) equipped with a broadband S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz). Cardiac dimensions and wall thicknesses were measured from two-dimensionally guided M-mode tracings according to the recommendations of the American Society of Echocardiography.[16] LV mass was computed by the Devereux-modified cube formula.[17] Left atrial volume was calculated using the biplane area-length method. The biplane Simpson method was applied to calculate LV end-diastolic and end-systolic volumes, stroke volume, and LVEF. LV diastolic function was assessed from the combination of transmitral Doppler flow, pulmonary venous flow, isovolumic relaxation time (IVRT) and myocardial tissue Doppler septal early diastolic filling velocity (E'). LV diastolic dysfunction was graded according to Nishimura and Tajik[18]: Grade 1=impaired relaxation with normal filling pressure, Grade 1a=impaired relaxation pattern with increased filling pressure, Grade 2=pseudonormalized pattern, Grade 3=restrictive pattern. Transmitral flow was acquired from the apical four-chamber view with the sample volume placed at the level of the tips of mitral leaflets. From these traces E/A ratio, E deceleration time (DT), A wave duration and IVRT were determined. Pulmonary venous flow was acquired from the same view by placing the sample volume within the right upper pulmonary vein. From this trace peak systolic

forward flow, diastolic forward flow, atrial reversal flow duration and peak velocity were measured. Radial wall thickening (radWT) was calculated using the formula: radWT = diastolic LV internal dimension (LVIDd) – systolic LV internal dimension (LVIDs)/2.

Color tissue Doppler and speckle tracking imaging

Real time color Doppler myocardial imaging was performed in the apical four-chamber, two-chamber and five-chamber views. Mitral annular peak systolic velocity, peak early diastolic filling velocity (E'), peak late diastolic (A') and isovolumic velocity (IVV) were recorded from the lateral, septal, inferior, anterior, posterior, anteroseptal LV walls. Isovolumic acceleration (m/s^2) was obtained by dividing IVV (cm/s) with the interval from the onset to the peak of IVV (ms) multiplied by 10. The width of the image sector and the depth of the imaging were adjusted to achieve a frame rate more than 180/frames. Pulse repetition frequency was set at the lowest possible level without aliasing. An insonation angle not exceeding 20^o of the Doppler beam with the myocardial segment of interest was maintained.

Myocardial deformation was measured using speckle tracking imaging (STI). To optimize STI two-dimensional grayscale images were acquired at a frame rate of 60-80 Hz in the apical four-chamber, two-chamber, and three-chamber views and in the parasternal short-axis basal and mid papillary views and three cardiac cycles were recorded. The grayscale image recordings were analyzed offline using the QLAB 8.1 advanced ultrasound quantification software (Philips Ultrasound, Bothell, WA, USA). The LV wall was divided into 17 segments and each segment was individually analyzed. The average value of peak systolic longitudinal strain from the three apical views was then calculated as global LV longitudinal strain (GLS). Parasternal short-axis views were obtained: 1) basal: at the tips of

the mitral valve leaflets, 2) mid-papillary: just below the mitral valve level. The global circumferential and radial strains were calculated as the average of the respective peak systolic strains measured in the 6 basal and 6 mid papillary short axis view myocardial segments.

Statistical analysis

All continuous variables are expressed as mean+SD. Categorical variables are expressed as proportions. One-way analysis of variance (ANOVA) was used for statistical analysis and comparisons among groups were performed using Tukey's multiple comparisons test. The Kruskal–Wallis one-way analysis of variance was performed if Bartlett's test indicated heterogeneity of variances followed by Student's two-tailed t-test with Welch's correction. The level of significance was set at $p<0.05$. A receiver-operating characteristic curve (ROC) analysis was performed to determine the most predictive variable of LV systolic dysfunction and the cutoff point of that variable to differentiate normal LV function and LV systolic dysfunction with the highest sensitivity and specificity. Multiple linear regression analyses were carried out including age, gender, body mass index (BMI), LV diastolic dysfunction and LV mass (LVM)/body surface area (BSA) as independent variables. Statistical analysis was performed using GraphPad Prism5 (GraphPad Software Inc., San Diego, CA, USA).

Results

Patient characteristics

Hypertensive patients with (HTDD+) or without LV diastolic dysfunction (HTDD-) and healthy controls had similar gender distribution, height, body weight, body surface area, diastolic blood pressure, heart rate, estimated glomerular filtration rate, hemoglobin concentration. Medication was similar in the two hypertensive groups (Table 1). There was no difference in age between the control and the whole hypertensive patient group (66.1±4.4 vs. 69.4±7.7 years, the latter data are not shown in Table 1), however, patients in the HTDD+ group were slightly older than those in the control and HTDD- groups. The body mass index (BMI) was higher and the systolic blood pressure was similarly elevated in both patient groups vs. the control group. The serum creatinine value was higher in the HTDD+ group compared with the control group (Table 1). The heart rate measured during pulse wave velocity measurements (67±8/min for the control, 66±9/min for the HTDD- and 65±7/min for the HTDD+ groups; not shown in Table 1) was lower than that obtained during office visits (shown in Table 1) and showed no between-groups difference.

LV diastolic dysfunction

Mild, grade 1 or grade 1a LV diastolic dysfunction was present in 56/94(60%) of hypertensive patients and normal EF (HTDD+ group) and was absent in the remaining 40% (HTDD- group).

LV systolic function

No between-groups differences were found either in traditional LV systolic function indices [2D-guided M-mode EF measurement using the $LVIDd^2$-$LVIDs^2$/$LVIDd^2$ X100 formula, EF Simpson (EF(S)), stroke volume (SV), LV outflow tract time velocity integral

(LVOT-TVI), mitral annulus M-mode excursion] or in myocardial velocity measurements by tissue Doppler imaging (TDI) such as mitral annulus peak systolic velocity, isovolumic velocity (IVV) or isovolumic acceleration (IVA) (Table 2). A trend for a decrease in SV was observed in the HTDD+ group.

STI revealed LV systolic dysfunction in the hypertensive patients with normal EF. The absolute values of GLS were reduced in both patient groups compared with controls. There were no between-groups differences in circumferential and radial LV peak systolic Ss. The absolute values of GLS indexed to BMI (GLS/BMI) decreased in both patient groups versus the controls (Table 3).

LA and LV volumes and LV mass

No between-groups differences were found in LA volumes (Figure 1) and LV volumes [LV end-systolic (ESV) and end-diastolic (EDV) volumes] (Table 2).

LVM increased in the HTDD+ group compared with the control and HTDD- groups. LVM/BSA increased in both patient groups versus the controls, and in the HTDD+ group versus the HTDD- group (Figure 1). LVM/BMI increased in the HTDD+ group versus the controls and a borderline increase ($p=0.063$) was found in the HTDD+ versus the HTDD- group. EF(S) indexed to LVM or LVM and BSA (EF(S)/LVM and EF(S)/LVM/BSA), but not EF(S), decreased in the HTDD+ group compared with the control and HTDD- groups (Figure 1). EF(S) indexed to BMI or LVM and BMI (EF(S)/BMI and EF(S)/LVM/BMI) decreased in both patient groups compared with the controls, and the EF(S)/LVM/BMI further decreased in the HTDD+ group versus the HTDD- group. When LVM was indexed to height$^{2.7}$ as recommended[19] we obtained the same results as with indexation of LVM to BSA (data not shown). The hypertensive patient group was also subdivided into subgroups without

LVH (HT LVH-) and with LVH (HT LVH+) according to their LVM/BSA values (LVH was diagnosed when LVM/BSA was $\geq$96 g/m^2 in females and $\geq$116 g/m^2 in males). The HT LVH+ group was further subdivided into subgroups with mild (HT mild LVH: 96-108 g/m^2 and 116-131 g/m^2), moderate (HT moderate LVH: 109-121 g/m^2 and 132-148 g/m^2) and severe (HT severe LVH: $\geq$122 g/m^2 and $\geq$149 g/m^2 for female and male patients respectively) LVH. The absolute values of GLS and GLS/BMI and EF(S)/LVM/BMI decreased either siginificantly or showed a trend to decrease in line with the presence and the degree of LVH and in the HT LVH- group vs. controls (Table 4).

In multiple logistic regression analysis involving age, gender and LV diastolic dysfunction as independent variables, male gender [OR (95% CI): 3.42 (1.02-11.5), $p<0.05$] and LV diastolic dysfunction [OR (95% CI): 4.29 (1.42-13.0), $p<0.05$] were independent predictors of LV systolic dysfunction as expressed by EF(S)/LVM/BMI. In hypertensive patients LV diastolic dysfunction was identified as an independent predictor [OR (95% CI): 3.26 (1.09-9.71), $p<0.05$] of LV systolic dysfunction as expressed by GLS/BMI.

The best routine echocardiography parameter for the detection of subtle LV systolic dysfunction

Figure 2 Panel A shows ROC curves of EF(S) indexed to LVM, BMI and/or BSA [EF(S)/LVM, EF(S)/BMI, EF(S)/LVM/BSA, EF(S)/LVM/BMI], which were decreased either in the HTDD+ group or in both patient groups compared with the controls. EF(S)/LVM/BMI was the best parameter to detect LV systolic dysfunction and only EF(S)/LVM/BMI correlated ($p=0.016$) with GLS.

The ROC analysis demonstrated that GLS/BMI was a better myocardial deformation parameter than GLS to detect LV systolic dysfunction (Figure 2 Panel B). The results verify

that EF(S)/LVM/BMI can as accurately detect subtle LV systolic dysfunction as the best LV systolic myocardial deformation parameter.

Discussion

Major findings

Our results verified the MacIver-Townsend hypothesis in hypertensive patients with normal EF. MacIver and Townsend hypothesized, using a mathematical model of LV contraction that preserved absolute radial wall thickening due to increased LVH and not increased radial or circumferential systolic function is responsible for the normal EF in patients with HFPEF. Similarly to HFPEF, we verified a reduced LV systolic function in patients with hypertension and normal EF, the most common underlying cause and precursor state of HFPEF, using myocardial deformation imaging, which could not be detected by traditional echocardiography. We also identified a new routine echocardiography LV systolic function parameter, the EF(S)/LVM/BMI, which, in contrast to EF itself, could detect subtle LV systolic dysfunction with the same accuracy as the more complicated and still not routinely applied myocardial deformation parameters. An increased LVM in line with the degree of LV diastolic dysfunction, a decreased EF(S)/LVM/BMI and a trend to decrease in the absolute value of GLS in line with the degree of LVH and LV diastolic dysfunction seem to indicate that increased LVM[20] and a subtle progressive deterioration of LV systolic function can develop during the transition of hypertensive heart disease to HFPEF. In multiple logistic regression analysis involving age, gender and LV diastolic dysfunction as independent variables, male gender and LV diastolic dysfunction were found to be

independent predictors of LV systolic dysfunction.

A possible mechanism of normal EF in HFPEF

The underlying causes of HFPEF (such as hypertension, diabetes, obesity, etc.) first damage the most susceptible longitudinally arranged subendocardial myocardial fibers that will result in impaired longitudinal LV systolic function and decreased SV. The same underlying diseases cause LVH due to increased oxidative stress and/or afterload, resulting in a decreased EDV. EF equals to the ratio of SV/EDV. If the EDV and SV decrease in parallel, the EF remains unchanged. This possible mechanism is consistent with our results and the MacIver-Townsend hypothesis. Our results show only a trend for decreased SV and EDV in the HTDD+ group.

Improved clinical detection of LV systolic dysfunction in HFPEF

In contrast to other authors[21], we did not find decreased systolic mitral annular velocities in our hypertensive patients compared with the normal controls. The mitral annulus excursion and IVV were also unchanged in the hypertensive patients.

In contrast to the inability of EF to detect mild to moderate impairment of longitudinal LV systolic function, the EF(S)/LVM/BMI was decreased in our hypertensive patients. The ROC analysis identified EF(S)/LVM/BMI as the best routine echocardiographic parameter for the detection of LV systolic dysfunction.

Although earlier human studies[2-4,15] reported results consistent with certain elements of the MacIver-Townsend hypothesis, to the best of our knowledge, this is the first direct

testing of the hypothesis, providing a novel insight into the pathogenesis of HFPEF in patients. Our results are important, because there is a growing belief that abnormalities of diastolic function may not be the only pathophysiological factors at play in HFPEF, and that the abnormalities of systole may be just as central.[22]

Our results demonstrate that in the hypertensive patients with normal EF with or without mild LV diastolic dysfunction the pathological process probably involved only the longitudinally arranged subendocardial myofibers resulting in reduced longitudinal LV systolic function. The midwall myofibers responsible mainly for circumferential and radial deformation remained relatively preserved, resulting in normal EF. In earlier publications midwall fractional shortening was a reliable indicator of LV systolic dysfunction[4-6] and its prognostic value was verified[23]. We used myocardial deformation imaging instead of midwall fractional shortening, because it can directly evaluate LV systolic dysfunction, while midwall fractional shortening is based on mathematical assumptions. There is a significant linear relationship between mean circumferential S and midwall fractional shortening,[24] and circumferential S has similar excellent prognostic value to midwall fractional shortening[25].

Limitations

Our suggestion that, unlike EF, the application of EF(S)/LVM/BMI is a simple routine tool to diagnose subtle LV systolic dysfunction, should be tested in a greater number of patients.

Myocardial deformation parameters are load-dependent (an increased preload increases, an increased afterload decreases the absolute value of myocardial S), but we did not measure the relation of myocardial deformation to loading conditions. However, the participants were either normal controls or patients with uncomplicated hypertension without

or with mild LV diastolic dysfunction, and none of them had heart failure. Both increased and decreased preload are unlikely as only two patients had grade 1a LV diastolic dysfunction suggesting increased LA filling pressure, and there were no between-groups differences in EDV and LA volumes and in LVOT velocities and LVOT-VTI as well. It has been consistently demonstrated that meridional (longitudinal) and circumferential end-systolic wall stresses were lower in hypertensive patients with LVH than in normal controls, indicating decreased afterload. Thus, the decreased LV longitudinal and circumferential systolic function cannot be attributed to increased afterload in hypertensive patients with LVH.[4,5,21] It was also demonstrated that the systolic wall stress was either significantly decreased, or showed a trend for decrease, but was not increased in hypertensive patients without LVH[5] or in a hypertensive study population in which only 25% had LVH[21] compared with that of the control group. Long axis fractional shortening was not closely related to meridional (longitudinal) stress[4], suggesting that factors other than afterload have a significant influence on longitudinal fractional shortening. In summary, although an important limitation of our study is that we did not measure myocardial deformation simultaneously with systolic wall stress, it seems unlikely that loading conditions significantly influenced the conclusions of this study.

Another limitation of the study is that patients with intraventricular conduction disturbances were not excluded from the study. However, only a small minority of hypertensive patients (10.5% in the HTDD- and 10.7% in the HTDD+ groups) had intraventricular conduction disturbance. The STI strain results were the same after exclusion of these patients from the statistical analysis, therefore, we could rule out that intraventricular conduction disturbance in a few patients biased the results.

The cardiovascular event rate was very low in our relatively healthy hypertensive population with uncomplicated hypertension, therefore, this patient cohort was not suitable for the investigation of the prognostic impact of EF(S)/LVM/BMI on cardiovascular morbidity.

Slow and incomplete inclusion of participants into the study was an additional limitation.

Conclusions

Our results verify the validity of MacIver-Townsend hypothesis, which is based on a mathematical model of LV contraction, in patients with hypertension and normal EF, namely that reduced longitudinal LV systolic function and yet normal EF is not due to a compensatory increase in radial and circumferential LV systolic function but to preserved absolute radial wall thickening caused by LVH. Mild to moderate impairment of LV systolic function can be detected by EF(S)/LVM/BMI but not by EF measured by any method in these patients and probably in HFPEF as well.

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Conflict of Interest: none declared

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Figure legends

Figure 1: LV mass, left atrial volume (LAV) and EF Simpson indexed to LV mass (LVM), body surface area (BSA) and body mass index (BMI). Panel A: LVM, LVM/BSA, LAV, LAV/BSA. Panel B: LVM/BMI, LAV/BMI. Panel C: EF Simpson/LVM, EF Simpson/LVM/BSA and EF Simpson/LVM/BMI. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs. control group; $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$, $^{\#\#\#}$ $p<0.001$ vs. HTDD- group. For further explanation see text.

Figure 2: Receiver-operator characteristic (ROC) curves of EF Simpson and global longitudinal left ventricular peak systolic strain (GLS) indexed to different parameters. Panel A: Among EF Simpson and EF Simpson indexed to different parameters the best echocardiographic parameter to detect LV systolic dysfunction was EF Simpson/LVM/BMI with a cutoff point of <15.73 m^2/kg^2 (AUC: 0.804, $p<0.001$, sensitivity: 75.6%, specificity: 82.4%). The AUCs and p values of other investigated parameters were the following: 0.594, $p=0.21$ (EF Simpson); 0.726, $p<0.01$ (EF Simpson/LVM); 0.743, $p<0.01$ (EF Simpson/BMI); 0.738, $p<0.01$ (EF Simpson/LVM/BSA) respectively. Panel B: ROC curves of GLS and GLS/BMI demonstrating that GLS/BMI detects better LV systolic dysfunction than GLS (AUC: 0.79 vs. 0.73, $p<0.001$ vs $p<0.01$, sensitivity: 73.4% vs. 72.5%, specificity: 72.2% vs. 66.7%.; the cutoff value for GLS/BMI was >-0.646 m^2/kg for GLS was >-16.4%). These data show that EF Simpson/BMI can detect LV systolic dysfunction at least as well or even slightly more accurately than the better myocardial deformation parameter GLS/BMI.

Table 1. Patient characteristics

	Controls (n = 18)	HTDD- (n = 38)	HTDD+ (n= 56)
Age (years)	66.1 ± 4.4	66.1 ± 5.6	71.6 ± 8.1$^{*, \#\#}$
Sex (F/M)	12/6	29/9	33/23
Duration of HT (years)	0	11.5 ± 11.6	14.4 ± 12.2
Height (cm)	168.7 ± 8.4	164.3 ± 7.5	164.8 ± 8.6
Weight (kg)	70.1 ± 13.2	74.3 ± 18	80.2 ± 25
BMI (kg/m^2)	24.6 ± 3.7	27.6 ± 5.8*	28 ± 4$^{**, \#}$
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.3
Se creatinine (μmol/L)	71.6 ±14.8	70.3 ± 14.8	82.8 ± 25.2$^{\#}$
eGFR (mL/min)	82.6 ± 19.9	88.4 ± 26.6	75.4 ± 27.1
SBP (mmHg)	129.5 ± 16.6	146.5 ± 16.2**	148.9 ± 17.9***
DBP (mmHg)	83.8 ± 9.1	85.9 ± 10.9	88.9 ± 10.8
Heart rate (1/min)	71.1 ± 8.3	74.9 ± 9.3	72.2 ± 8.0
Hemoglobin conc. (g/L)	140.9 ± 12.6	137.2 ± 13.1	138.9 ± 14.8
Medications (number of patients)			
BB	1	22	30
ACEI	0	19	35
ARB	0	9	13
CCB	0	15	27
Diuretics	0	22	35
Aldosterone antagonists	0	0	0
Platelet inhibitors	0	14	24
Statin	3	13	29
PPI	2	10	8

* p<0.05, ** p<0.01, *** p<0.001 vs. control; $^{\#}$ p<0.05, $^{\#\#}$ p<0.01, $^{\#\#\#}$ p<0.001 vs. HTDD- groups.
HT=hypertension, BMI=body mass index, BSA=body surface area, eGFR=estimated glomerular filtration rate, SBP=systolic blood pressure, DBP=diastolic blood pressure, BB=beta-adrenergic receptor blocker, ACEI=angiotensin convertase enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel antagonist, PPI=proton pump inhibitor

Table 2. Traditional and myocardial tissue Doppler left ventricular function parameters

Parameter	Control	HTDD-	HTDD+	Significance
2D-guided M-mode EF (%)	65.89 ± 7.99	66.21 ± 5.96	68.66 ± 8.17	ns
EF Simpson (%)	67.61 ± 5.6	66.45 ± 4.8	64.53 ± 7.03	ns
Stroke volume (mL)	71.4 ± 20	68.8 ± 17.9	63.7 ± 18.8	ns
ESV (mL)	34.8 ± 12.4	34.7 ± 12.0	36.9 ± 14.6	ns
EDV (mL)	106.2 ± 30.2	103.6 ± 28.2	101.7 ± 27.3	ns
LV outflow tract time velocity integral (cm)	23.75 ± 3.98	23.55 ± 2.91	23.55 ± 4.88	ns
Mitral annulus M-mode excursion (mm)	15.3 ± 2.3	15.05 ± 2.26	15 ± 2.11	ns
Mitral annulus peak systolic velocity (cm/s)	8.44 ± 1.04	7.96 ± 1.06	8.12 ± 1.4	ns
Isovolumic velocity (IVV) (cm/s)	7.59 ± 1.46	6.58 ± 1.09	6.82 ± 1.82	ns
Isovolumic acceleration (IVA) (m/s^2)	1.91 ± 0.3	1.75 ± 0.27	1.83 ± 0.66	ns

EF=ejection fraction, ESV=end-systolic volume, EDV=end-diastolic volume, LV=left ventricular

Table 3. Myocardial deformation parameters

Parameter	Control	HTDD-	HTDD+
Global longitudinal LV peak systolic S (%)	-17.25±2.22	-15.66±1.75*	-15.35±1.88**
Global longitudinal LV peak systolic S/BMI (m^2/kg)	-0.72±0.14	-0.59±0.14**	-0.55±0.1***
The mean of the circumferential LV peak systolic S (%)	-20.33±3.23	-21.05±4.24	-20.4±4.11
The mean of the radial LV peak systolic S (%)	28.95±3.29	28.48±5.87	27.13±5.42
Radial wall thickening (mm)	9.8±1.9	10.0±1.9	10.8±1.9

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs. the control group.

Table 4. The relationship of myocardial deformation parameters and EF Simpson/LVM/BMI to LVH

Parameter	**Control n=18**	**HT LVH- n=34**	**HT LVH+ n=60**	**HT mild LVH n=23**	**HT moderate LVH n=15**	**HT severe LVH n=22**
GLS (%)	-17.25±2.22	-15.49±1.76*	-15.39±1.93**	-15.51±1.92	-15.31±1.86	-15.06±2.01*
GLS/BMI (m^2/kg)	-0.72±0.14	-0.59±0.13**	-0.55±0.12***	-0.52±0.11***	-0.54±0.08**	-0.56±0.15**
Circumferential S (%)	-20.33±3.23	-20.92±3.95	-20.51±4.35	-19.8±3.97	-22.37±3.81	-19.38±4.45
Radial S (%)	28.95±3.29	27.48±5,34	27.96±5.92	27.3±5.68	28.53±4.8	26.97±6.54
EF Simpson/LVM/BMI (m^2/kg^2)	17.65±4.34	16.65±5.11	10.54±3.57***,###	12.23±3.76**,##	11.26±3.54**,##	8.7±3.72***,###,^

GLS= Global longitudinal LV peak systolic strain, Circumferential S= The mean of the circumferential LV peak systolic strain, Radial S= The mean of the radial LV peak systolic strain. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs. the control group, # $p<0.05$, ## $p<0.01$, ### $p<0.001$ vs. the HT LVH- group, ^ $p<0.05$ vs. the HT mild LVH subgroup.