



Myocardial strain indices and coronary flow reserve are only mildly affected in healthy hypertensive patients

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Abstract

To investigate changes in two-dimensional myocardial strain echocardiography (2DSTE) indices following a dipyridamole stress test (DIPSE) in relatively healthy hypertensive patients and healthy controls. Forty-seven male hypertensive patients (aged 57 ± 9 years) with normal ejection fraction and without left ventricular (LV) hypertrophy and 20 healthy male subjects were studied with conventional and 2DSTE echocardiography at rest and post DIPSE. Coronary flow reserve (CFR) in the left anterior descending artery following DIPSE was also evaluated. Global longitudinal strain (GLS) and TWIST were higher while UNTWIST rate was lower in hypertensives versus controls ($p < 0.05$ for all); TWIST remained higher in hypertensives ($p = 0.021$) after adjustment for differences in age and body mass index (BMI) between the groups. CFR was higher in controls compared to hypertensives even after adjustment for confounders (4.14 vs. 2.53, $p = 0.001$). DIPSE-induced changes did not differ between the groups after adjustment for age and BMI ($p > 0.05$ for all). DIPSE-induced improvement in GLS was associated with higher CFR only in hypertensive patients ($r = -0.372$, $p = 0.010$). The current study showed that well controlled hypertensive patients have only mild echocardiographic differences compared to controls; some of these differences appear to depend on age and BMI. A ‘hyper-rotation’ phenomenon (i.e. higher TWIST) early in hypertension may be a compensatory mechanism to preserve global systolic LV function. Coronary microcirculatory function was impaired in hypertensive patients, albeit within normal range, and was associated with DIPSE-induced changes in myocardial long-axis systolic function.

Keywords Arterial hypertension · Myocardial strain · Speckle tracking · Dipyridamole stress test · Coronary flow reserve

Introduction

Arterial hypertension (AH) is a major risk factor for cardiovascular disease and is associated with functional and structural changes in the heart and the vasculature. AH promotes myocardial hypertrophy, cardiomyocyte apoptosis and myocardial fibrosis through various mechanical (wall tension,

volume load, blood viscosity) and neurohormonal pathophysiological pathways (activation of sympathetic and renin angiotensin aldosterone system, activation or inhibition of several humoral and genetic factors and other intracellular signals) [1]. These alterations may lead to impaired diastolic filling and systolic contraction of the left ventricle (LV) associated with clinical or subclinical cardiac dysfunction.

AH also affects the peripheral vasculature causing arterial endothelial dysfunction, accelerated vascular stiffening, increased progression of interstitial and perivascular fibrosis [2], vascular remodeling and reduction in the number of small arterioles (i.e. microangiopathy) [3]. Coronary microcirculation may be damaged either directly from vascular changes [2] or through the elevation of the LV diastolic pressure causing increased extravascular compression leading to impaired coronary flow reserve (CFR). Previous clinical studies have shown that impaired CFR may lead to exercise-induced myocardial ischaemia and to exercise-induced LV

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diastolic [4] and systolic dysfunction [5] in patients with AH.

Echocardiography plays a pivotal role in the assessment of the cardiac effects of AH. Conventional echocardiographic evaluation of hypertensive patients focuses on: (a) LV hypertrophy and geometry, (b) severity of diastolic dysfunction, (c) global systolic function, (d) left atrial volume and function and (e) the thoracic aorta [6]. The development of two-dimensional myocardial strain imaging with echocardiography (2DSTE) during the last decade has facilitated the simple and angle-independent measurement of LV myocardial deformation in the longitudinal, circumferential, and radial directions [7] as well as the assessment of LV rotational function [8]. Stress echocardiography with a vasodilator, such as dipyridamole (DIPSE), is used either to induce myocardial ischemia or to measure CFR in the left anterior descending territory; decreased CFR has been associated with the presence of significant microvascular and epicardial vascular dysfunction [9–11].

The aim of the current study was to investigate whether early (relatively healthy) hypertensive patients with normal LV ejection fraction may differ in 2DSTE indices at baseline and in response to a stress test such as dipyridamole, compared to healthy controls. Identification of indices that could differentiate early hypertensive patients would be helpful in risk stratification as well as monitoring of medical management of these patients. In the current study, the associations of 2DSTE indices and their changes following DIPSE with other studied parameters were also assessed.

Methods

Population

We prospectively evaluated 47 consecutive male patients with a history of AH between January 2012 and October 2013. Patients were followed-up at the Hypertension Clinic of the Nephrology Department of the University Hospital of Ioannina, Ioannina, Greece and had been on stable treatment for at least 3 months. Furthermore, we enrolled 20 healthy male subjects as a control group; participants in the control group belonged mainly to the hospital personnel. Subjects who were > 80 years old, had any history of coronary artery disease, left ventricular ejection fraction (LVEF) < 50%, any conduction disorder, poor echocardiographic window, any moderate-severe valvular heart disease were excluded from the study. Patients underwent a thorough physical examination and detailed echocardiographic analysis. The study protocol was approved by the local Ethics Committee. The study complied with the Declaration of Helsinki and all participants provided written informed consent.

Echocardiographic evaluation

Echocardiographic studies were performed by a single operator (DE). The echocardiographic evaluation was performed using a commercially available system (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway) as previously described [12]. Images were acquired from cine loops with high frame rates in standard parasternal and apical views and data were stored digitally in still images of high analysis (i.e. 1024 × 768 pixels) and in cine loop format for 3 consecutive analyzable beats.

Initially, a detailed basic echocardiogram was performed and all classic systolic and diastolic indices of LV function were assessed. Left atrial volume and LV mass were indexed to patients' body surface area. All indices were assessed on the basis of the European Society of Cardiology and European Association of Cardiovascular Imaging guidelines [13]. Secondly, 2DSTE acquisition was performed.

Offline analysis was performed using a dedicated software for echocardiographic quantification (EchoPAC version 113, GE Healthcare Vingmed Ultrasound AS, Horten, Norway). The exact endocardial borders of the LV were manually traced and the region of interest was thus acquired. When necessary, the myocardial borders were manually corrected through this dedicated software. The timings of mitral and aortic valve opening and closure were defined by pulse wave Doppler of mitral and LV outflow tract. Tracking was accepted only if both visual estimation and EchoPAC related software analysis were adequate. If more than two myocardial segments at each view were not clearly visualized, the patient was excluded. However, there was not any exclusion by means of poor 2DSTE analysis. Global longitudinal and circumferential strain (GLS, GCS) were assessed for all patients. LV rotation was also assessed through acquisition of short axis views (apical, mid cavity and basal). LV TWIST was computed as the difference between basal and apical rotations. UNTWIST rate was then calculated as the peak negative derivative of time concerning twist, during diastole. Time to maximal UNTWIST was calculated as the interval of time from the peak of the R wave in the electrocardiogram of the patient to the maximal UNTWIST. Images were considered as inadequate for measurement of rotation and cardiac twist, when at least > 2 segments in each view were not adequately tracked.

Following the baseline echocardiographic examination, intravenous infusion of dipyridamole was started (0.84 mg/kg over 6 min). The assessment of CFR in the area of LAD coronary artery was performed before and after intravenous infusion. CFR was calculated as the ratio between hyperaemic and basal coronary flow (the highest

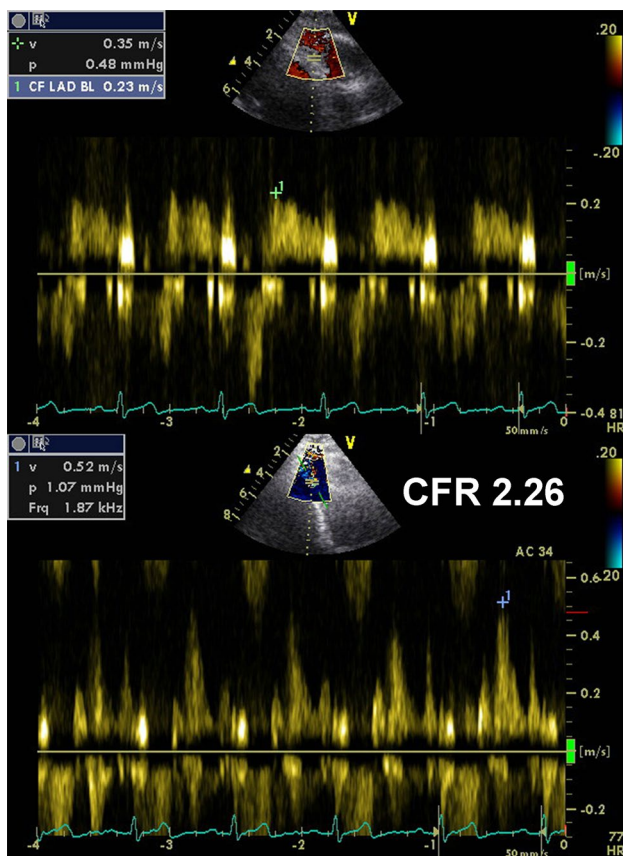


Fig. 1 The flow in the distal portion of the left anterior descending coronary artery is visualized by 2D colour Doppler in an apical modified foreshortened 2- or 3-chambers view. Coronary flow velocities are measured by pulsed-wave Doppler as a laminar flow signal directed towards the transducer pre (top) and post-dipyridamole infusion (bottom). Coronary flow reserve (CFR) is calculated as the ratio of pre- and post-dipyridamole coronary flow velocities

three measurements were averaged for each of the parameters) (Fig. 1). A cut-off value of <2 was used to discriminate significant LAD stenosis and/or microvascular dysfunction in the LAD area [14]. Two minutes after the end of dipyridamole infusion, a new echocardiographic evaluation was performed, which focused mainly on LV systolic and diastolic function indices. At the end of the dipyridamole infusion, 125–250 mg of aminophylline, depending on the patient, were administered to counteract the effects of dipyridamole. During dipyridamole infusion and recovery, all patients were monitored with electrocardiogram and blood pressure (BP) measurements. Beverages containing methylxanthines (e.g. coffee, tea, chocolate) were not allowed at least 24 h before the study.

In studies performed on two separate days (5–10 days apart) in 10 subjects by a single operator, the within-subject coefficient of variation of E/E' , GLS, TWIST, UNTWIST and CFR were 9.6%, 3.4%, 8.6%, 7.8% and 6.5% respectively.

Statistical analysis

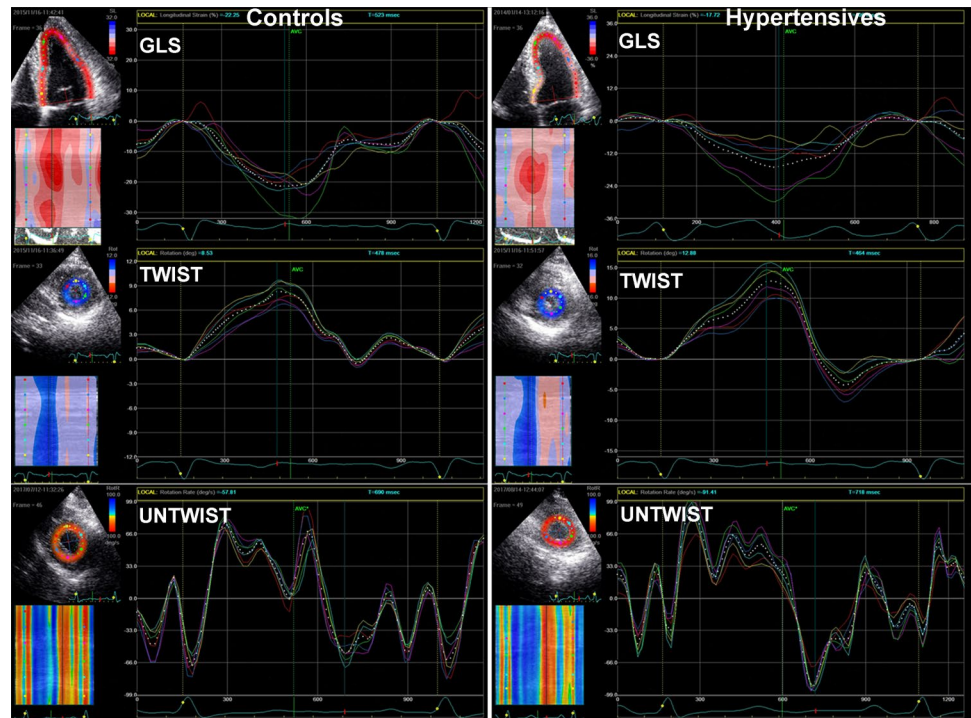
Shapiro–Wilk test was used to identify continuous variables that were not normally distributed. Continuous data are presented as median (interquartile range) for not normally distributed variables and mean \pm SD for normally distributed variables. Student's t-test and Mann–Whitney U test were used to compare various parameters between hypertensive patients and healthy controls. Differences in various studied parameters between the two groups were adjusted for confounders using the General Linear Model. Paired t-test and Wilcoxon test were used to compare various parameters at baseline vs. after dipyridamole. Repeated measures ANOVA analysis was used to assess any differences in DIPSE-induced changes between hypertensive patients and healthy controls. The sphericity assumption regarding the interaction of time-point vs. group was not violated in any of the studied variables. Association analysis included the assessment of Spearman and Pearson correlation coefficients. p values were always two-sided and a value of $p < 0.05$ was considered significant. The SPSS statistical software package (IBM SPSS Statistics, Version 23) was used.

Results

Hypertensive patients were older, had higher BMI, systolic and diastolic BP ($p < 0.05$ for all) compared to healthy controls (Table 1). After adjustment for age and BMI, MAPSE septal and lateral, IVRT, SI were lower while TvSv was higher in hypertensive patients vs. controls ($p < 0.05$ for all). Regarding 2DSTE indices, GLS [-17.8 ($-19.4, -16.4$) vs. -20.1 ($-22.4, -18.3$), $p < 0.001$] and TWIST [14.3 ($9.5, 18.8$) vs. 8.3 ($7.2, 10.6$), $p = 0.002$] were higher while UNTWIST rate [-80.6 ($-101.3, -62.5$) vs. -60.2 ($-75.0, -50.8$), $p = 0.018$] was lower in hypertensives compared to controls respectively; however, after adjustment for age and BMI only TWIST remained significantly higher in hypertensives ($p = 0.021$) (Fig. 2).

Statistically significant associations of 2DSTE indices with other clinical and echocardiographic parameters at baseline in hypertensive patients and healthy controls are shown in Table 2. In hypertensive patients, lower GCS was significantly associated with lower UNTWIST rate ($r = 0.403$, $p = 0.005$), higher TWIST was associated with lower UNTWIST rates ($r = -0.303$, $p = 0.043$) and higher time to peak TWIST was related to higher time to UNTWIST ($r = 0.349$, $p = 0.025$) (Fig. 3a–c). In healthy controls, lower CCS was significantly associated with higher TWIST ($r = -0.627$, $p = 0.003$), while time to peak TWIST was positively associated with time to UNTWIST ($r = 0.596$, $p = 0.006$) (Fig. 3d, e).

Fig. 2 Myocardial strain indices, including Global longitudinal strain (GLS), TWIST and UNTWIST, in controls (left) and hypertensive patients (right)



DIPSE-induced changes

No wall motion abnormalities were seen with DIPSE in either healthy controls or hypertensive patients. Heart rate increase with dipyridamole was similar in both groups (35% in controls vs. 26% in hypertensives, $p=0.189$). CFR values were significantly higher in healthy controls compared to hypertensive patients even after adjustment for age and BMI [4.14 (IQ 3.39, 4.54) vs. 2.53 (IQ 2.03, 2.95) respectively, $p=0.001$]. All controls and 87% of the hypertensive patients had a normal CFR value i.e. >2.0 . Only in controls was higher CFR associated with lower UNTWIST rate ($r = -0.453$, $p=0.045$) (Fig. 3f); no other association of CFR with 2DSTE indices was observed in either hypertensives or controls.

DIPSE-induced changes in various studied echocardiographic parameters in hypertensive patients and healthy controls are shown in Table 3. DIPSE caused a significant increase in LVOT-VTI, LVEF, MAPSE septal and lateral, Sm and Sl and a decrease in IVRT, GLS and GCS ($p < 0.05$ for all) in both groups. Furthermore, DIPSE caused a significant increase in E/E' and TWIST and a decrease in MVDT, UNTWIST rate and time to UNTWIST ($p < 0.05$ for all) only in hypertensive patients. On the other hand, DIPSE resulted in a significant decrease in time to peak TWIST ($p=0.02$) only in healthy controls. DIPSE-induced changes in various studied parameters did not differ significantly between the two groups after adjustment for age and BMI (RMANOVA, $p > 0.05$ for all). The associations of changes among various

studied echocardiographic parameters following DIPSE in hypertensive patients are presented in Table 4. No significant associations of DIPSE-induced changes among various echocardiographic parameters was found in the control group (data not shown).

Discussion

The current study systematically investigated the combination of various novel echocardiographic biomarkers and the stress response to dipyridamole including CFR, in the assessment of early hypertension. We demonstrated that relatively healthy patients with early hypertension showed sub-clinical deterioration in several echocardiographic indices of systolic (LVEF, MAPSE septal and lateral, S lateral and GLS) and diastolic (IVRT, E' and E/E') LV function compared to healthy controls. However, hypertensive patients were older (by ca. 10 years) and had a higher BMI, factors that may affect all the above mentioned indices [15–18]. Indeed, after adjustment for age and BMI, significant differences remained between hypertensives and healthy controls in MAPSE septal and lateral, S lateral and IVRT, but not in GLS. It has been previously shown that impairment of LV long-axis systolic function occurs at the very first stages in many heart diseases including AH; this has been considered as a useful tool in the evaluation of the hypertensive patient even before the appearance of LV hypertrophy [19–22]. Changes in LV longitudinal systolic function may also be

Table 1 Demographic, clinical and classic echocardiographic indices in hypertensives (n=47) and controls (n=20)

	Hypertensives	Controls	p value	*p value
Age (years)	57±9	46±5	<0.001	–
Body mass index (kg/m ²)	28.7±2.9	26.7±2.2	0.005	–
Smoking, n (%)	10 (21)	6 (30)	0.443	–
Systolic BP (mmHg)	139±17	128±16	0.017	–
Diastolic BP (mmHg)	85±13	76±9	0.004	–
Heart rate (bpm)	70±11	65±12	0.148	–
Coronary flow reserve	2.53 (2.03, 2.95)	4.14 (3.39, 4.54)	<0.001	0.001
LAVI (ml/m ²)	28.6±6.7	27.5±4.9	0.536	0.516
LVMi (g/m ²)	92.9±20.5	94.8±19.5	0.672	0.793
LVEF (%)	63.5±5.7	67.3±5.8	0.017	0.314
LVOT VTI (cm)	21.6 (20.1, 24.8)	20.7 (19.3, 24.0)	0.503	0.969
MAPSE _{sep} (mm)	13.0 (12.0, 14.0)	14.5 (13.3, 16.0)	0.006	0.017
MAPSE _{lat} (mm)	15.1±2.8	17.1±2.5	0.010	0.020
MV _{DT} (ms)	217±45	209±41	0.569	0.340
E/A	0.93±0.28	1.14±0.29	0.008	0.635
IVRT (ms)	88±22	101±17	0.013	0.005
E' (cm/s)	9.4±2.4	12.7±2.3	<0.001	0.064
E/E'	7.25 (6.20, 8.10)	5.85 (4.64, 6.69)	0.002	0.152
Sm (cm/s)	8.5 (7.0, 10.0)	9.0 (8.0, 10.0)	0.236	0.498
Sl (cm/s)	9.0 (8.0, 11.0)	12.0 (9.5, 13.0)	0.002	0.012
GLS (%)	– 17.8 (– 19.4, – 16.4)	– 20.1 (– 22.4, – 18.3)	<0.001	0.109
GCS (%)	– 23.5 (– 27.8, – 20.3)	– 22.9 (– 28.0, – 21.2)	0.686	0.706
TWIST (degrees)	14.3 (9.5, 18.8)	8.3 (7.2, 10.6)	0.002	0.021
Time to peak TWIST (ms)	340±73	340±91	0.985	0.489
UNTWIST (degrees/s)	– 80.6 (– 101.3, – 62.5)	– 60.2 (– 75.0, – 50.8)	0.018	0.251
Time to UNTWIST (ms)	467 (411, 510)	402 (374, 500)	0.139	0.733

Continuous variables are presented as mean±SD or median (interquartile range)BP Blood Pressure, E/A ratio of early to late diastolic mitral inflow velocities, E' early diastolic mitral annulus velocity, E/E' ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, GCS Global Circumferential Strain, GLS Global Longitudinal Strain, IVRT Isovolumic Relaxation Time, LAVI Left Atrial Volume Index, LVEF Left Ventricular Ejection Fraction, LVMi Left Ventricular Mass Index, LVOT VTI Left Ventricular Outflow Tract Velocity-Time Integral, MAPSE_{lat} Mitral Annulus Peak Systolic Excursion in lateral wall, MAPSE_{sep} Mitral Annulus Peak Systolic Excursion in septal wall, MV_{DT} Mitral Valve Deceleration Time, Sm Peak Mitral Annulus Systolic Velocity in medial site, Sl Peak Mitral Annulus Systolic Velocity in lateral site, TWIST Peak twist angle, UNTWIST rate Peak Untwisting Velocity*Adjustment was performed for differences in age and body mass index between groups

affected by the presence of other factors such as increased body weight and age, as suggested in our study; therefore, these factors should be taken into account when evaluating patients with AH. Similar to our findings, no deterioration in circumferential systolic function (i.e. GCS) has been previously reported in relatively healthy hypertensive patients without overt cardiomyopathy or heart [21, 23, 24] while GCS deteriorates in the presence of LV hypertrophy [24]. Furthermore, diastolic function has been shown to deteriorate in hypertensive patients in accordance to previous studies [25].

Moreover in hypertensive patients, lower GLS (i.e. improved) was currently associated with lower LV mass, improved indices of systolic LV function and cardiac output (MAPSE and LVOT VTI) as well as ameliorated diastolic

function as assessed by higher E' velocity. These findings have been previously described in hypertensive populations [24, 26]. The close relation of systolic and diastolic function in hypertensive patients has been attributed to myocardial changes observed in the presence of AH related to increased loading conditions, increased wall stress and myocardial fibrosis [27–29]. Importantly, neither GLS nor GCS was related to LVEF in hypertensive patients in contrast to healthy controls; this finding may strengthen the use of myocardial strain indices as measures of subclinical deterioration of LV systolic function long before the overt decrease of measures of global systolic function such as LVEF and the appearance of clinical symptoms.

Hypertensive patients showed higher TWIST and lower UNTWIST rate compared to healthy controls in the current

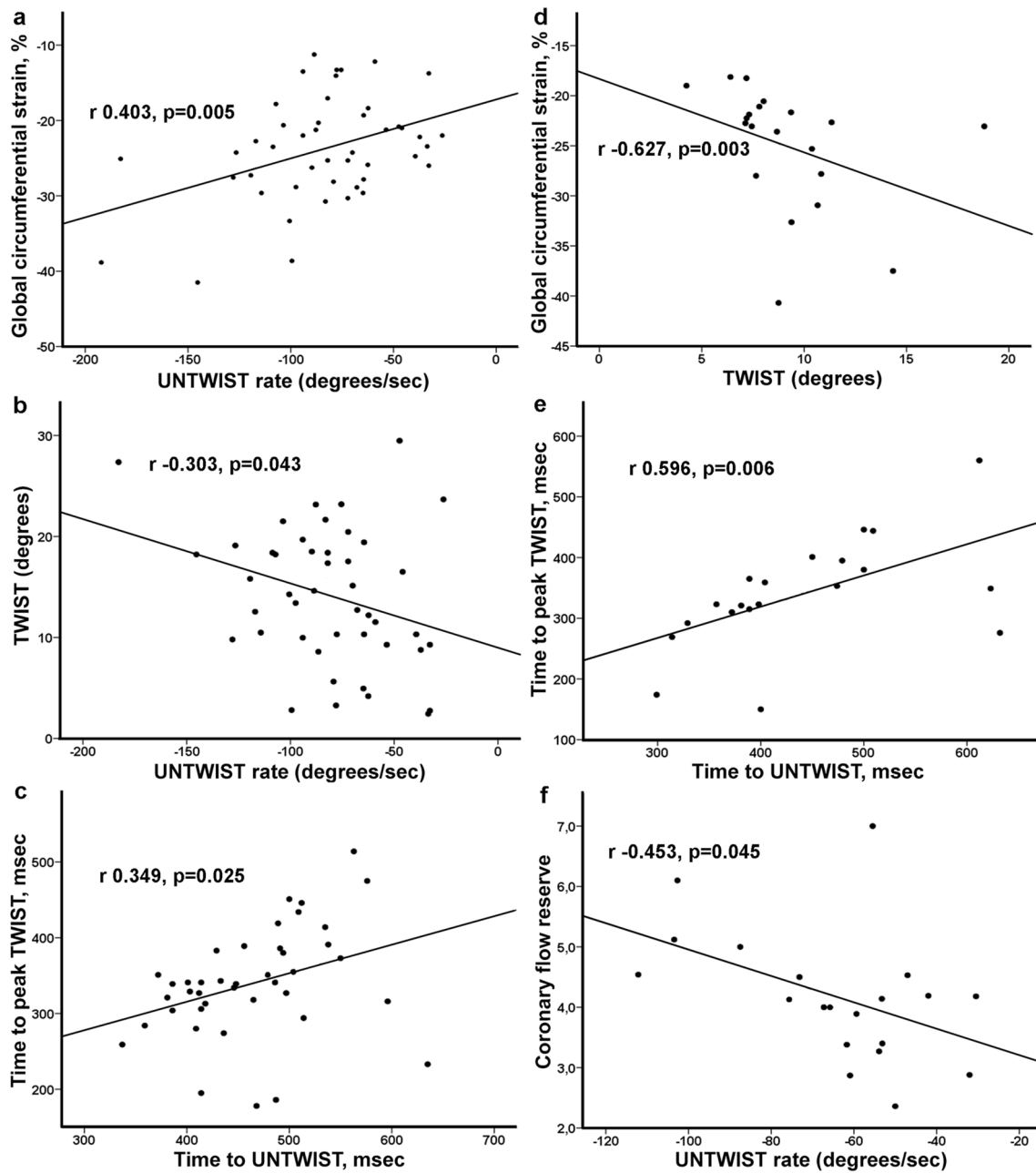


Fig. 3 Scatterplots showing the individual data for the statistically significant associations of (A) two-dimension myocardial strain indices at baseline in hypertensive patients (a–c) and healthy controls

(d, e) and (B) coronary flow reserve with dipyridamole-induced changes in two-dimension myocardial strain indices (f) in healthy controls

study; TWIST, and not UNTWIST rate, remained significantly higher in hypertensives even after adjustment for age and BMI. Although unanticipated, this finding has been previously reported in hypertensive populations with mild diastolic dysfunction without advanced heart disease or heart failure [30–32] while in cases of hypertensive patients with advanced LV hypertrophy and diastolic dysfunction or reduced systolic LV function, TWIST was significantly reduced [30, 31, 33]. Similarly, lower UNTWIST rate has

been also described in hypertensive patients early in the course of AH [30]. It has been suggested that this “hyper-rotation” phenomenon may be a compensatory mechanism early in patients with AH to maintain a relatively normal global systolic LV function (i.e. normal LVEF). Twisting and untwisting are tightly coupled since the greater the LV twist the more potential energy is stored for subsequent higher LV untwisting rate [34, 35] leading to preserved LV filling in the early stages of hypertensive cardiomyopathy.

Table 2 Correlations of 2D myocardial strain indices of left ventricle with other clinical and echocardiographic parameters at baseline in hypertensive patients and healthy controls at significance level $p < 0.1$

GLS	GCS	TWIST	UNTWIST
Hypertensive patients			
LVMI $r = 0.324, p = 0.026$	Diuretics $r = -0.293, p = 0.05$	IVRT $r = -0.339, p = 0.023$	RAS blockers $r = -0.327, p = 0.029$
LVOT VTI $r = -0.294, p = 0.047$			
MAPSE _{lat} $r = -0.297, p = 0.043$			
E' $r = -0.326, p = 0.027$			
Healthy controls			
LVEF $r = -0.693, p = 0.001$	LVEF $r = -0.590, p = 0.006$		MV _{DT} $r = 0.462, p = 0.04$
Sm $r = -0.651, p = 0.002$	IVRT $r = 0.546, p = 0.013$		
	Sm $r = -0.440, p = 0.05$		

E' early diastolic mitral annulus velocity, GCS Global Circumferential Strain, GLS Global Longitudinal Strain, IVRT Isovolumic Relaxation Time, LVEF Left Ventricular Ejection Fraction, LVMI Left Ventricular Mass Index, LVOT VTI Left Ventricular Outflow Tract Velocity-Time Integral, MAPSE_{lat} Mitral Annulus Peak Systolic Excursion in lateral wall, MV_{DT} Mitral Valve Deceleration Time, RAS Renin Angiotensin System, Sm Peak Mitral Annulus Systolic Velocity in medial site, TWIST Peak twist angle, UNTWIST rate Peak Untwisting Velocity

Pathophysiologically, the early subendocardial dysfunction observed in hypertensive patients (i.e. decreased longitudinal systolic LV function) is probably compensated by subepicardial myocardial fibers function and the imbalance results in increased TWIST [36]. However, as the disease progresses, subepicardial myocardium is affected by pathological changes, and therefore LV twist may be reduced in the later stages in AH patients accompanied by decreased LVEF and advanced diastolic dysfunction.

In hypertensive patients, it was currently shown that various anti-hypertensive medications were associated with potential beneficial effects on myocardial deformation mechanics. Circumferential myocardial systolic LV function (i.e. GCS) was associated with the use of diuretics while UNTWIST rate was better in patients receiving renin-angiotensin system inhibitors. It has been previously reported that telmisartan (an angiotensin II receptor inhibitor) improved longitudinal and circumferential strain as well as TWIST without affecting UNTWIST rate [37]. The involvement of renin-angiotensin system in the promotion of myocardial fibrosis and the increase of afterload of LV is well established [27, 38]. The potential benefit of anti-hypertensive medications on regional myocardial function is probably related to their anti-fibrotic and vasodilating effects; whether certain medications may affect specific aspects of myocardial deformation mechanics is not known and further studies are needed to address this issue.

Dipyridamole stress echocardiography is a highly reproducible method to evaluate CFR in various populations [39].

In the absence of significant coronary stenosis, CFR is a marker of coronary microcirculatory function [11]. It has been previously shown that CFR is impaired in the early stages of hypertension [4] as well as in the pre-hypertension stage [40] before LV hypertrophy is apparent [41]. Similarly, we demonstrated that CFR is decreased in relatively healthy patients with AH even after adjustment for potential confounders such as increased body weight and age; almost half of the hypertensive cohort presented with abnormal CFR i.e. < 2.0 . Decreased CFR (measured with DIPSE) has been associated with mortality in patients with known or suspected coronary artery disease [42] although in patients with AH the prognostic role of CFR has not been studied.

Furthermore, DIPSE induced several changes in systolic and diastolic function indices in patients with AH. A significant improvement of left ventricular systolic function, including classic indices of LV systolic function (i.e. LVOT VTI, LVEF, MAPSE_{sep}, MAPSE_{lat}, Sm, Slat) and myocardial strain indices (i.e. GLS, GCS, TWIST) was observed while an improvement in UNTWIST rate was also shown. These changes did not differ in a statistically significant manner between healthy controls and hypertensives. Similar changes have been previously reported in other populations as well [12] and underline the importance of DIPSE as a stress test for systolic and diastolic myocardial reserve [12, 43, 44]. Interestingly, DIPSE-induced improvement in GLS was significantly associated with higher CFR suggesting a close pathophysiological relationship between coronary microcirculatory function and myocardial long-axis

Table 3 Comparisons of echocardiographic parameters at baseline and following dipyridamole administration in hypertensives patients and healthy controls

	Hypertensives		p value	Controls		p value
	Baseline	Post-DIPSE		Baseline	Post-DIPSE	
Heart rate (bpm)	70 ± 11	88 ± 12	< 0.001	65 ± 12	88 ± 14	< 0.001
LVOT VTI (cm)	21.6 (20.1, 24.8)	26.0 (22.8, 29.0)	< 0.001	20.7 (19.3, 24.0)	25.4 (23.6, 30.2)	0.001
LVEF (%)	64 ± 6	72 ± 5	< 0.001	67 ± 6	73 ± 6	0.001
E/A	0.86 (0.73, 1.14)	0.88 (0.76, 1.09)	0.743	1.14 (0.86, 1.37)	1.04 (0.84, 1.28)	0.247
MV _{DT} (ms)	217 ± 45	193 ± 56	0.01	205 ± 36	194 ± 26	0.333
IVRT (ms)	85 (74, 105)	78 (67, 92)	0.047	101 ± 17	86 ± 10	< 0.001
MAPSE _{sep} (mm)	13 (12, 14)	15 (14, 16)	< 0.001	15 ± 3	18 ± 3	0.001
MAPSE _{lat} (mm)	15.1 ± 2.8	17.3 ± 2.6	< 0.001	17 ± 3	20 ± 3	0.001
Sm, (cm/s)	8.5 (7.0, 10.0)	10.0 (8.0, 12.0)	0.002	9.1 ± 1.7	11.4 ± 2.6	0.001
Sl (cm/s)	9.0 (8.0, 11.0)	11.0 (9.0, 13.0)	0.015	11.4 ± 2.5	13.2 ± 2.4	0.007
E' (cm/s)	9.4 ± 2.4	9.8 ± 3.0	0.347	12.7 ± 3.0	13.7 ± 2.8	0.087
E/E'	7.3 (6.1, 8.1)	8.0 (6.6, 9.8)	0.029	5.9 (4.6, 6.7)	6.3 (5.6, 7.8)	0.156
GLS (%)	- 17.8 (- 19.4, - 16.4)	- 19.3 (- 21.7, - 17.7)	< 0.001	- 20.1 (- 22.4, - 18.3)	- 24.5 (- 25.8, - 22.2)	< 0.001
GCS (%)	- 23.5 (- 27.8, - 20.3)	- 28.2 (- 31.3, - 19.5)	0.048	- 22.9 (-28.0, -21.2)	- 29.0 (- 32.5, - 23.4)	0.009
TWIST (degrees)	14.3 (9.5, 18.8)	17.2 (12.5, 23.8)	0.001	8.3 (7.2, 10.6)	8.7 (7.1, 11.3)	0.247
Time to TWIST (ms)	343 ± 74	324 ± 64	0.092	336 (297, 391)	306 (259, 321)	0.020
UNTWIST (degrees/s)	- 80.6 (- 101.3, - 62.5)	- 106 (- 141.2, - 69.4)	0.005	- 60.2 (- 75.0, - 50.9)	- 73.7 (- 82.6, - 60.6)	0.093
Time to UNTWIST (ms)	465 ± 74	436 ± 61	0.026	402 (374, 500)	387 (339, 469)	0.067

E/A ratio of early to late diastolic mitral inflow velocities, *E'* early diastolic mitral annulus velocity, *E/E'* ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, *GCS* Global Circumferential Strain, *GLS* Global Longitudinal Strain, *IVRT* Isovolumic Relaxation Time, *LVEF* Left Ventricular Ejection Fraction, *LVOT VTI* Left Ventricular Outflow Tract Velocity-Time Integral, *MAPSE_{lat}* Mitral Annulus Peak Systolic Excursion in lateral wall, *MAPSE_{sep}* Mitral Annulus Peak Systolic Excursion in septal wall, *MV_{DT}* Mitral Valve Deceleration Time, *Sl* Peak Mitral Annulus Systolic Velocity in lateral site, *Sm* Peak Mitral Annulus Systolic Velocity in medial site, *TWIST* Peak twist angle, *UNTWIST rate* Peak Untwisting Velocity

systolic function, as shown in previous studies [45]. On the other hand, DIPSE-induced increase in TWIST was associated with greater DIPSE-induced increase in *E/E'* ratio and decrease in *E'*; this finding suggests a complex interplay between diastolic function and torsional deformation in hypertensive patients. As discussed above, increased LV twist acts as a compensatory mechanism in patients with AH while it may also be a marker for the early stage of diastolic dysfunction in these patients.

Conclusion

The current study aimed to identify novel echocardiographic indices that could potentially differentiate early hypertensive patients from healthy controls; these indices could be proven to be helpful in risk stratification and monitoring of medical management of these patients. The study showed that well-controlled hypertensive patients with normal LV mass and geometry have only mild differences in echocardiographic indices compared to controls, using both conventional and

speckle tracking echocardiography. These mild differences as well their clinical significance need to be validated in larger studies due to the limitations related to the sample of the current work. The higher TWIST in AH patients compared to healthy controls as well as the association of DIPSE-induced increase in TWIST with greater DIPSE-induced increase in *E/E'* ratio may suggest that a 'hyper-rotation' early in AH could serve as a mechanism to compensate for a stress-induced impairment of diastolic filling and to maintain a relatively normal global systolic LV function. CFR was found to be decreased in AH patients, albeit within normal range, even after adjustment for potential confounders. The association of CFR with DIPSE-induced improvement in GLS indicates a close pathophysiological relationship between coronary microcirculatory function and myocardial long-axis systolic function. Further research is needed to explore the progression of these observations with longer duration of AH, the occurrence of comorbidities and the effect of treatment with various antihypertensive agents. The prognostic role of DIPSE-induced changes in myocardial strain indices should also be further investigated.

Table 4 Associations of changes among various studied echocardiographic parameters following dipyridamole infusion in hypertensive patients

Δ GLS	Δ GCS	Δ TWIST	Δ UNTWIST	$\Delta E/E'$	$\Delta E'$	Δ Sm	Δ SI
CFR r – 0.372, p=0.010	Δ UNTWIST r 0.319, p=0.031	$\Delta E/E'$ r 0.395, p=0.007	Δ HR r -0.326, p=0.027	$\Delta E'$ r – 0.659, p<0.001	Δ Sm r 0.664, p<0.001	Δ SI r 0.644, p<0.001	Δ Sm r 0.644, p<0.001
Δ LVOT-VTI r – 0.331, p=0.024		$\Delta E'$ r – 0.355, p=0.018	Δ GCS r 0.319, p=0.031	Δ Sm r – 0.474, p=0.001	$\Delta E/E'$ r – 0.659, p<0.001	$\Delta E'$ r 0.664, p<0.001	$\Delta E'$ r 0.456, p=0.001
Δ UNTWIST r – 0.291, p=0.049			Δ MV _{DT} r – 0.292, p=0.049	Δ SI r – 0.466, p=0.001	Δ SI r 0.456, p=0.001	$\Delta E/E'$ r – 0.474, p=0.001	$\Delta E/E'$ r – 0.466, p=0.001
			Δ GLS r – 0.291, p=0.049	Δ TWIST r 0.395, p=0.007	Δ TWIST r – 0.355, p=0.018	Δ LVEF r 0.336, p=0.023	Δ IVRT r – 0.371, p=0.01
					Δ LVEF r 0.301, p=0.042	Δ HR r 0.313, p=0.034	Δ MAPSElat r 0.311, p=0.036

Δ Dipyridamole-induced changes, *CFR* Coronary Flow Reserve, *E'* early diastolic mitral annulus velocity, *E/E'* ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, *GCS* Global Circumferential Strain, *GLS* Global Longitudinal Strain, *HR* Heart Rate, *IVRT* Isovolumic Relaxation Time, *LVEF* Left Ventricular Ejection Fraction, *LVOT VTI* Left Ventricular Outflow Tract Velocity-Time Integral, *MAPSElat* Mitral Annulus Peak Systolic Excursion in lateral wall, *MV_{DT}* Mitral Valve Deceleration Time, *SI* Peak Mitral Annulus Systolic Velocity in lateral site, *Sm* Peak Mitral Annulus Systolic Velocity in medial site, *TWIST* Peak twist angle, *UNTWIST rate* Peak Untwisting Velocity

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Compliance with ethical standards

Conflict of interest There are no known conflicts of interest associated with this publication.

Ethical approval This study has been performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All patients included in the study gave their informed consent prior to their inclusion for participation in the study and the publication of their data. All details that might disclose the identity of the subjects have been omitted.

References

- Greenwood JP, Scott EM, Stoker JB et al (2001) Hypertensive left ventricular hypertrophy: Relation to peripheral sympathetic drive. *J Am Coll Cardiol* 38:1711–1717. [https://doi.org/10.1016/s0735-1097\(01\)01600-x](https://doi.org/10.1016/s0735-1097(01)01600-x)
- Schwartzkopff B, Motz W, Frenzel H et al (1993) Structural and functional alterations of the intramyocardial coronary arterioles in patients with arterial hypertension. *Circulation* 88:993–1003. <https://doi.org/10.1161/01.cir.88.3.993>
- Heagerty AM, Aalkjaer C, Bund SJ et al (1993) Small artery structure in hypertension. Dual processes of remodeling and growth. *Hypertension* 21:391–397. <https://doi.org/10.1161/01.hyp.21.4.391>
- Galderisi M, Cicala S, Caso P et al (2002) Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. *Am J Cardiol* 90:860–864. [https://doi.org/10.1016/s0002-9149\(02\)02708-x](https://doi.org/10.1016/s0002-9149(02)02708-x)
- Vasan RS, Benjamin EJ, Levy D (1995) Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. *J Am Coll Cardiol* 26:1565–1574. [https://doi.org/10.1016/0735-1097\(95\)00381-9](https://doi.org/10.1016/0735-1097(95)00381-9)
- Marwick TH, Gillebert TC, Aurigemma G et al (2015) Recommendations on the use of echocardiography in adult hypertension: a report from the european association of cardiovascular imaging

- (eacvi) and the american society of echocardiography (ase). *J Am Soc Echocardiogr* 28:727–754. <https://doi.org/10.1016/j.echo.2015.05.002>
7. Hurlburt HM, Aurigemma GP, Hill JC et al (2007) Direct ultrasound measurement of longitudinal, circumferential, and radial strain using 2-dimensional strain imaging in normal adults. *Echocardiography* 24:723–731. <https://doi.org/10.1111/j.1540-8175.2007.00460.x>
 8. Helle-Valle T, Crosby J, Edvardsen T et al (2005) New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 112:3149–3156
 9. Hozumi T, Yoshida K, Akasaka T et al (1998) Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by doppler echocardiography: comparison with invasive technique. *J Am Coll Cardiol* 32:1251–1259. [https://doi.org/10.1016/s0735-1097\(98\)00389-1](https://doi.org/10.1016/s0735-1097(98)00389-1)
 10. Ali Raza J, Reeves WC, Movahed A (2001) Pharmacological stress agents for evaluation of ischemic heart disease. *Int J Cardiol* 81:157–167. [https://doi.org/10.1016/s0167-5273\(01\)00536-8](https://doi.org/10.1016/s0167-5273(01)00536-8)
 11. Bartel T, Yang Y, Muller S et al (2002) Noninvasive assessment of microvascular function in arterial hypertension by transthoracic doppler harmonic echocardiography. *J Am Coll Cardiol* 39:2012–2018. [https://doi.org/10.1016/s0735-1097\(02\)01906-x](https://doi.org/10.1016/s0735-1097(02)01906-x)
 12. Lakkas L, Naka KK, Bechlioulis A et al (2020) The prognostic role of myocardial strain indices and dipyridamole stress test in renal transplantation patients. *Echocardiography* 37:62–70. <https://doi.org/10.1111/echo.14570>
 13. Lang RM, Badano LP, Mor-Avi V et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the american society of echocardiography and the european association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 16:233–27
 14. Britten MB, Zeiher AM, Schachinger V (2004) Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. *Coron Artery Dis* 15:259–264. <https://doi.org/10.1097/01.mca.0000134590.99841.81>
 15. Lumens J, Delhaas T, Arts T et al (2006) Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using mri. *Am J Physiol Heart Circ Physiol* 291:H1573–H1579. <https://doi.org/10.1152/ajpheart.00074.2006>
 16. van Dalen BM, Soliman OI, Vletter WB et al (2008) Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol* 295:H1705–H1711. <https://doi.org/10.1152/ajpheart.00513.2008>
 17. Hollingsworth KG, Blamire AM, Keavney BD et al (2012) Left ventricular torsion, energetics, and diastolic function in normal human aging. *Am J Physiol Heart Circ Physiol* 302:H885–H892. <https://doi.org/10.1152/ajpheart.00985.2011>
 18. Sugimoto T, Dulgheru R, Bernard A et al (2017) Echocardiographic reference ranges for normal left ventricular 2d strain: results from the eacvi norre study. *Eur Heart J Cardiovasc Imaging* 18:833–840. <https://doi.org/10.1093/ehjci/jex140>
 19. Koulouris SN, Kostopoulos KG, Triantafyllou KA et al (2005) Impaired systolic dysfunction of left ventricular longitudinal fibers: a sign of early hypertensive cardiomyopathy. *Clin Cardiol* 28:282–286. <https://doi.org/10.1002/clc.4960280605>
 20. Triantafyllou KA, Karabinos E, Kalkandi H et al (2009) Clinical implications of the echocardiographic assessment of left ventricular long axis function. *Clin Res Cardiol* 98:521–532. <https://doi.org/10.1007/s00392-009-0046-9>
 21. Galderisi M, Lomoriello VS, Santoro A et al (2010) Differences of myocardial systolic deformation and correlates of diastolic function in competitive rowers and young hypertensives: a speckle-tracking echocardiography study. *J Am Soc Echocardiogr* 23:1190–1198. <https://doi.org/10.1016/j.echo.2010.07.010>
 22. Imbalzano E, Zito C, Carerj S et al (2011) Left ventricular function in hypertension: new insight by speckle tracking echocardiography. *Echocardiography* 28:649–657. <https://doi.org/10.1111/j.1540-8175.2011.01410.x>
 23. Mizuguchi Y, Oishi Y, Miyoshi H et al (2008) The functional role of longitudinal, circumferential, and radial myocardial deformation for regulating the early impairment of left ventricular contraction and relaxation in patients with cardiovascular risk factors: a study with two-dimensional strain imaging. *J Am Soc Echocardiogr* 21:1138–1144. <https://doi.org/10.1016/j.echo.2008.07.016>
 24. Mizuguchi Y, Oishi Y, Miyoshi H et al (2010) Concentric left ventricular hypertrophy brings deterioration of systolic longitudinal, circumferential, and radial myocardial deformation in hypertensive patients with preserved left ventricular pump function. *J Cardiol* 55:23–33. <https://doi.org/10.1016/j.jjcc.2009.07.006>
 25. Nishikage T, Nakai H, Lang RM et al (2008) Subclinical left ventricular longitudinal systolic dysfunction in hypertension with no evidence of heart failure. *Circ J* 72:189–194. <https://doi.org/10.1253/circj.72.189>
 26. Narayanan A, Aurigemma GP, Chinali M et al (2009) Cardiac mechanics in mild hypertensive heart disease: a speckle-strain imaging study. *Circ Cardiovasc Imaging* 2:382–390
 27. Brilla CG, Janicki JS, Weber KT (1991) Impaired diastolic function and coronary reserve in genetic hypertension. Role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. *Circ Res* 69:107–115. <https://doi.org/10.1161/01.res.69.1.107>
 28. Komuro I, Katoh Y, Kaida T et al (1991) Mechanical loading stimulates cell hypertrophy and specific gene expression in cultured rat cardiac myocytes. Possible role of protein kinase c activation. *J Biol Chem* 266:1265–1268
 29. Kang SJ, Lim HS, Choi BJ et al (2008) Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. *J Am Soc Echocardiogr* 21:907–911. <https://doi.org/10.1016/j.echo.2008.01.015>
 30. Park SJ, Miyazaki C, Bruce CJ et al (2008) Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. *J Am Soc Echocardiogr* 21:1129
 31. Wang J, Khoury DS, Yue Y et al (2008) Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. *Eur Heart J* 29:1283–1289. <https://doi.org/10.1093/eurheartj/ehn141>
 32. Ahmed MI, Desai RV, Gaddam KK et al (2012) Relation of torsion and myocardial strains to lv ejection fraction in hypertension. *JACC Cardiovasc Imaging* 5:273–281. <https://doi.org/10.1016/j.jcmg.2011.11.013>
 33. Cameli M, Lisi M, Righini FM et al (2013) Left ventricular remodeling and torsion dynamics in hypertensive patients. *Int J Cardiovasc Imaging* 29:79–86. <https://doi.org/10.1007/s10554-012-0054-0>
 34. Wang J, Khoury DS, Yue Y et al (2007) Left ventricular untwisting rate by speckle tracking echocardiography. *Circulation* 116:2580–2586. <https://doi.org/10.1161/CIRCULATIONAHA.107.706770>
 35. Fukuda N, Terui T, Ishiwata S et al (2010) Titin-based regulations of diastolic and systolic functions of mammalian cardiac muscle. *J Mol Cell Cardiol* 48:876–881. <https://doi.org/10.1016/j.yjmcc.2009.11.013>
 36. Sengupta PP, Khandheria BK, Narula J (2008) Twist and untwist mechanics of the left ventricle. *Heart Fail Clin* 4:315–324. <https://doi.org/10.1016/j.hfc.2008.03.001>

37. Mizuguchi Y, Oishi Y, Miyoshi H et al (2010) Possible mechanisms of left ventricular torsion evaluated by cardioreparative effects of telmisartan in patients with hypertension. *Eur J Echocardiogr* 11:690–697. <https://doi.org/10.1093/ejehocardiography/jeq044>
38. Weber KT, Brilla CG (1991) Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 83:1849–1865. <https://doi.org/10.1161/01.cir.83.6.1849>
39. Dimitrow PP, Galderisi M, Rigo F (2005) The non-invasive documentation of coronary microcirculation impairment: role of transthoracic echocardiography. *Cardiovasc Ultrasound* 3:18. <https://doi.org/10.1186/1476-7120-3-18>
40. Erdogan D, Yildirim I, Ciftci O et al (2007) Effects of normal blood pressure, prehypertension, and hypertension on coronary microvascular function. *Circulation* 115:593–599. <https://doi.org/10.1161/CIRCULATIONAHA.106.650747>
41. Brush JE Jr, Cannon RO, Schenke WH et al (1988) Angina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. *N Engl J Med* 319:1302–1307. <https://doi.org/10.1056/NEJM198811173192002>
42. Cortigiani L, Rigo F, Gherardi S et al (2012) Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. *JACC Cardiovasc Imaging* 5:1079–1085. <https://doi.org/10.1016/j.jcmg.2012.08.007>
43. Cognet T, Vervueren PL, Derclé L et al (2013) New concept of myocardial longitudinal strain reserve assessed by a dipyridamole infusion using 2d-strain echocardiography: the impact of diabetes and age, and the prognostic value. *Cardiovasc Diabetol* 12:84. <https://doi.org/10.1186/1475-2840-12-84>
44. Cusma-Piccione M, Zito C, Oreto L et al (2015) Longitudinal strain by automated function imaging detects single-vessel coronary artery disease in patients undergoing dipyridamole stress echocardiography. *J Am Soc Echocardiogr* 28:1214–1221. <https://doi.org/10.1016/j.echo.2015.06.001>
45. Ikonomidis I, Tzortzis S, Paraskevaidis I et al (2012) Association of abnormal coronary microcirculatory function with impaired response of longitudinal left ventricular function during adenosine stress echocardiography in untreated hypertensive patients. *Eur Heart J Cardiovasc Imaging* 13:1030–1040. <https://doi.org/10.1093/ehjci/jes071>

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