

Attenuation of Stress-based Ventricular Contractility in Patients with Heart Failure and Normal Ejection Fraction

Liang Zhong,¹ PhD, Kian Keong Poh,² MD, Li Ching Lee,² MD, Thu Thao Le,¹ MSc, Ru San Tan,¹ MD

Abstract

Introduction: The maximal rate of change of pressure-normalised wall stress $d\sigma^*/dt_{max}$ has been proposed as cardiac index of left ventricular (LV) contractility. In this study, we assessed the capacity of $d\sigma^*/dt_{max}$ to diagnose heart failure with normal ejection fraction (HFNEF). **Materials and Methods:** One hundred healthy normal controls and 140 patients admitted with heart failure (100, HFREF and 40, HFNEF) underwent echocardiography for stress-based contractility $d\sigma^*/dt_{max}$. Patients with significant valvular heart disease were excluded. Tissue Doppler indices were also measured. **Results:** $d\sigma^*/dt_{max}$ was $4.43 \pm 1.27 \text{ s}^{-1}$ in control subjects; reduced in HFNEF, $3.02 \pm 0.98 \text{ s}^{-1}$; and HFREF, $2.00 \pm 0.67 \text{ s}^{-1}$ ($P < 0.001$). In comparison with age- and sex-matched groups ($n = 26$ each), we found similar trend on reduction of $d\sigma^*/dt_{max}$ (normal control; $3.91 \pm 0.87 \text{ s}^{-1}$; HFNEF, $2.90 \pm 0.84 \text{ s}^{-1}$; HFREF, $1.84 \pm 0.59 \text{ s}^{-1}$, $P < 0.001$). On multivariate analysis, $d\sigma^*/dt_{max}$ was found to be the independent predictor of HFNEF and HFREF. The area under the curve of the receiver operating characteristics (ROC) in detecting HFNEF compared with normal controls ($d\sigma^*/dt_{max} > 3.2 \text{ s}^{-1}$) was 0.84 ($P < 0.0001$), and in detecting HFREF compared with HFNEF ($d\sigma^*/dt_{max} > 2.32 \text{ s}^{-1}$) was 0.88 ($P < 0.0001$). **Conclusion:** This data confirms that $d\sigma^*/dt_{max}$ on echocardiography is a powerful independent predictor in patients with HFNEF. In a population with a high suspicion of HFNEF, $d\sigma^*/dt_{max}$ may significantly contribute to early diagnosis and hence be useful in the triage and management of HFNEF patients.

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Key words: Echocardiography, Heart failure with normal ejection fraction, Normalised wall-stress

Introduction

Heart failure (HF) is a major health care burden: it is the leading cause of hospitalisation in persons older than 65 years,¹ and confers an annual mortality of 10%.² HF can occur with either normal or reduced left ventricular (LV) ejection fraction (EF). Patients with heart failure with normal ejection fraction (HFNEF) generally have concentric LV remodeling with increased wall thickness (due to increased cardiomyocyte diameter and extracellular matrix collagen), whereas patients with HFREF often exhibit eccentric remodeling with an increase in end-diastolic volume (due to increased cardiomyocyte length).³ Both HF with normal EF (HFNEF) and HF with reduced EF (HFREF), also commonly known as diastolic and systolic HF, respectively, have equally poor prognosis.⁴ Many studies have reported that various systolic function indices are mildly depressed in patients with HFNEF.^{5,6} Abnormalities

demonstrated include a reduction in long-axis shortening,⁷ a decline in systolic velocity of basal myocardial and mitral valve annular motion⁸ and abnormalities of both strain and strain rate.⁹ Indeed, it is well recognised that impairments in myocardial contractility may coexist with HFNEF.¹⁰ A novel LV contractility index, $d\sigma^*/dt_{max}$ (maximal rate of change of pressure-normalised wall stress) was previously validated¹¹ and used in recent study.¹² The objective of this study is to establish the clinical utility of $d\sigma^*/dt_{max}$ as a tool for diagnosis of HFNEF.

Materials and Methods

Subjects

Patients referred to our echocardiography service with symptoms and signs of heart failure as assessed by expert cardiologists by use of the Framingham criteria¹³ underwent echocardiography and electrocardiography (ECG). Patients

¹ Department of Cardiology, National Heart Centre, Singapore

² Cardiac department, National University Hospital, Singapore

Address for Correspondence: Dr Liang Zhong, National Heart Centre, Mistri Wing 17, Third Hospital Avenue, 168752, Singapore.

Email: zhong.liang@nhcs.com.sg

with atrial fibrillation, more than mild mitral or aortic valvular regurgitation, and unsatisfactory echocardiographic images were excluded. All patients had either NYHA III or IV heart failure. Patients with HF possessing a LVEF $\geq 50\%$ were deemed to have normal LVEF, in accordance with recent consensus recommendations.¹⁴ All subjects gave informed consent. The hospital ethics committee approved the study.

Echocardiography Study

Transthoracic echocardiography was performed using echocardiographic imaging system (Vivid 7, GE, Vingmed) by registered diagnostic cardiac sonographers. Ventricular dimensions, wall thickness, chamber volumes, stroke volume and myocardial volume were determined from 2-dimensional and M-mode measurement using standard methods.¹⁴ For measurement of LV diastolic filling pattern, mitral flow velocities were obtained from the apical 4-chamber view using pulsed wave Doppler technique with the sample volume at the tips of the mitral valve leaflets. Peak E (peak early trans-mitral filling velocity during early diastole) and A (peak trans-mitral atrial filling velocity during late diastole) wave velocities (cm/s) were measured and E/A ratio was calculated. E wave deceleration time (DT) was also calculated as the time elapsed between peak E velocity and the point where the extrapolation of the deceleration slope of E velocity crosses the zero baseline measured in milliseconds. LV outflow tract velocity was obtained from apical 5-chamber view, using pulsed wave Doppler technique with the sample volume at the aortic annular level. LVOT maximal velocity V_{peak} was measured. Myocardial tissue Doppler (TDI) velocities were also estimated at the septal and lateral mitral annular positions, in the apical 4 chamber view. All measurements were averaged over 3 cardiac cycles. Brachial blood pressure was determined by sphygmomanometry. End-systolic pressure was determined from the product of $0.9 \times$ systolic blood pressure. Effective arterial elastance ($E_a = \text{end-systolic pressure} \div \text{stroke volume}$) and circumferential end-systolic wall stress (cESS) were determined as measures of ventricular afterload.¹⁰

Assessment of Ventricular Contractility in Terms of Stress-based Index $d\sigma^*/dt_{\text{max}}$

During LV contraction, myocardial sarcomere activation generates myocardial wall stress, which in turn induces intracavitary pressure. Rate of pressure development is assessed by maximal dP/dt . As myocardial wall stress precedes LV intracavitary pressure, we believe myocardial wall stress to be a logical substrate for development of quantitative assessment of ventricular performance. By

using biomechanical model,¹¹

LV wall stress is expressed as:

$$\sigma = P \left(\frac{3V}{2V_m} + \frac{1}{2} \right) \quad (1)$$

where σ is wall stress,

P and V are LV intracavitary pressure and volume, and V_m is myocardial volume.

Rearranging the equation, we get:

$$\sigma^* = \frac{\sigma}{P} = \left(\frac{3V}{2V_m} + \frac{1}{2} \right) \quad (2)$$

Analogous to dP/dt_{max} , we defined $d\sigma^*/dt_{\text{max}}$ as:

$$d\sigma^*/dt_{\text{max}} = \frac{3(dV/dt)_{\text{max}}}{2V_m} \quad (3)$$

where σ^* is σ/P or pressure-normalised wall stress, and dV/dt_{max} , maximal flow rate.

The latter is easily calculated from standard echocardiography: product of maximal left ventricular outflow tract (LVOT) velocity on pulse-wave Doppler echo, V_{peak} , and LVOT area:

$$dV/dt_{\text{max}} = V_{\text{peak}} \times \pi D^2/4 \quad (4)$$

where D is the LVOT diameter measured in the 2-dimensional parasternal long-axis image of the heart. Myocardial volume is calculated from the quotient of LV mass (obtained from standard M-mode echocardiography) and myocardial density (assumed to be 1.05 g/ml).

Statistical Analysis

Results from normally distributed continuous data are shown as mean $\pm$ SD. Continuous variables were compared by the use of one-way analysis of variance (ANOVA) with Bonferroni correction. In the age- and sex-matched study, multinomial logistic regression analysis was performed to find predictor for HFNEF and HFREF. In addition, receiver operating characteristics (ROC) curves were used to determine the predictive power of $d\sigma^*/dt_{\text{max}}$ for HFNEF and HFREF. A P value of <0.05 was considered significant. Statistical analysis was performed with SPSS software.

Results

Patients

We recruited 100 subjects with heart failure and reduced ejection fraction (HFREF) and 40 with heart failure and normal ejection fraction (HFNEF), and compared to these with 100 healthy subjects. The subject characteristics are listed in Table 1. HFNEF patients were likely to be older,

female, and had higher prevalence of hypertension than normal controls. Mean $d\sigma^*/dt_{max}$ was $4.43 \pm 1.27 \text{ s}^{-1}$ in control subjects; reduced in HFNEF, $3.02 \pm 0.98 \text{ s}^{-1}$; and HFREF, $2.00 \pm 0.67 \text{ s}^{-1}$. There were significantly higher values of LVEF, heart rate (HR), and systolic blood pressure (SBP) in HFNEF compared to normal controls. As expected, diastolic function (i.e., higher peak A, DT, septal E/E' and lateral E/E', lower E/A ratio, septal E' and lateral E')

Table 1. Patients Characteristics and Echocardiographic Measurements in Control, HFNEF and HFREF

Variables	Controls (n = 100)	HFNEF (n = 40)	HFREF (n = 100)
Age (years)	38 ± 17	69 ± 11 [§]	63 ± 12 ^{§*}
Male, %	70	30 [§]	77*
Height, cm	168 ± 9	155 ± 9 [§]	161 ± 12 ^{§*}
Weight, kg	63 ± 10	65 ± 15	65 ± 16
BSA (m ²)	1.71 ± 0.16	1.66 ± 0.20	1.69 ± 0.18
HR (beats/min)	63 ± 10	71 ± 11 [§]	78 ± 12 ^{§*}
Hypertension, %	20	30 [§]	35 [§]
DBP (mmHg)	71 ± 11	75 ± 12	74 ± 14
SBP (mmHg)	125 ± 21	136 ± 24 [§]	123 ± 24*
LVEF (%)	67 ± 5	71 ± 7 [§]	27 ± 9 ^{§*}
Echocardiographic Measurement			
EDD (cm)	4.81 ± 0.41	4.52 ± 0.64 [§]	5.87 ± 0.80 ^{§*}
EDV (ml) (M-mode)	109 ± 22	96 ± 32	176 ± 53 ^{§*}
EDV (ml) (Biplane)	110 ± 27	93 ± 24	164 ± 50 ^{§*}
Stroke volume index (ml/m ²)	43 ± 10	43 ± 10	28 ± 8 ^{§*}
LV mass index (g/m ²)	74 ± 16	114 ± 31 [§]	126 ± 37 [§]
Relative wall thickness	0.33 ± 0.06	0.51 ± 0.13 [§]	0.32 ± 0.11*
LV Diastolic Function			
E (cm/s)	79 ± 16	74 ± 24	74 ± 22
A (cm/s)	53 ± 17	90 ± 26 [§]	64 ± 24 ^{§*}
E/A ratio	1.64 ± 0.60	0.84 ± 0.27 [§]	1.44 ± 0.96*
DT (ms)	182 ± 27	237 ± 62 [§]	152 ± 47 ^{§*}
Septal E' (cm/s)	12.3 ± 3.5	7.8 ± 3.8 [§]	6.0 ± 1.9 ^{§*}
Septal E/E'	6.9 ± 2.0	10.4 ± 4.2 [§]	13.3 ± 5.3 ^{§*}
Lateral E' (cm/s)	16.3 ± 4.8	8.8 ± 3.4 [§]	7.7 ± 2.2 [§]
Lateral E/E'	5.2 ± 1.6	9.2 ± 3.9 [§]	10.2 ± 4.0 [§]
LV Systolic Function			
Septal S' (cm/s)	9.0 ± 1.8	8.5 ± 3.0	5.8 ± 2.5 ^{§*}
Lateral S' (cm/s)	11.4 ± 3.0	9.6 ± 3.5 [§]	6.5 ± 2.0 ^{§*}
$d\sigma^*/dt_{max}$ (s ⁻¹)	4.4 ± 1.2	3.0 ± 0.9 [§]	2.0 ± 0.7 ^{§*}

A: mitral atrial flow velocity on echo-Doppler; BSA: body surface area; HR: heart rate; DBP: diastolic blood pressure; SBP: systolic blood pressure; EDD: end-diastolic diameter; EDV: end-diastolic volume; DT: mitral E deceleration time; E: mitral early velocity; E': septal mitral annular myocardial velocity on tissue Doppler imaging; LVEF: left ventricular ejection fraction.

The values are expressed as mean ± SD.

§ and * denote statistically significant difference of HF compared to controls, HFREF compared to HFNEF patients, respectively. (Bonferroni pairwise test, *P* value <0.05)

Table 2. Echocardiographic Measurements in Age- and Sex-matched Control, HFNEF and HFREF

Variables	Controls (n = 26)	HFNEF (n = 26)	HFREF (n = 26)
EDD (cm)	4.81 ± 0.38	4.61 ± 0.61	5.74 ± 0.84 ^{§*}
EDV (ml) (M-mode)	109 ± 19	100 ± 31	167 ± 53 ^{§*}
EDV (ml) (Biplane)	100 ± 23	90 ± 31	154 ± 48 ^{§*}
LVEF (%)	68.3 ± 5.1	66.5 ± 4.9	33 ± 13.7 ^{§*}
LV diastolic function			
E/A ratio	0.96 ± 0.38	0.78 ± 0.24	1.26 ± 0.90*
DT (ms)	214 ± 47	214 ± 67	157 ± 41 ^{§*}
Septal E/E'	8.48 ± 2.10	9.79 ± 3.29	13.68 ± 4.78 ^{§*}
Lateral E/E'	6.64 ± 1.55	8.39 ± 2.76	10.28 ± 3.40 ^{§*}
LV afterload			
E _a (mmHg/ml)	1.70 ± 0.49	1.80 ± 0.60	2.69 ± 0.82 ^{§*}
cESS (g/cm ²)	133 ± 42	102 ± 26	231 ± 99 ^{§*}
LV systolic function			
Septal S' (cm/s)	7.3 ± 3.7	8.2 ± 3.1	5.4 ± 1.5*
Lateral S' (cm/s)	8.8 ± 4.8	9.3 ± 3.3	5.8 ± 1.5 ^{§*}
$d\sigma^*/dt_{max}$ (s ⁻¹)	3.91 ± 0.87	2.90 ± 0.84 ^{§*}	1.84 ± 0.59 ^{§*}

A: mitral atrial flow velocity on echo-Doppler; BSA: body surface area; HR: heart rate; DBP: diastolic blood pressure; SBP: systolic blood pressure; MBP: mean blood pressure; EDD: end-diastolic diameter; EDV: end-diastolic volume; DT: mitral E deceleration time; E: mitral early velocity; E': septal mitral annular myocardial velocity on tissue Doppler imaging; LVEF: left ventricular ejection fraction.

The values are expressed as mean ± SD.

[§] and * denote statistically significant difference of HF compared to controls, HFREF compared to HFNEF patients, respectively. (Bonferroni pairwise test, *P* value <0.05)

Table 3. Multivariate Logistic Regression for Each Variable to Predict (a) HFNEF Compared with Controls, (b) HFREF Compared with Controls, (c) HFREF Compared with HFNEF

Variables	Controls vs HFNEF Coefficient (95% CI)	Controls vs HFREF Coefficient (95% CI)	HFNEF vs HFREF Coefficient (95% CI)
Septal E/E'	-0.048 (-0.48, 0.38)	0.56 (-0.073, 1.20)	0.60 (0.039, 1.16)*
Lateral E/E'	0.51 (-0.13, 1.14)	0.15 (-0.64, 0.95)	-0.31 (-0.88, 0.26)
E/A ratio	-2 (-4.61, 0.64)	-1.06 (-3.58, 1.46)	0.54 (-1.34, 2.43)
DT	-0.002 (-0.019, 0.016)	-0.019 (-0.043, 0.004)	-0.018 (-0.036, 0)*
$d\sigma^*/dt_{max}$ (s ⁻¹)	-1.80 (-3.08, -0.51)*	-5.90 (-9.20, -2.92)*	-4.17 (-6.91, -1.46)*

*represents *P* <0.05

is impaired in HFNEF. Longitudinal systolic velocities septal S' and lateral S' are depressed in HFNEF compared to normal control.

In age- and sex-matched 26 subjects in each of three groups, mean $d\sigma^*/dt_{max}$ was 3.91 s⁻¹ (95%CI, 3.56-4.26 s⁻¹) in control subjects; reduced in HFNEF, 2.90 s⁻¹ (95% CI, 2.56-3.24 s⁻¹); and HFREF, 1.84 (95% CI, 1.60-2.07 s⁻¹) (Table 2). Amongst clinical and echocardiographic variables, $d\sigma^*/dt_{max}$ was the only independent predictor of HFNEF and HFREF on multinomial logistic regression analysis (Table 3). The coefficient for $d\sigma^*/dt_{max}$ was -1.80 (*P* = 0.006) between HFNEF and controls, and -5.90 (*P*

<0.001) between HFREF and controls, respectively. Area under ROC (receiver operating characteristic) curve for the prediction of HFNEF with $d\sigma^*/dt_{max}$ <3.20 s⁻¹ was 0.84 (*P* <0.001) (Fig. 1A) compared with controls; while area under ROC curve for the prediction of HFREF with $d\sigma^*/dt_{max}$ <2.32 s⁻¹ was 0.88 (*P* <0.001) (Fig. 1B) compared with HFNEF, respectively.

Chi-square model was performed for diagnosis of HFNEF compared with normal controls. Figure 2 showed that $d\sigma^*/dt_{max}$ was the greatest contributor (incremental χ^2) to the total model χ^2 for predicting HFNEF among normal LVEF subjects in this study. The marked increase in the cumulative

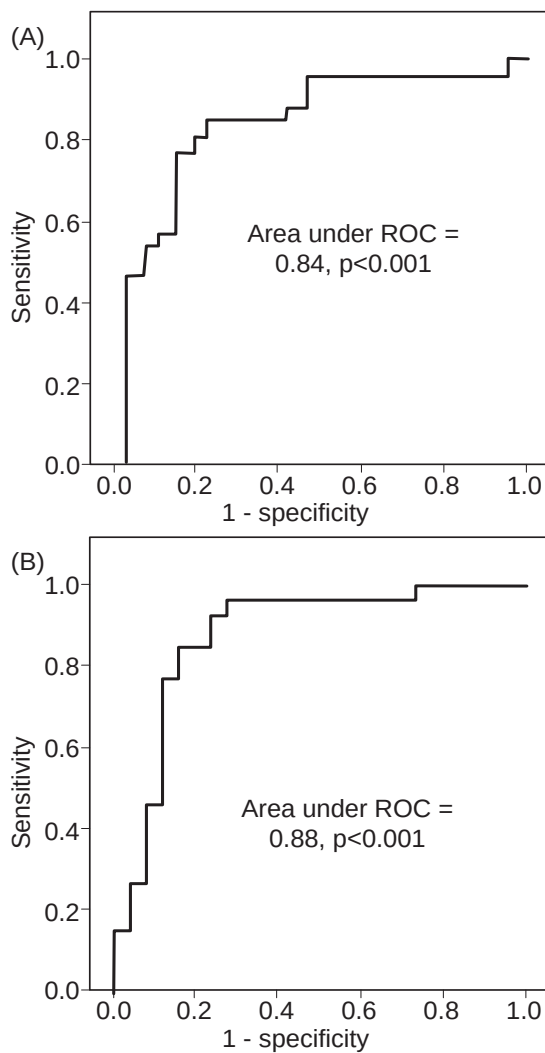


Fig. 1. The area under the receiver operating characteristic (ROC) curve is used for the detection of HFNEF and controls (A) and in HFREF and HFNEF patients (B), using decreased $d\sigma^*/dt_{max}$.

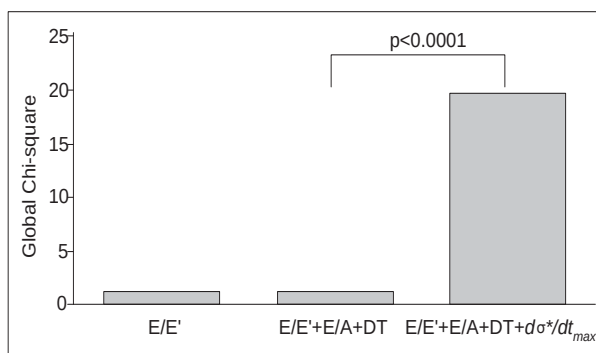


Fig. 2. Incremental value of E/E', E/A and DT and $d\sigma^*/dt_{max}$ variables for predicting heart failure with normal ejection fraction (HFNEF). Note the marked increase in the cumulative prognostic information provided by $d\sigma^*/dt_{max}$ over the presence of abnormal E/A and DT added to other tissue Doppler echocardiographic variables (i.e., septal E/E').

prognostic information provided by $d\sigma^*/dt_{max}$ was noted over the presence of abnormal E/A and DT added to other tissue Doppler echocardiographic variables (i.e., septal E/E').

Discussion

This study shows that patients with HFNEF have significantly reduced $d\sigma^*/dt_{max}$ compared to normal controls. On multinomial logistic regression analysis, $d\sigma^*/dt_{max}$ is the only independent predictor for HFNEF versus normal, and outperforms conventional diastolic and systolic parameters. This finding raises the possibility that patients with HFNEF have impaired ventricular contractility undetected by the measurements usually made when patients with suspected heart failure undergo echocardiographic assessment. Before accepting this point of view, one must ask what exactly does $d\sigma^*/dt_{max}$ measure and why should this index identify abnormalities apparently missed by conventional indices such as fractional shortening and left ventricular ejection fraction?

$d\sigma^*/dt_{max}$, the change rate of normalised wall stress derived from biomechanical model,¹¹ is quite different from left ventricular ejection fraction and other conventional measurement of left ventricular systolic function. It is related more to myocardial contractility.¹¹ Consistent with other study in the literature, LV wall stress was proposed as an intrinsic measure of LV contractile function.^{15,16} Since pressure is not always easily measurable, we conceived maximum pressure-normalised stress as a contractility indicator. This eliminates the pressure term and facilitates calculation of the index from noninvasive measurements. Pressure-normalised stress (σ/P) is, by no means, an arbitrary concept. It has also been employed by other investigators as an index of wall stress since it is a pure geometric parameter and represents the left ventricle's physical response to loading, and allows comparison between ventricles at different pressure. Furthermore, normalisation of ventricular measurements to the myocardial volume or mass has been used to standardise pressure volume relations.¹⁷⁻¹⁹ We have hence extended this concept and formulated an expression where $d\sigma^*/dt_{max}$ can be represented as the quotient of maximal left ventricular flow rate and myocardial volume.¹¹ Indeed, HFNEF have been reported to correlate with left ventricular mass and LV concentric hypertrophy, as evident from the studies, which reported a high LV wall mass-volume ratio in HFNEF.²⁰ This phenomenon allows the preservation of endocardial motion despite reduced shortening of individual fibers such that the EF remains normal.²¹ On the other hand, progressive LV remodeling contributes to a decrease in outflow rate.²² Our change rate of normalised wall stress index $d\sigma^*/dt_{max}$ is only dependent on outflow rate and wall volume of LV chamber and represents an integrated assessment of LV contractility.¹¹ These studies

provide a rationale supporting our observations relating $d\sigma^*/dt_{max}$ with HFNEF and HFREF.

Assessment of Patient with HFNEF

Although mechanisms for HFNEF remain incompletely understood, diastolic dysfunction is said to play a dominant role: i.e., impaired relaxation, increased passive stiffness, increased end-diastolic pressure (EDP). The increased EDP can be obtained by cardiac catheterisation and estimated by Doppler echocardiography. The recent criteria proposed by the European Society of Cardiology (ESC) included this condition for evaluation diastolic dysfunction in the diagnosis of HFNEF.²³ If the ratio E/E' is <8 , it is likely that LV filling pressure is normal; conversely, if the ratio is >15 , it is very unlikely that filling pressure is less than 15 mmHg. However, a ratio of 8 to 15 is more ambiguous, this limits the usage on diagnosis of HFNEF whose E/E' are located in this range. In our data, both the values of septal E/E' and lateral E/E' are 9.79 ± 3.29 and 8.39 ± 2.76 in HFNEF. This is the reason that E/E' is not the independent predictor for diagnosis of HFNEF in this study.

In fact, it is not the aim of this study to demonstrate the use of $d\sigma^*/dt_{max}$ as a sole clinical and diagnostic parameter to diagnose HFNEF. It will obviously require a different study design to demonstrate the diagnostic efficacy of $d\sigma^*/dt_{max}$ either in isolation or in combination with other parameters. Nevertheless, in this study, we aim to examine an index that we have developed from engineering precepts, and translated it into the clinical arena. We found that $d\sigma^*/dt_{max}$ can better differentiate normal versus HFNEF than conventional parameters of diastolic function. That our formulation for $d\sigma^*/dt_{max}$ reduces to so simple a formulation is a bonus that should garner clinical applicability. Further, the notion of LV mass as an independent diagnostic parameter in HF has been corroborated by preliminary reports by other groups.²⁰ However, none of these have arrived at this notion via the rational process and rigorous mathematical modeling that we have originated.

Contractility in Patients with HFNEF

The abnormal myocardial contractility may coexist with normal EF because concentric hypertrophy preserves the extent of endocardial motion in HFNEF.²¹ A number of studies have reported abnormalities in regional systolic function such as the longitudinal axis⁵⁻⁸ and strain and strain rate.⁹ However, all these measurements have been questioned because they can be altered by acute or chronic changes in preload, afterload and contractility and influenced by remodeling.³ Therefore, factors such as preload and afterload must be incorporated into the analysis to determine a true change in contractility. In this data, there is no significant

difference on preload (i.e. EDV) and afterload (i.e., effective arterial elastance E_a and circumferential end-systolic wall stress, $cESS$) in HFNEF compared to normal controls (Table 2). We measured systolic mitral annular velocity (septal S' and lateral S') and found septal S' and lateral S' are lower in HFNEF compared to controls (Table 1) (septal S' , 8.5 ± 3.0 cm/s vs 9.0 ± 1.8 cm/s, $P = 0.43$; lateral S' , 9.6 ± 3.4 cm/s vs 11.4 ± 3.0 cm/s, $P = 0.001$). Our index $d\sigma^*/dt_{max}$ in this study shows significantly impaired LV contractility in HFNEF. In a recent large, population-based study from ($n = 2042$), patients with HFNEF did display impaired contractility compared with normal controls subjects.¹⁰

Of course, there is increasing recognition that a “load-independent index of contractility” can not truly exist, because loading itself alter myofilament Ca^{2+} sensitivity and force-generation capacity.^{24,25} We performed load sensitivity testing of $d\sigma^*/dt_{max}$ in human subjects, which inevitably limits the extent of physiological manipulation in previous study.¹¹ Fortunately, there is no significant difference on loading condition (i.e, preload and afterload) in HFNEF compared to normal controls (Table 2).

Study Limitations

The present study is relatively small and uses a select referral-based retrospective population which may limit the statistical power and predictability. Further, the lack of gold standard for the diagnosis of HFNEF impacts the selection of patients. In this study, the diagnosis of heart failure was based on expert cardiology assessment of symptoms, signs, x-ray and response to diuretics treatment, following the Framingham recommendation.¹³

Conclusion

The diagnosis and management of HF and the evaluation of new therapeutic agents require sensitive measure of cardiac function. Because both the disease and its treatment are chronic processes, noninvasive methods that can be used serially are highly desirable. Our study suggests that decreased $d\sigma^*/dt_{max}$ is a reliable indicator of HF with normal ejection fraction. Because it is easily obtained at a steady state, it has clinical appeal. Future studies will need to assess the use of this parameter for improving the understanding of heart failure and targeting of heart failure therapies.

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REFERENCES

- Krumholz HM, Chen YT, Wang Y, Caccarino V, Radford MJ, Horwita RI. Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J* 2000;139:72-7.
- Stefan N. The failing heart – an engine out of fuel. *N Engl J Med* 2007;356:1140-51.
- Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation* 2006;113:296-304.
- Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004;43:317-27.
- Yip G, Wang M, Fung JWH. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for redefinition? *Heart* 2002;87:12-5.
- Garcia EH, Perna ER, Farias EF. Reduced systolic performance by tissue Doppler in patients with preserved and abnormal ejection fraction: new insight in chronic heart failure. *Int J Cardiol* 2006;108:181-8.
- Petrie MC, Caruana L, Berry C. Diastolic heart failure or heart failure caused by subtle left ventricular systolic function? *Heart* 2002;87:29-31.
- Bruch C, Gradaus R, Gunia S. Doppler tissue analysis of mitral annular velocities: evidence for systolic abnormalities in patients with diastolic heart failure. *J Am Soc Echocardiogr* 2003;16:1031-6.
- Pellerin D, Sharma R, Elliott P. Tissue Doppler, strain, and strain rate echocardiography for the assessment of left and right systolic ventricular function. *Heart* 2003;89:iii9-iii17.
- Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease: insights into the pathogenesis of heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2009;54:410-8.
- Zhong L, Tan RS, Ghista DN, Ng EYK, Chua LP, Kassab GS. Validation of a novel cardiac index of left ventricular contractility in patients. *Am J Physiol Heart Circ Physiol* 2007;292:H2764-H2772.
- Zhong L, Sola S, Tan RS, Le TT, Ghista DN, Kurra V, Navia JL, Kassab G. Effects of surgical ventricular restoration on LV contractility assessed by a novel contractility index. *Am J Cardiol* 2009;103:674-9.
- McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441-6.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for cardiac chamber quantification. *Eur J Echocardiogr* 2006;7:79-108.
- Nakano K, Sugawara M, Ishihara K, Kanazawa S, Corin WJ, Denslow S, et al. Myocardial stiffness derived from end-systolic wall stress and logarithm of reciprocal of wall thickness: contractility index independent of ventricular size. *Circulation* 1990;82:1352-61.
- DeAnda A Jr, Komeda M, Moon MR, Green GR, Bolger AF, Nikolic SD, et al. Estimation of regional left ventricular wall stress in intact canine heart. *Am J Physiol Heart Circ Physiol* 1998;275:H1879-H1885.
- De Wildet DJ, Sangster B. An evaluation of derived aortic blood flow parameters as indices of myocardial contractility in rate. *J Pharmacol Methods* 1983;10:55-64.
- Belcher P, Boerboom LE, Olinger GN. Standardization of end-systolic pressure-volume relation in the dog. *Am J Physiol Heart Circ Physiol* 1985;249:H547-H553.
- Goto T, Slinker BK, LeWinter MM. Similar normalized Emax and O2 consumption pressure-volume area relation in rabbit and dog. *Am J Physiol Heart Circ Physiol* 1988;255:H366-H374.
- Van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JGF, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006;113:1966-73.
- De Simone G, Devereux RB. Rationale of echocardiographic assessment of left ventricular wall stress and midwall mechanics in hypertensive heart disease. *Eur J Echocardiogr* 2002;3:192-8.
- Gerdes AM. Cardiac myocyte remodeling in hypertrophy and progression to failure. *J Card Fail* 2002;8:5264-8.
- Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
- Burkhoff D, de Tombe PP, Hunter WC, Kass DA. Contractile strength and mechanical efficiency of left ventricle are enhanced by physiological afterload. *Am J Physiol Heart Circ Physiol* 1991;260:H569-H578.
- Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;289:H501-H512.