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ORIGINAL RESEARCH

Association of Myocardial Deformation With Mortality Independent of Myocardial Ischemia and Left Ventricular Hypertrophy

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OBJECTIVES The aim of this study was to investigate the relative contributions of left ventricular hypertrophy (LVH) and myocardial ischemia to the association between abnormal myocardial deformation during dobutamine stress echocardiography (DSE) and mortality.

BACKGROUND Both left ventricular hypertrophy (LVH) and myocardial ischemia are known to convey a significant adverse prognostic impact. In addition, myocardial deformation is an independent predictor of outcome in patients undergoing DSE. The mechanism of this association, however, is undefined.

METHODS We studied 223 consecutive individuals with normal resting LV function undergoing DSE. The LV mass was indexed to height ($g/m^{2.7}$) (LVMI), and LVH was designated as LVMI $\geq$51 $g/m^{2.7}$. Myocardial ischemia was defined on the basis of new, inducible wall motion abnormalities. Customized software was used to measure global strain rate (SRs), which was averaged in 18 myocardial segments at peak stress. Individuals were followed for all-cause mortality over a mean of 5.4 $\pm$ 1.4 years.

RESULTS Left ventricular hypertrophy was identified in 83 individuals (37%), and 63 (28%) had ischemia documented at DSE. In a Cox proportional hazards model, the strongest predictor of all-cause mortality for the total population was SRs (hazard ratio: 2.16, 95% confidence interval: 1.63 to 2.87, $p < 0.01$). Both LVH ($p < 0.01$) and ischemia ($p < 0.05$) had a significant adverse prognostic impact. Individuals with both LVH and ischemia had the worst outcome ($p = 0.02$) in comparison with the rest of the population. Among LV geometric patterns, concentric LVH had the worst outcome ($p < 0.01$). However, SRs was the strongest predictor of mortality in both LVH and ischemia. In a model reflecting clinical practice, SRs provided a significant increment in model power over baseline and variables identified at DSE.

CONCLUSIONS The SRs is a powerful, independent predictor of all-cause mortality in individuals undergoing DSE and provides incremental information over baseline clinical and echocardiographic variables. Whereas SRs is influenced by both LVH and myocardial ischemia, both independently and additively, its predictive power for mortality is independent of both. (J Am Coll Cardiol Img 2009;2: 793–801) © 2009 by the American College of Cardiology Foundation

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Although patients presenting with cardiac symptoms with normal left ventricular (LV) systolic function generally have a favorable outcome, echocardiographic assessment is able to identify subgroups of varying risk. Left ventricular hypertrophy (LVH) (1) and LV filling abnormalities (2) are associated with increased mortality. The results of dobutamine stress echocardiography (DSE) have been linked to both cardiac and overall outcome (3). The presence of LVH significantly adds to the prognostic information provided by DSE (4).

Deformation to applied stress is related to myocardial properties and might be due to myocardial scar (5), ischemia (6), and hypertrophy (7). Interstitial fibrosis is another important mechanism of myocardial disease—although linked to hypertrophy, its etiology and progression seem to be independent of myocyte hypertrophy (8). In this study of patients with normal resting LV function, we sought to link deformation and outcome independent of the effects of LVH, ischemia, and infarction.

ABBREVIATIONS AND ACRONYMS

DSE = dobutamine stress echocardiography

LV = left ventricle/ventricular

LVH = left ventricular hypertrophy

LVMI = left ventricular mass index

RWT = relative wall thickness

SBP = systolic blood pressure

SEs = global end-systolic strain at peak stress

SRs = global peak systolic strain rate at peak stress

(+) = presence of

(−) = absence of

METHODS

Study population. Between 1998 and 2000, our laboratory performed 520 consecutive DSE studies in patients with normal resting LV function. Patients with >1 DSE had their first DSE included (n = 17). Other exclusions were due to poor image quality and acquisition problems (n = 68) or inability to accurately estimate left ventricular mass index (LVMI) (n = 156). Outcome data was not available for 56 patients. Therefore, the final study population comprised 223 patients (Table 1).

Resting and stress echocardiography. Beta-adrenoceptor and calcium channel antagonists were withdrawn on the day before the test. Cine loops from 3 apical views (4-chamber, 2-chamber, and apical long-axis) were recorded with gray-scale harmonic and tissue Doppler modes at rest and each stage of stress with a standard DSE protocol. The LV was divided into 16 segments and coded as: 1 = normal, 2A = hypokinetic, 2B = severely hypokinetic, 3 = akinetic, or 4 = dyskinetic. Ischemia was identified by an experienced reader due to the presence of inducible wall motion abnormalities.

Calculation of LV mass. M-mode LV mass was calculated with the formula: LV mass = $0.8 \times \{1.04[([\text{LV internal dimension} + \text{septal wall thickness} + \text{posterior wall thickness}]^3 - \text{LV internal dimension}^3)]\} + 0.6$ g. Left ventricular mass was indexed to height$^{2.7}$, and LVH was defined as ≥51 g/m$^{2.7}$ for both sexes (9). Relative wall thickness (RWT) was calculated with the formula: (2 · posterior wall thickness)/LV internal dimension. The RWT is abnormal if it is >0.42. The mean LVMI for the total population was 48 ± 14 g/m$^{2.7}$, mean RWT was 0.46 ± 0.11, and ejection fraction was 63 ± 8%.

Analysis of myocardial deformation. Myocardial deformation was measured with automated software (Matlab, MathWorks Inc., Natick, Massachusetts) (10). Longitudinal strain rate (SRs) was calculated from the velocity gradient along the ultrasound beam and strain as the temporal integral of strain rate. Measurements were made by 1 experienced observer blinded to clinical data. The coefficient of variation was 16% (intraobserver) and 17% (interobserver) (10). The SRs was defined as the most negative SRs value during the ejection period (Fig. 1). End-systolic strain (SEs) was defined as the strain value at aortic valve closure. The SRs and SEs were calculated at peak stress and then averaged in 18 myocardial segments to provide global values.

Follow-up. The primary end point of the study was all-cause mortality. The follow-up period was deemed to have commenced on the day of DSE.

Statistical analysis. Student *t* test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. Univariate analysis was performed to establish the relationship between baseline clinical and echocardiographic variables and all-cause mortality. Survival after DSE was expressed with Kaplan-Meier analysis and log-rank tested for significance both overall and between strata. The independence and incremental value of SRs over baseline and DSE-obtained variables was assessed in a series of Cox models. Variables known at baseline, then variables obtained at DSE, and finally SRs were entered into the model in a series of steps. Model chi-square was then compared at each step. All continuous variables were assessed per unit SD to facilitate comparisons. Significance was measured as <0.05.

RESULTS

Clinical characteristics. The clinical characteristics of the 223 study patients were not significantly different from the 297 patients excluded, with the exception of a significantly higher prevalence of hypertension in the included group (Table 1).

Table 1. Population Demographic Data

	Included (n = 223)	Excluded (n = 297)
Age (yrs)	59.5 ± 11.8	60.2 ± 12.8
Weight (kg)	78.2 ± 16.9	78.3 ± 22.0
Height (m)	1.68 ± 0.10	1.69 ± 0.11
Body mass index (kg/m^2)	27.7 ± 5.5	27.7 ± 5.8
Body surface area (m^2)	1.87 ± 0.2	1.90 ± 0.3
Male sex	122 (54.5)	177 (59.6)
Diabetes mellitus (fasting glucose >7.0 mmol/l)	49 (21.9)	43 (14.5)
Hypertension (BP >140/90 mm Hg)	121 (54.0)	126 (42.4)*
Hypercholesterolemia (total cholesterol >4.0 mmol/l)	96 (42.9)	126 (42.4)
Current or previous angina	93 (41.5)	128 (43.1)
Smoking	46 (20.5)	69 (23.2)
Current use of beta-blockers	73 (32.6)	107 (36.0)
Current use of calcium channel blockers	62 (27.7)	72 (24.2)
Current use of nitrates	55 (24.5)	79 (26.6)

Data are expressed as mean ± SD or n (%). *p < 0.05 compared with "Included" group.
BP = blood pressure.

LVH. Left ventricular hypertrophy was identified in 83 individuals (37%). These individuals were significantly older (62 ± 12 years vs. 58 ± 12 years, p < 0.01), had higher body mass index (29.6 ± 6.0 kg/m^2 vs. 26.7 ± 4.9 kg/m^2, p < 0.01), more diabetes (31% vs. 16%, p < 0.05) and hypertension (66% vs. 46%, p < 0.01), and accordingly higher resting systolic blood pressure (SBP) levels (150 ± 24 mm Hg vs. 139 ± 23 mm Hg, p < 0.01). There were no significant differences in the use of medications between those with and without LVH.

Myocardial ischemia. The DSE evidence of myocardial ischemia was identified in 63 patients (28%). These individuals were significantly older (64 ± 10 years vs. 58 ± 12 years, p < 0.01) and had lower resting heart rates (70 ± 13 beats/min vs. 78 ± 14 beats/min, p < 0.01), possibly because there was higher use of routine beta-blockade in this group (62% vs. 21%, p < 0.01) due to pre-existing angina (63% vs. 33%, p < 0.01).

The average peak SRs was −2.48 ± 0.62 s^{-1}, with SEs −12.1 ± 4.9%. The SRs was reduced in

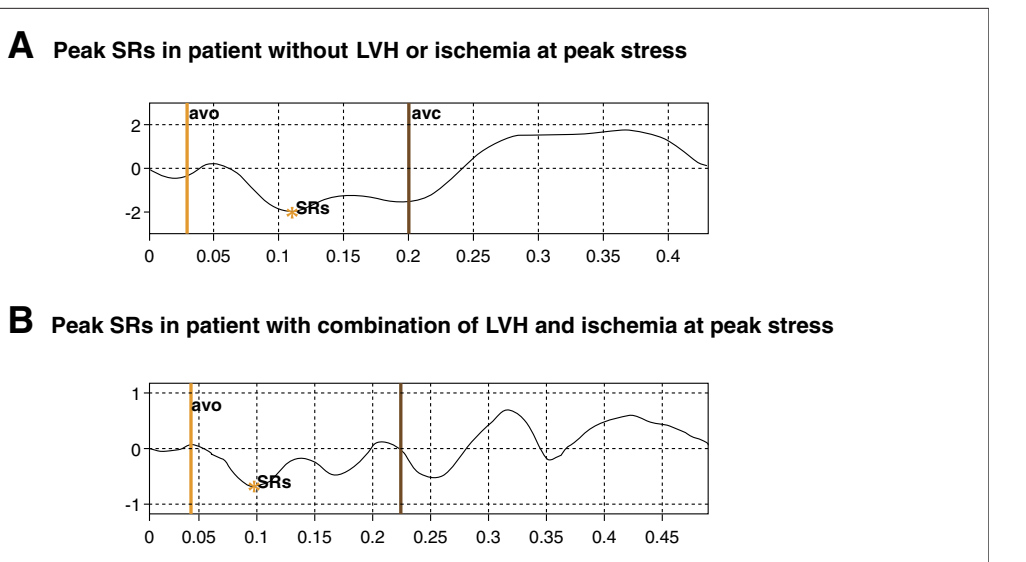

Figure 1. Examples of SRs Curves

Examples of peak systolic strain rate (SRs) curves in **(A)** patient without left ventricular hypertrophy (LVH) or ischemia at peak stress and **(B)** patient with LVH and ischemia at peak stress. avc = aortic valve closure; avo = aortic valve opening.

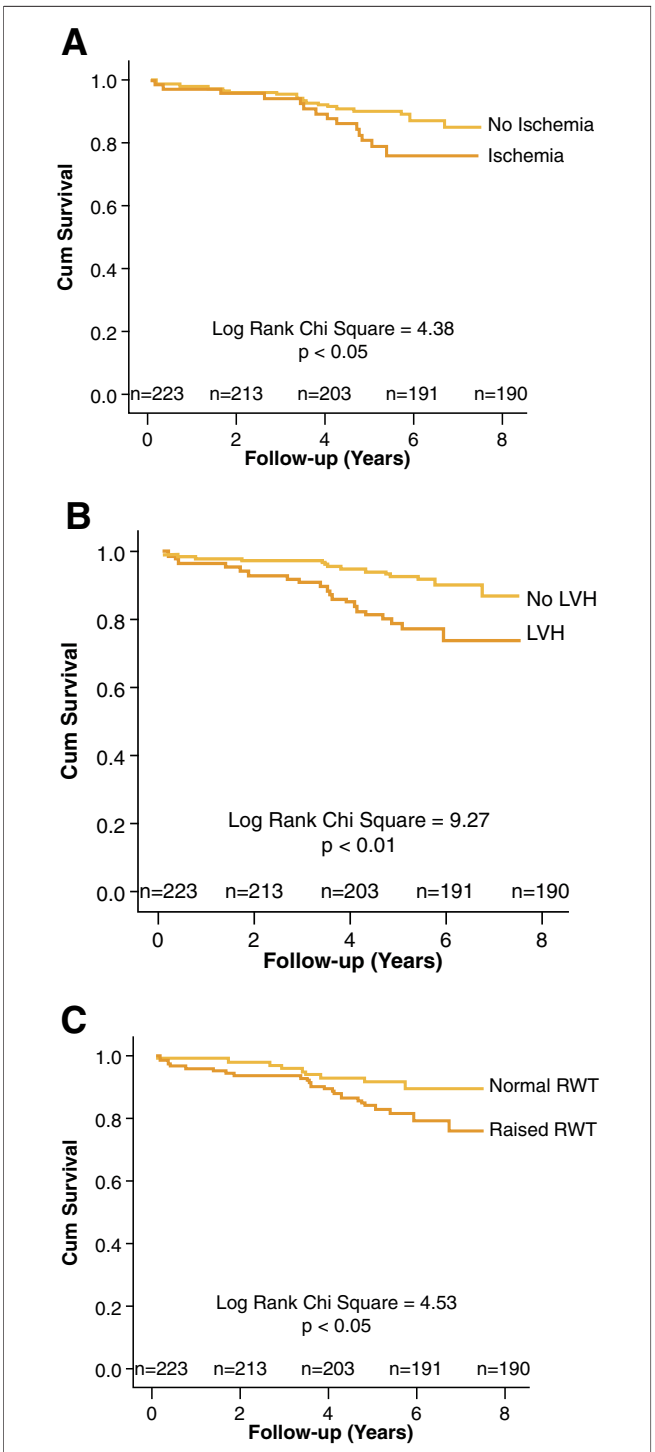

Figure 2. Kaplan-Meier Curves Depicting Event-Free Survival for Ischemia, LVH, and RWT

Kaplan-Meier curves depicting event-free survival in **(A)** individuals with and without myocardial ischemia at dobutamine stress echocardiography, **(B)** individuals with and without left ventricular hypertrophy (LVH), and **(C)** individuals with normal and raised relative wall thickness (RWT). The n values along the x-axis show individuals at risk for each follow-up period.

the 63 patients with ischemia (−1.97 ± 0.50 vs. −2.68 ± 0.55, $p < 0.01$) and the 83 patients with LVH (−2.31 ± 0.69 vs. −2.58 ± 0.55; $p < 0.01$). Likewise, global SEs was reduced in both ischemia (−9.1 ± 4.5 vs. −13.3 ± 4.7; $p < 0.01$) and LVH (−11.1 ± 5.0 vs. −12.8 ± 4.7; $p < 0.05$).

Follow-up. The mean follow-up time was 5.4 ± 1.4 years, and over the course of follow up, 33 individuals died (14.8%). The significant univariate predictors of mortality from data known before DSE were: LVH (hazard ratio [HR]: 2.82, 95% confidence interval [CI]: 1.40 to 5.68); diabetes (HR: 2.32, 95% CI: 1.14 to 4.73); resting heart rate (HR: 1.44, 95% CI: 1.06 to 1.94); and RWT (HR: 1.42, 95% CI: 1.11 to 1.83). Significant univariate predictors of mortality from data obtained from DSE were: SRs (HR: 2.22, 95% CI: 1.66 to 2.96); ischemia (HR: 2.07, 95% CI: 1.03 to 4.14); SEs (HR: 1.52, 95% CI: 1.11 to 2.09); peak heart rate (HR: 0.97, 95% CI: 0.95 to 1.00), and peak SBP (HR: 0.67, 95% CI: 0.47 to 2.09). Left ventricular hypertrophy was the strongest baseline clinical predictor of outcome, and SRs was the strongest predictor at peak stress.

TOTAL POPULATION. For the total population, the baseline LVH (HR: 2.80, 95% CI: 1.39 to 5.63, $p < 0.01$) and resting heart rate (HR: 1.45, 95% CI: 1.06 to 1.99, $p < 0.05$) were significant independent predictors. However, after the addition of variables obtained from DSE, only SRs (HR: 2.16, 95% CI: 1.63 to 2.87, $p < 0.01$) and peak SBP (HR: 0.69, 95% CI: 0.48 to 0.99, $p < 0.05$) were significant.

MYOCARDIAL ISCHEMIA. Ischemia was associated with reduced survival (Fig. 2). The independent predictors of all-cause mortality in those without ischemia at DSE were LVH (HR: 3.64, 95% CI: 1.42 to 9.33, $p < 0.01$) and resting heart rate (HR: 1.91, 95% CI: 1.30 to 2.82, $p < 0.01$). The addition of variables obtained from DSE to the model demonstrated that strain rate was the strongest predictor (HR: 1.74, 95% CI: 1.16 to 2.63, $p < 0.01$), although resting heart rate was also retained (HR: 1.65, 95% CI: 1.12 to 2.45, $p < 0.05$). In those with ischemia, none of the clinical variables were significant predictors, but SRs was a significant predictor (HR: 3.09, 95% CI: 1.66 to 5.74, $p < 0.01$).

LVH. The effect of LVH on survival is shown in Figure 2. Only diabetes (HR: 3.67, 95% CI: 2.10 to 27.78, $p < 0.01$) was a significant predictor in those

Table 2. Comparison of Patients With/Without Ischemia and LVH

	LVH (−) Ischemia (−) (n = 106)	LVH (+) Ischemia (−) (n = 54)	LVH (−) Ischemia (+) (n = 34)	LVH (+) Ischemia (+) (n = 29)
Age (yrs)	56.4 ± 11.9	60.0 ± 12.3	62.3 ± 10.3	66.8 ± 8.3*†
Weight (kg)	75.6 ± 15.8	81.8 ± 19.6	73.4 ± 14.1	79.6 ± 17.8
Height (m)	1.69 ± 0.09	1.66 ± 0.11	1.70 ± 0.09	1.65 ± 0.10*
Body mass index (kg/m^2)	26.4 ± 5.1	29.7 ± 6.3‡	27.4 ± 4.2	29.2 ± 5.4*
Body surface area (m^2)	1.86 ± 0.21	1.89 ± 0.24	1.90 ± 0.19	1.86 ± 0.23
Male sex	50.9	53.7	64.7	55.2
Diabetes mellitus (fasting glucose >7.0 mmol/l)	11.3	33.3‡	29.4§	27.6*
Hypertension (BP >140/90 mm Hg)	44.3	64.8‡	52.9	69*†
Hypercholesterolemia (total cholesterol >4.0 mmol/l)	35.8	37.0	34.7§‖	51.7*
Current or previous angina	36.8	27.8	70.6§‖	48.3*
Smoking	24.5	14.8	17.6	17.2
Beta-blocker therapy	18.9	27.8	70.6§‖	44.8*†
Calcium channel blockers	21.7	33.3	29.4	34.5
Nitrate therapy	17	14.8	47.1§‖	41.4*†¶
Strain SEs (%)	−13.66 ± 4.21	−12.73 ± 4.86	−9.94 ± 4.95§‖	−8.07 ± 3.73*†¶
Strain rate SRs (s^{-1})	−2.75 ± 0.46	−2.56 ± 0.67	−2.08 ± 0.51§‖	−1.85 ± 0.47*†¶

All data are expressed as mean ± SD; SRs, resting heart rate, peak SBP all analyzed per unit SD. Data are expressed as % unless otherwise stated. Scheffe post hoc testing was used for between-groups analysis of variance (ANOVA). Chi square testing was carried out for differences between categorical variables. *$p < 0.05$ overall between 4 groups (ANOVA); †$p < 0.05$ overall between groups 1 and 4; ‡$p < 0.05$ between groups 1 and 2; §$p < 0.05$ between groups 1 and 3; ‖$p < 0.05$ between groups 2 and 3; ¶$p < 0.05$ between groups 2 and 4.
BP = blood pressure; LVH = left ventricular hypertrophy; SEs = global end-systolic strain at peak stress; SBP = systolic blood pressure; SRs = global peak systolic strain rate at peak stress.

without LVH from baseline variables. The addition of variables obtained from DSE to the model retained diabetes (HR: 7.64, 95% CI: 2.10 to 27.78, $p < 0.01$) but also added SRs (HR: 3.66, 95% CI: 2.12 to 6.30, $p < 0.01$) and peak SBP (HR: 0.37, 95% CI: 0.21 to 0.66, $p < 0.01$). In those with LVH the only significant predictor was SRs (HR: 1.61, 95% CI: 1.08 to 2.39, $p < 0.01$).

LVH AND ISCHEMIA. The group was partitioned into 4 groups on the basis of the presence or absence of LVH and the presence or absence of ischemia at DSE (Table 2). Log-rank comparison between groups showed significantly better survival in patients with neither LVH nor ischemia ($p < 0.05$) compared with each of the other 3 groups (Fig. 3).

The SRs was the only variable found to be a significant, independent predictor of all-cause mortality in each of these 4 groups. It was also the strongest predictor in the overall group and in 3 of the 4 subgroups (Table 3). When the presence/absence of ischemia and LVH were combined, there was a clear stepwise gradation in SRs and SEs from the group without LVH or ischemia toward the group with both (Fig. 3).

LV geometry and RWT. The combination of LVMI and RWT allows for partition into 4 categories of LV geometry: normal (LVMI <51 g/m$^{2.7}$, RWT ≤0.42, n = 76 [34.1%]), concentric remodeling (LVMI <51 g/m$^{2.7}$, RWT >0.42, n = 64 [28.7%]), eccentric hypertrophy (LVMI ≥51 g/m$^{2.7}$, RWT ≤0.42, n = 23 [10.3%]), and concentric hypertrophy (LVMI ≥51 g/m$^{2.7}$, RWT >0.42, n = 60 [26.9%]). The only significant difference in outcome was between the normal geometry and concentric LVH groups ($p < 0.01$) (Fig. 3). Predictors of outcome for each geometric group are shown in Table 4. The SRs was the strongest predictor in every group apart from eccentric LVH. This is most likely due to the inability of the test to establish predictors in such a small sample (n = 23).

Mean RWT for the total population was 0.46 ± 0.11. Those with abnormal RWT (n = 124) had worse survival compared with normal RWT (n = 99; $p < 0.05$) (Fig. 2). In contrast to LVH, however, there was no significant difference between the groups for SRs (normal RWT 2.54 ± 0.58 s^{-1} vs. abnormal RWT 2.44 ± 0.65 s^{-1}, $p > 0.05$). Diabetes (HR: 2.90, 95% CI: 1.28 to 6.56, $p < 0.01$) predicted outcome in those with abnormal RWT. However, after entering variables obtained at DSE, SRs (HR: 2.31, 95% CI: 1.66 to 3.23, $p < 0.01$) was the only predictive factor (Table 4). In those with normal

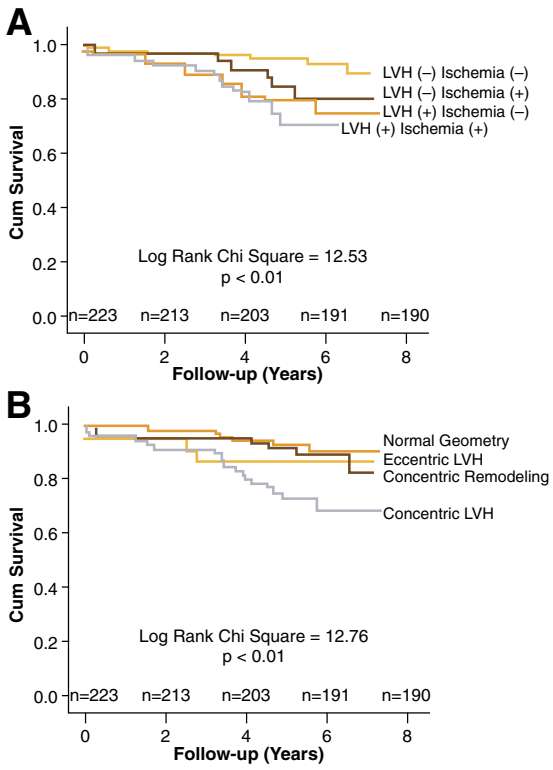

Figure 3. Kaplan-Meier Curves Depicting Event-Free Survival for Subgroups on the Basis of Presence/Absence of Ischemia and LVH and LV Geometry

Kaplan-Meier curve depicting event-free survival for individuals **(A)** grouped by the presence (+)/absence (−) of left ventricular hypertrophy (LVH) and ischemia and **(B)** according to their left ventricular geometry. The n values along the x-axis show individuals at risk for each follow-up period.

RWT, none of the baseline or subsequent DSE variables was predictive of mortality.

Independent and incremental value of SRs over baseline and DSE-obtained variables. For the population as a whole, the model was fitted to reflect the variables taken into account in routine clinical practice. Baseline variables had an overall chi-square of 16.15. The addition of variables obtained at DSE increased the model's power significantly. The incremental value of SRs led to a further significant increase in model power (Fig. 4). The same series of stepwise Cox models were undertaken for those with and without ischemia and those with and without LVH (Fig. 5). The SRs was significantly incremental to the model in each subgroup, with the exception of those without ischemia ($p = 0.19$).

Fewer than one-third of patients were receiving maintenance therapy with negative inotropic drugs, which were withdrawn before testing. There was no significant difference in strain rate between those taking and those not taking calcium channel blockers ($-2.42 \pm 0.66\ s^{-1}$ vs. $-2.51 \pm 0.61\ s^{-1}$, $p = 0.62$). Those taking chronic beta-blockade had reduced global SRs compared with those who were not ($-2.22 \pm 0.53\ s^{-1}$ vs. $-2.61 \pm 0.63\ s^{-1}$, $p < 0.05$), possibly influenced by the significant increase in the number of individuals with ischemia in this group compared with those not taking beta-blockers (51.4% vs. 17.2%, $p < 0.01$).

Table 3. Predictors of All-Cause Mortality in Those With/Without LVH and Myocardial Ischemia

	Baseline				Baseline and DSE Obtained			
		HR	95% CI	p Value		HR	95% CI	p Value
LVH (−) Ischemia (−) (n = 106)	Resting heart rate	2.18	1.30–3.65	<0.01	SRs	3.83	1.60–9.15	<0.05
					Resting heart rate	2.29	1.34–3.94	<0.01
LVH (−) Ischemia (+) (n = 34)					SRs	4.98	1.75–14.16	<0.01
					Peak SBP	0.30	0.10–0.83	<0.05
LVH (+) Ischemia (−) (n = 54)								
LVH (+) Ischemia (+) (n = 29)					SRs	11.73	2.13–64.45	<0.01

SRs, resting heart rate, peak SBP all analyzed per unit SD.
CI = confidence interval; DSE = dobutamine stress echo; HR = hazard ratio; (+) = presence of; (−) = absence of; other abbreviations as in Table 2.

Table 4. Predictors of All-Cause Mortality From LV Geometric Patterns

	Baseline				Baseline and DSE Obtained			
		HR	95% CI	p Value		HR	95% CI	p Value
Normal geometry (n = 76)					SRs	2.16	1.05–4.43	<0.05
Concentric remodeling (n = 64)	Diabetes	6.31	1.39–28.74	<0.05	SRs	7.24	2.18–24.05	<0.01
					Peak SBP	0.12	0.02–0.69	<0.05
Eccentric LVH (n = 23)								
Concentric LVH (n = 60)					SRs	1.76	1.18–2.63	<0.01
Normal RWT (n = 99)								
Raised RWT (n = 124)	Diabetes	2.90	1.28–6.56	<0.01	SRs	2.31	1.66–3.23	<0.01

SRs, peak SBP, and relative wall thickness (RWT) all analyzed per unit SD.
Abbreviations as in Tables 2 and 3.

DISCUSSION

The association of myocardial deformation with stress and outcome might arise from not only ischemia but also LV hypertrophy, fibrosis, and infarction. In this study, although 5-year mortality was associated with ischemia, LVH, and their combination, myocardial deformation had an association with outcome that was independent of each. In groups divided according to the presence or absence of ischemia or LVH, SRs was the only common variable associated with mortality across the 4 groups and the strongest correlate in 3 groups (Table 3). These data suggest a contribution of myocardial properties to outcome.

The measurement of SRs is important, because this is a marker of regional contractile function (11), which is preferable to strain as a marker of myocardial function, especially during stress (6). Strain rate was the strongest predictor of mortality, independent of LVH and myocardial ischemia.

Increased LVMI was identified in 37% of our population. Left ventricular hypertrophy has many deleterious effects on myocardium, including decreased myocardial perfusion reserve and myocardial efficiency (12). Coronary microcirculatory dysfunction is present in LVH with raised RWT, with the subendocardium preferentially affected (13).

The association between LVH and SRs during DSE has not been previously described; our finding of reduced SRs in association with LVH clearly has implications for the use of this quantitative parameter as an adjunct to the interpretation of DSE. There is a paucity of published data concerning myocardial deformation and LVH. Our study has investigated the ability of these techniques to detect subclinical myocardial change in a clinical population undergoing DSE.

Not only LV mass but also LV geometry is a determinant of outcome. The increasing risk associated with progression from normal geometry to concentric remodeling and then concentric hypertrophy (1,14) was witnessed in our population. Individuals with concentric LVH have a worse prognosis than those with eccentric LVH, irrespective of ischemic status (15). Resting SRs is significantly lower in those with concentric hypertrophy compared with those with normal geometry, independent of age, sex, and blood pressure (16). These findings suggest that SRs might reflect interstitial changes in those with concentric geometry.

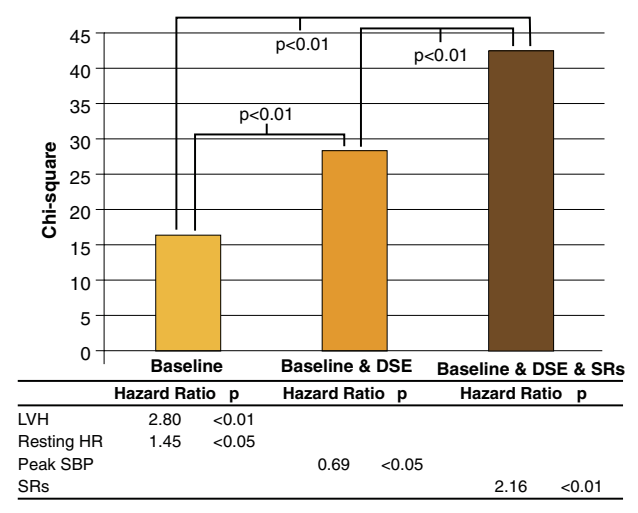

Figure 4. Prediction of Outcome for the Total Population

Model chi-square values are presented for a series of Cox models, together with a table showing significant predictors of outcome from each block. *p < 0.01. DSE = variables obtained at dobutamine stress echocardiography; HR = heart rate; LVH = left ventricular hypertrophy; SBP = systolic blood pressure; SRs = strain rate.

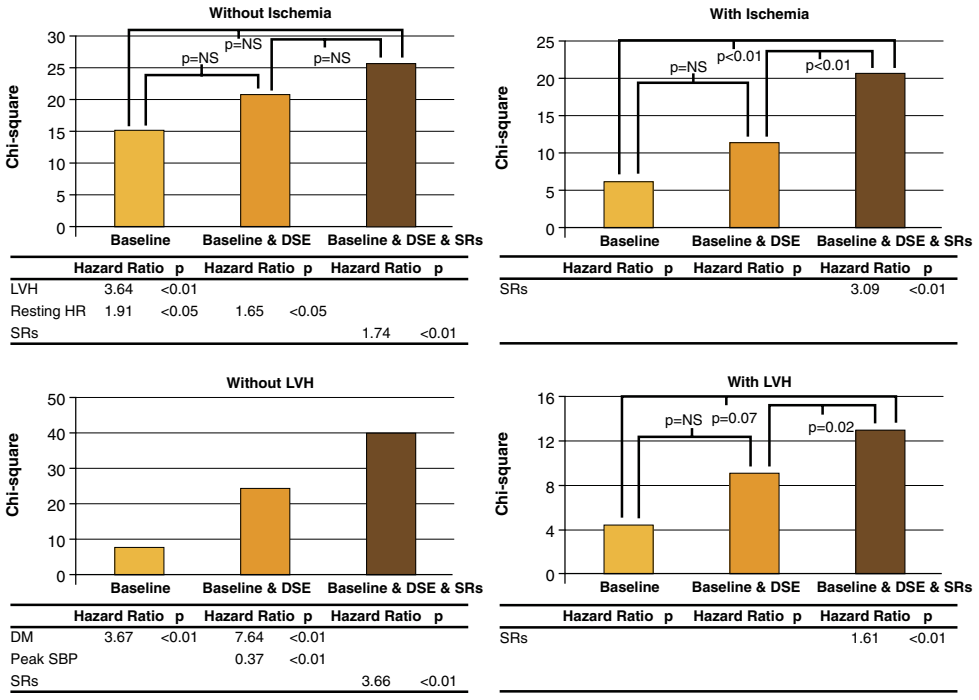

Figure 5. Prediction of Outcome in Individuals With and Without Ischemia and LVH

Model chi-square values for a series of Cox models predicting outcome in individuals with/without ischemia and individuals with/without LVH, with significant predictors of outcome from each model. DM = diabetes mellitus; other abbreviations as in Figure 4.

As previously described, the combination of LVH and ischemia demonstrated the additive influence of these parameters on subsequent mortality (Fig. 3). Interestingly, the combination of these pathologies was reflected in abnormal SRs; the progression from normal geometry to LVH alone, ischemia alone, and then LVH and ischemia combined was paralleled by a stepwise reduction of SRs. This corresponded with the independent association of SRs with mortality.

Study limitations. Despite the consistent message from the study results, several limitations of the study need to be considered. First, the use of Doppler-based strain rate permitted assessment of longitudinal rather than radial and circumferential myocardial deformation. Second, the diagnosis of ischemia was based on the subjective assessment of an experienced observer. This reflects the performance of DSE in the clinical evaluation of our patients—among whom a negative test for ischemia (72% of our population) would not normally result in the patient proceeding to diagnostic coronary angiography. Moreover, individuals without ischemia diagnosed at DSE were indeed at low risk of coronary heart disease (men 3 ± 2%, women 5 ± 3%) (17). Third, although some patients were taking medical therapy, we do not think this is a major issue for several reasons, because <30% had been taking either drug, and our standard protocol is to withdraw beta-adrenoceptor and calcium channel antagonists on the day before the test. Finally, all-cause mortality rather than cardiac mortality was examined, because the classification of cardiac death is often problematic (18). However, because the mean age of our population was 60 ± 12 years, we would expect most deaths to be cardiac in origin.

CONCLUSIONS

Both LVH and myocardial ischemia have a strong association with prognosis. However, the associations of both LV geometry and deformation on outcome suggest that other processes, including LV interstitial changes, might be associated with mortality.

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