Original Research

Extent of load-independence of pressure-normalized stress in swine

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Abstract

A load-independent index of myocardial contractility provides a measure of cardiac function. Previous contractility indices have been shown to be either load-dependent or invasive. We sought to determine the extent of load (preload and afterload)-independence of $d\sigma^*/dt_{max}$ (σ^* is pressure-normalized stress) in comparison with other well-established indices. Six anaesthetized pigs underwent left ventricular pressure–volume measurements under various load conditions. The average preload was decreased by $70.0 \pm 15.0\%$ (from 39.2 ± 6.4 mL to 11.7 ± 7.7 mL) and increased by $49.3 \pm 5.9\%$ (from 35.1 ± 7.4 mL to 51.7 ± 8.9 mL). The average afterload was increased by $74.3 \pm 43.5\%$ (from 3.3 ± 0.6 mmHg/mL to 5.7 ± 1.7 mmHg/mL). When preload was reduced within an average of 21.7% (39.2 ± 6.4 mL to 30.7 ± 6.2 mL) using occlusion of the inferior vena cava, $d\sigma^*/dt_{max}$ did not change significantly ($6.50 \pm 1.10\ s^{-1}$ vs $6.60 \pm 0.90\ s^{-1}$, $P =$ non-significant [NS]). When preload was increased within an average of 29.3% (35.1 ± 7.4 mL to 45.4 ± 7.3 mL) from infusion of normal saline, $d\sigma^*/dt_{max}$ did not change significantly ($7.04 \pm 1.00\ s^{-1}$ vs $7.29 \pm 1.10\ s^{-1}$, $P =$ NS). When afterload was increased within an average of 42.4% (3.3 ± 0.6 mmHg/mL to 4.7 ± 1.0 mmHg/mL) using intra-aortic balloon occlusion, $d\sigma^*/dt_{max}$ did not change significantly ($6.72 \pm 1.18\ s^{-1}$ vs $6.89 \pm 1.28\ s^{-1}$, $P =$ NS). As expected, $d\sigma^*/dt_{max}$ was significantly increased with dobutamine. A linear regression showed no correlation between $d\sigma^*/dt_{max}$ and preload ($r^2 = 0.02$, $P = 0.17$) within a maximum range of -30% to $+50\%$ of preload change, or between $d\sigma^*/dt_{max}$ and afterload ($r^2 = 0.03$, $P = 0.36$) within maximum range of 0–100% of afterload increase, respectively. In conclusion, $d\sigma^*/dt_{max}$ is independent of loading conditions within an average of 21.7% of preload decrease, 29.3% of preload increase, 42.4% of afterload increase, and sensitive to dobutamine infusion.

Keywords: preload, afterload, cardiac function, wall stress, cardiac mechanics

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Introduction

Many indices have been used to assess myocardial contractility,[1–6] including dP/dt_{max},[7–9] E_{max},[10,11] preload adjusted maximal power (PAMP),[12,13] peak aortic velocity (V_{peak})[14,15], and ejection fraction (EF). Despite the utility of these indices, most are load-dependent,[1,3,7,9–12,14,15] which precludes comparison under different load (preload and afterload) conditions. Although E_{max} is considered the 'gold standard' of load-independent indices of ventricular contractility, it requires multiple invasive pressure–volume measurements with varying loading conditions,[10,11] hence rendering it impractical for routine clinical use. Although EF is clinically practical and can be measured non-invasively with standard imaging (e.g. echocardiography, magnetic resonance imaging [MRI], etc.), it is known to be load-dependent and has significant shortcomings when the left ventricular (LV) volume increases as in heart failure (HF). It is thus clear that there is a clinical need for a load-independent, non-invasive measure of cardiac contractility.

Zhong *et al.*[16] recently validated a LV pressure-normalized wall stress index ($d\sigma^*/dt_{max}$) which can measure the ventricular contractility non-invasively using echocardiography[17,18] or MRI,[19,20] and its load-independent features have been confirmed in the range of clinical conditions.[16]

Since it is impractical to vary the preload and afterload more significantly in patients, the full range of the load-independence of this stress index remains unknown. The primary objective of this study was to evaluate the extent of the load-independent features of $d\sigma^*/dt_{max}$ under a wide variety of hemodynamic conditions with selective manipulation of preload and afterload and contractility. A secondary objective was to evaluate other well-established parameters such as EF, dP/dt_{max}, PAMP, and E_{max} under the same loading conditions for comparison.

Materials and methods

The maximal rate of change of pressure-normalized stress, $d\sigma^*/dt_{max}$, was derived based on a biomechanical model of the LV wall.[16] An analytical formulation showed that the pressure-normalized stress can be expressed in terms of LV cavity volume and myocardial volume as[16]:

$$(d\sigma^*/dt)_{max} = 3(dV/dt)_{max}/(2V_m) \quad (1)$$

where V_m represents the LV myocardial volume, dV/dt_{max} represents the maximal rate of change of LV cavity volume during systole.

Animal preparation

Six pigs of either sex (body weight of 30–70 kg) were anaesthetized with intravenous injection of telazol–ketamine–xylazine (TKX, 4.4 mg T/kg, 2.2 mg K/kg, and 2.2 mg X/kg). In the supine position, the animal was intubated and ventilated (Summit Medical, serial 20763) with a tidal volume of 400 mL at 12 strokes/min. Two litres per minute of oxygen with 2% isoflurane were provided via the respirator to maintain the anaesthesia. The right carotid artery, jugular vein, right femoral artery, and right femoral vein were exposed by blunt dissection and were cannulated with different size sheaths (e.g. 7Fr, 7Fr, 12Fr, 12Fr, respectively). Heparin (3000 U) was given intravenously after sheath placement. Arterial blood pressure was continuously monitored via the right femoral artery. All animal procedures complied with the approval of the Institutional Animal Care and Use Committee at Indiana University.

PV conductance catheter and system calibration

The electrodes of the pressure volume (PV) catheter (5Fr, model no.SPR-554-11 Millar Instruments, Houston, TX, USA) were soaked in body temperature saline at least 30 min prior to use. The PV catheter was connected with the Millar PV system (MPVS Ultra, Millar), and the PV catheter-related parameters at both Catheter Configuration and Rho Cuvette interface were selected. The pressure sensor in the PV catheter was then placed just below the surface of saline to perform auto zero at the catheter–calibration interface. The specific conductivity of blood was measured with a Rho Cuvette connected to an amplifier. The PV catheter was introduced into the LV via the right carotid artery sheath under fluoroscopic guidance, and the tip of the catheter was aligned with the apex. The data were displayed and recorded with the Labcharts software (Millar Instruments).

After stabilization of the recordings for 15 min, a 2-point pressure/volume calibration was performed. The pressure and volume signals were then continuously recorded with the MPVS Ultra software and displayed on a computer. The data for the baseline (steady state) condition were acquired for later use. Electrocardiogram, blood oxygen saturation, and invasive femoral artery blood pressure were continuously monitored during the entire experimental duration.

Preload changes

Two types of changes were examined: (A) decrease of preload by inferior vena cava occlusion (IVCO) and (B) increase of preload by saline infusion. During the IVCO procedure, a balloon catheter was introduced into the IVC just below the right atrium via the right femoral vein sheath. Preload volume was decreased by balloon inflation in the following sequence: 1.5 mL, 2.0 mL, 2.5 mL, 3.0 mL (Fogarty, 120805F, Edwards Lifesciences, USA), 4–15 mL (CODA balloon catheter, Cook, USA). Each preload condition was maintained for about 1 min to establish a steady state. Ventricular pressure and volume signals were recorded over at least 25 consecutive beats at baseline and under various preload conditions. The recovery time after each volume withdrawal was 1 min. The balloon catheter was then removed and the baseline was recovered for 10 min. Normal saline fast infusion was given (500 mL in 30 min) via right jugular vein sheath to increase preload (e.g. about 30–50% increase). During saline infusion, the ventricular pressure and volume data were recorded every 3 min. The respirator was turned off temporarily during all recordings of pressure–volume (P–V) data to avoid respiratory interference.

Afterload changes

Afterload was increased by intra-aortic balloon occlusion (IABO). After the P–V data at the baseline were recorded, the intra-aortic balloon was inserted into the root of the aorta and was inflated to increase the afterload in the following sequence: 1.5, 2.0, 2.5, and 3.0 mL (Fogarty), 4–15 mL (CODA balloon catheter) with 1 min recovery after each inflation of balloon. Once each afterload condition was maintained for about 1 min to establish steady state, the ventricular P–V signals were recorded over at least 25 consecutive beats. This manipulation was designed to increase the afterload by at least 50%. Arterial elastance ($[E_a]$ the ratio of end-systolic pressure $[P_{es}]$ over stroke volume [SV]) was used as a measure of afterload in this setting[21,22].

Myocardial contractility inotropic agent

Dobutamine was intravenously infused at a rate of 0.5–3.0 μg/kg per min to increase myocardial contractility. The ventricular P–V data were recorded at baseline and at every 5th minute after each dose. The electrocardiogram and femoral blood pressure were monitored continuously.

Volume calibration

After all above procedures were completed, 20% NaCl solution was injected in the right jugular vein. A rapid increase in LV conductance was observed with only a small decrease in LV pressure.[23] This volume calibration procedure was used to measure the parallel volume conductance (VP) which represents the parallel conductance contribution of the heart muscle and surrounding tissues to the total electrical conductance signal. The volume of 20% NaCl injection was calculated as: V (mL) = body weight (kg)/4.

Data analysis

All data were stored on a computer and exported to text files for subsequent data analysis (PVAN Ultra 1.1, Millar Instrument). A linear regression of the end diastolic (EDVs) and the end systolic volumes (ESVs) from baseline to peak increase of the composite volume were used to calculate the V_p value (during the hypertonic saline injection). This value was subtracted from the recorded volume to yield absolute volume. The echocardiographic SV (SV_{echo}) was considered as the reference, and the correct coefficient α for the conductance catheter was calculated as $\alpha = SV_{millar}/SV_{echo}$, where SV_{millar} and SV_{echo} were the SV measured by the Millar conductance catheter and by echocardiography, respectively. The α-value was used to calibrate the composite volume.

The following variables were used to calculate the contractility indices: heart rate (HR), ESV, EDV, and P_{es}. SV was calculated as EDV minus ESV, and EF was taken as the ratio of SV over EDV. Stroke work (SW) was the area of the P–V loop. The effective E_a, the ratio of LV P_{es}, and SV, was used as an index of LV afterload during IABO.[22] dP/dt_{max} was determined as the maximum rate of change of LV pressure during isovolumetric contraction. dV/dt_{max} was calculated from the LV blood volume signals as the maximum rate of LV blood volume change during isobaric contraction. $d\sigma^*/dt_{max}$ was calculated according to Zhong *et al.*[16] as

$$d\sigma^*/dt_{max} = \frac{3dV/dt_{max}}{2V_m}$$

where V_m is LV wall volume, measured using echocardiography.[24,25] The dV/dt_{max} was calculated directly by PVAN ultra software. Finally, PAMP was calculated as described by Segers *et al.*,[13] and E_{max} was determined based on previous methods.[26,27] Average arterial pressure (AP) was calculated from systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements as AP = [(SBP − DBP)/3] + DBP.

Echocardiography

Echocardiography (Phillip iE33) was performed on all animals before intervention. Two-dimensional LV apical four and two chamber views were acquired and endocardial contours were traced to determine LV EDVs and ESVs, respectively, and, consequently, SV using the Simpson biplane method.[24,25]

Statistical analysis

All data are expressed as mean ± SD. The load dependence was tested by one-way analysis of variance among multiple loading alterations, and the student-Newman-Keuls test was used for pairwise comparisons. Linear regression analysis was performed to assess the relationships between different LV contractility indices (e.g. EF, dP/dt_{max}, PAMP, E_{max}, and $d\sigma^*/dt_{max}$) and preload (EDV) and afterload (E_a). A paired t-test was used to compare the average change of load conditions, HR and $d\sigma^*/dt_{max}$ of the six pigs before and after each intervention. Statistical significance was defined at $P < 0.05$. SPSS 10.0 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

The average body weight of the six pigs of both genders was 43.1 ± 17.4 kg (30–70 kg). The wide range of body weight in both genders was used to confirm the independence of the contractility indices to these variables as no statistically significant differences were found between animals. The SBPs and DBPs were 95.0 ± 6.3 and 56.0 ± 3.0 mmHg, respectively, and the average pressure was 69.0 ± 3.2 mmHg. The average LV myocardial volume was 103.0 ± 27.1 mL, obtained from echocardiography.

Effects of preload, afterload and dobutamine

The IVCO resulted in a substantial decrease of EDV (70.0 ± 15.0%, from 39.2 ± 6.4 mL to 11.7 ± 7.7 mL, $P < 0.01$). Within the preload change from 39.2 ± 6.4 mL to 30.7 ± 6.2 mL (<21.7%, $P < 0.01$), the $d\sigma^*/dt_{max}$ did not change significantly (6.50 ± 1.10 s^{-1} to 6.60 ± 0.90 s^{-1}, P = non-significant [NS]; Table 1). Beyond this range (>21.7%), $d\sigma^*/dt_{max}$ was found to be preload-dependent.

Similarly, normal saline infusion of 500 mL resulted in a significant increase of EDV (49.3 ± 5.9%, from 35.1 ± 7.4 mL to 51.7 ± 8.9 mL, $P < 0.01$). Within the preload increase from 35.1 ± 7.4 mL to 45.4 ± 7.3 mL (<29.3%, $P < 0.01$), the $d\sigma^*/dt_{max}$ did not change significantly (7.04 ± 1.00 s^{-1} to 7.29 ± 1.10 s^{-1}; Table 2) albeit it did change when EDV increase was >29.3%.

Table 1 The range of preload decrease (IVCO), average pressure and heart rate, for which $d\sigma^*/dt_{max}$ remains constant

EDV (mL)		AP (mmHg)		HR (bpm)		$d\sigma^*/dt_{max}$ (s^{-1})	
Before	After	Before	After	Before	After	Before	After
39.2 ± 6.4	30.7 ± 6.2*	66.0 ± 7.6	61.0 ± 5.8	85 ± 13	94 ± 24	6.50 ± 1.10	6.60 ± 0.90

IVCO: inferior vena cava occlusion; EDV: end diastolic volume; AP: average pressure; HR: heart rate; bpm: beat per minute.
The maximal EDV decrease ranged from 39.2 ± 6.4 mL to 11.7 ± 7.7 mL. Only within the preload change listed in the table, did $d\sigma^*/dt_{max}$ remain constant.
*$P < 0.05$, compared with 'before'.

Table 2 The range of preload increase (NS infusion), average pressure and heart rate, for which $d\sigma^*/dt_{max}$ remains constant

EDV (mL)		AP (mmHg)		HR (bpm)		$d\sigma^*/dt_{max}$ (s^{-1})	
Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
35.1 ± 7.4	45.4 ± 7.3*	67.5 ± 8.9	68.9 ± 7.9	89 ± 17	87 ± 17	7.04 ± 1.00	7.29 ± 1.10

NS: normal saline; EDV: end diastolic volume; AP: average pressure; HR: heart rate; bpm: beat per minute.
The maximal EDV increase ranged from 35.1 ± 7.4 mL to 51.7 ± 8.9 mL. Only within the preload change from 35.1 ± 7.4 mL to 45.4 ± 7.3 mL, did $d\sigma^*/dt_{max}$ remain constant.
*$P < 0.05$, compared with 'before'.

Table 3 The range of arterial elastance increase (ABO), average pressure and heart rate, for which $d\sigma^*/dt_{max}$ remains constant

E_a		EDV (mL)		HR (bpm)		$d\sigma^*/dt_{max}$ (s^{-1})	
Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
3.3 ± 0.6	4.7 ± 1.0*	39.6 ± 5.5	40.7 ± 9.9	90 ± 14	89 ± 16	6.72 ± 1.18	6.89 ± 1.28

ABO: aortic balloon occlusion; E_a: arterial elastance; EDV: end diastolic volume; HR: heart rate; bpm: beat per minute.
The maximal E_a increase ranged from 3.3 ± 0.6 mmHg/mL to 5.7 ± 1.7 mmHg/mL. Only within the E_a increases from 3.3 ± 0.6 mmHg/mL to 4.7 ± 1.0 mmHg/mL, did $d\sigma^*/dt_{max}$ remain constant.
*$P < 0.05$, compared with 'before'.

Table 4 Dobutamine intravenous infusion to increase myocardial contractility

Dosage	Baseline	0.5 μg/min/kg	1 μg/min/kg	2 μg/min/kg	3 μg/min/kg
SV (mL)	31.1 ± 1.0	31.6 ± 1.0	33.8 ± 0.08*	35.9 ± 0.6*	41.8 ± 1.3*
EF (%)	46.4 ± 1.4	49.6 ± 2.5#	58.9 ± 3.0*	72.3 ± 2.4*	80.6 ± 0.4*
SW (mmHg × mL)	1779.8 ± 50.5	2143.6 ± 87.4*	2616.2 ± 102.4*	2833.2 ± 194.5*	3221.0 ± 205.3*
dP/dt_{max} (mmHg/s)	854.0 ± 39.1	1276.0 ± 25.1*	1998.0 ± 29.5*	3130 ± 52.4*	3946.0 ± 128.4*
$d\sigma^*/dt_{max}$ (s^{-1})	6.38 ± 0.64	6.71 ± 1.18	8.09 ± 0.78*	9.50 ± 0.73*	10.29 ± 0.61*

SV: stroke volume; EF: ejection fraction; SW: stroke work.
*$P < 0.01$; #$P < 0.05$, compared with baseline.

IABO resulted in a significant increase in E_a (74.3 ± 43.5%, from 3.3 ± 0.6 mmHg/mL to 5.7 ± 1.7 mmHg/mL). Within the range of 3.3 ± 0.6 mmHg/mL to 4.7 ± 1.0 mmHg/mL (<42.4%, $P < 0.01$), $d\sigma^*/dt_{max}$ remained constant (6.72 ± 1.18 s^{-1} to 6.89 ± 1.28 s^{-1}; Table 3) but changed for E_a variation >42.4%.

With infusion of dobutamine, $d\sigma^*/dt_{max}$ increased significantly from 6.38 ± 0.64 s^{-1} to 10.29 ± 0.61 s^{-1} ($P < 0.01$). Likewise, dP/dt_{max} increased from 854 ± 39.1 mmHg/s to 3946 ± 128.4 mmHg/s ($P < 0.01$), EF increased from 46.4 ± 1.4% to 80.6 ± 0.4% ($P < 0.01$), and SW increased from 1779.8 ± 50.5 mmHg·mL to 3221.0 ± 205.3 mmHg·mL ($P < 0.01$) after dobutamine infusion, respectively (Table 4).

Relationship between various load changes and contractility indices

In the figures that follow, we only present the range of preload and afterload changes for which $d\sigma^*/dt_{max}$ was found to be constant. Figures 1 and 2 show each index (EDV and E_a) normalized to its respective baseline value since normalized plots enable relative percentage change in each index versus load to be discerned. For preload changes, linear regression confirmed that within −30% to +50% of EDV changes, $d\sigma^*/dt_{max}$ was not related to preload conditions ($r^2 = 0.02$, $P = 0.17$; Figure 1a); E_{max} was not found to be sensitive to preload change ($r^2 = 0.02$, $P = 0.14$; Figure 1b); dP/dt_{max} was not sensitive to EDV changes ($r^2 = 0.01$ $P = 0.39$; Figure 1d). However, EF ($r^2 = 0.42$, $P < 0.01$) and PAMP ($r^2 = 0.87$, $P < 0.01$) were sensitive to preload changes (Figure 1c and e). During IABO, linear regression showed that within 0–100% of E_a increase, $d\sigma^*/dt_{max}$ was not correlated with E_a ($r^2 = 0.03$, $P = 0.36$; Figure 2a); E_{max} ($r^2 = 0.03$, $P = 0.41$) was also not correlated with E_a (Figure 2b). EF ($r^2 = 0.49$, $P < 0.0001$), dP/dt_{max} ($r^2 = 0.86$, $P < 0.01$), and PAMP ($r^2 = 0.19$, $P < 0.05$), however, were all significantly correlated with E_a (Figure 2c–e).

Discussion

This study demonstrated that $d\sigma^*/dt_{max}$ (an index of LV contractility) was independent of loading conditions within a significant range (an average change of 21.7% of preload decrease, 29.3% of preload increase, and 42.4% of afterload increase corresponding to maximum range of EDV and E_a of −30% to +50% and 0% to 100%, respectively), while it showed load-dependence beyond this

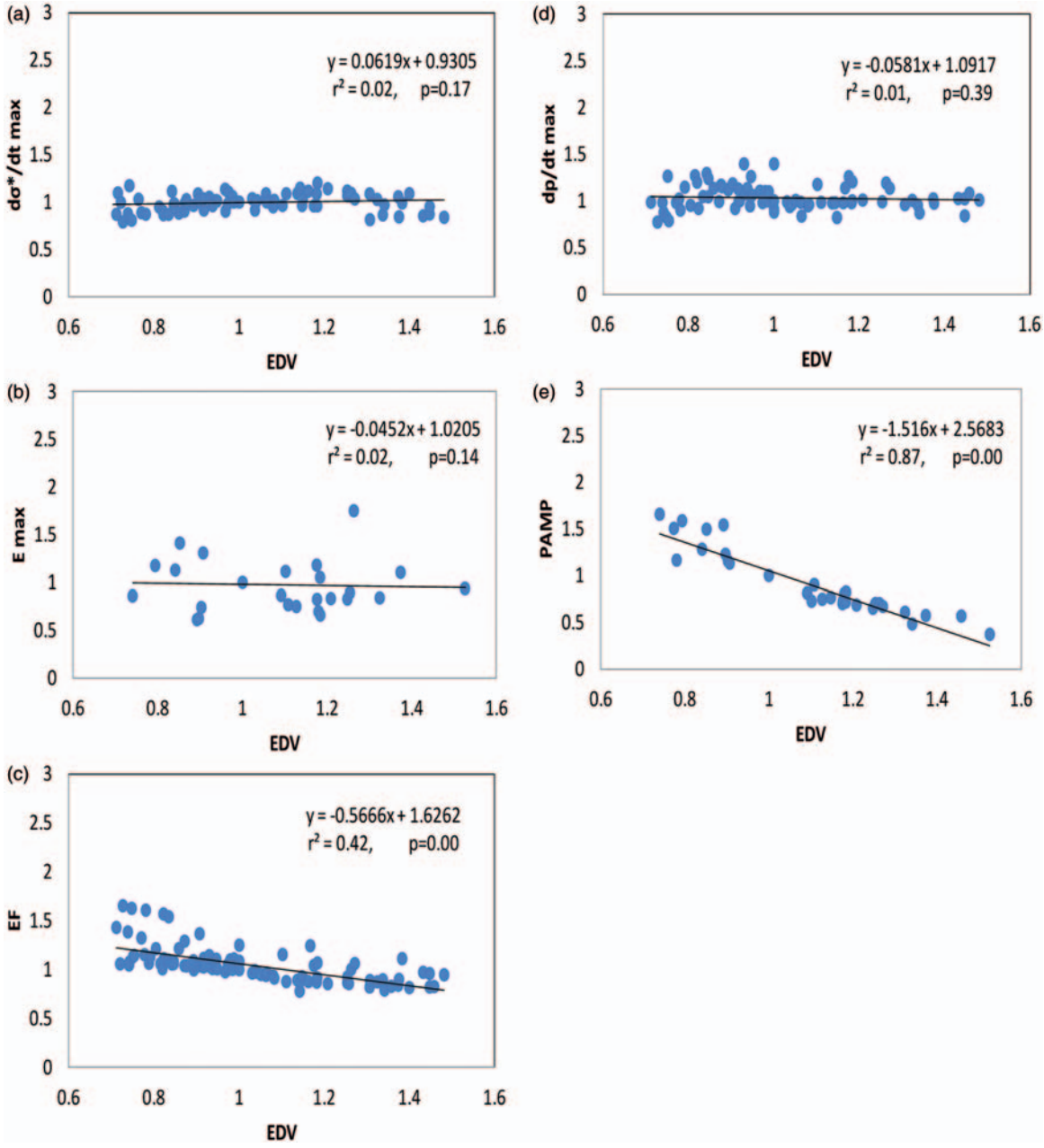

Figure 1 Effect of preload changes (EDV) on $d\sigma^*/dt_{max}$ and other contractility indices. Within −30% to +50% (0.7–1.5) of end diastolic volume range, linear regression analysis demonstrated that $d\sigma^*/dt_{max}$ and E_{max} were not sensitive to end diastolic volume (EDV) alterations ($r^2 = 0.02$, $P = 0.17$ and $r^2 = 0.02$, $P = 0.14$, respectively, a and b), while ejection fraction (EF) and preload adjust maximal power (PAMP) were significantly related to EDV changes ($r^2 = 0.42$, $P < 0.0001$; and $r^2 = 0.87$, $P < 0.0001$, respectively, c and e). dP/dt_{max} was not sensitive to EDV ($r^2 = 0.01$, $P = 0.39$; d). $d\sigma^*/dt_{max}$: s^{-1}; E_{max}: mmHg/m; dP/dt_{max}: mmHg/s; PAMP: $w.mL^{-2}.10^{-4}$; EDV: mL. All values were normalized by dividing the absolute value by baseline value. (A color version of this figure is available in the online journal)

range. EF, dP/dt_{max}, and PAMP are load-dependent, however, in the same ranges of pre- and after-load changes.

$d\sigma^*/dt_{max}$ as an index of LV contractility

Zhong *et al.*[16] first demonstrated non-invasively that $d\sigma^*/dt_{max}$ was sensitive to inotropic state and insensitive to the loading condition of heart in patients using echocardiography. $d\sigma^*/dt_{max}$, the change rate of normalized wall stress (σ^*) derived from a biomechanical model of the heart,[16] differs from LV EF and other conventional measures of LV contractility. Consistent with other studies in the literature, LV wall stress was proposed as an intrinsic measure of LV contractile function.[28,29] Since pressure is not always easily measurable, we conceived of maximum pressure-normalized stress as a contractility index.[16,18,30] We have further extended this concept and formulated an expression, where $d\sigma^*/dt_{max}$ can be represented as the quotient of the maximal rate of change of ventricular volume (dV/dt_{max}) and myocardial volume.[16,31,32] We have used echocardiography to determine $d\sigma^*/dt_{max}$ in normal and

HF patients with preserved EF.[17] $d\sigma^*/dt_{max}$ was impaired in HF even when EF was unchanged, suggesting early adverse LV contractility changes. Furthermore, we have used MRI to determine $d\sigma^*/dt_{max}$ in HF patients before and after surgery.[19,20] We previously performed load sensitivity testing of $d\sigma^*/dt_{max}$ in human subjects non-invasively using echocardiography in a limited physiological state.[16]

Here, we extended the evaluation of $d\sigma^*/dt_{max}$ over a much broader loading range using a conductance catheter in swine. Confirmatory changes were seen in $d\sigma^*/dt_{max}$ with a change in LV contractility using dobutamine. No significant change in $d\sigma^*/dt_{max}$ was observed with pre- and afterload manipulation (i.e. IVCO, saline infusion, intra-aorta occlusion) within a limited range of this loading alternations. As shown in Tables 1–3, $d\sigma^*/dt_{max}$ remained constant within −21.7% to +29.3% of preload changes, and 40.9 ± 15.5% of afterload (E_a) increase. Furthermore, a linear regression analysis showed that $d\sigma^*/dt_{max}$ is load-independent within −30% to +50% of preload changes (Figure 1a) and 0–100% of afterload (E_a) increase (Figure 2a), similar to the 'gold standard' LV contractility index, E_{max}. It should be noted that the values of HR (i.e. 65 bpm), average blood pressure (i.e. 61 mmHg), and EF (i.e. 46%) presented at baseline in Table 4 were lower than values observed in awake swine[33] due to anaesthesia. Since the study is based on relative changes, the effect of anaesthesia which was maintained constant during the duration of the study is unlikely to impact the overall conclusions.

Black *et al.*[34] reported a preload-dependence of $d\sigma^*/dt_{max}$ in canines based on IVCO. This disagreement is likely multi-factorial. First, our study focused on steady

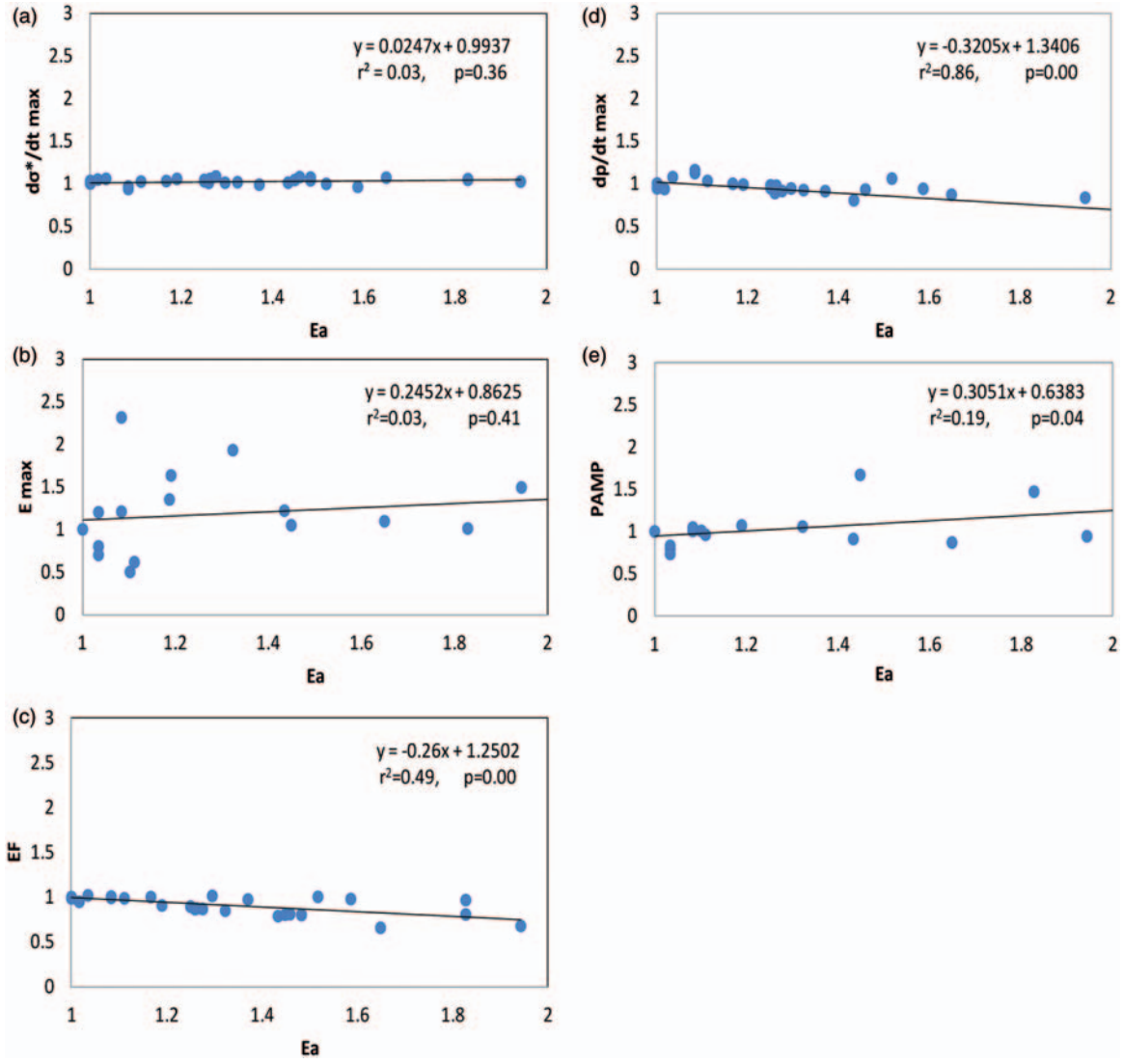

Figure 2 Effect of afterload changes (E_a) on $d\sigma^*/dt_{max}$ and other contractility indices. Within 0–100% (1.0–2.0) of arterial elastance (E_a) increase, $d\sigma^*/dt_{max}$ and E_{max} were not related to E_a changes ($r^2 = 0.03$, $P = 0.36$ and $r^2 = 0.03$, $P = 0.41$, respectively, a and b), while ejection fraction (EF), dP/dt_{max} and preload-adjusted maximal power (PAMP) were all significantly related to E_a increase ($r^2 = 0.49$, $P = 0.00$; $r^2 = 0.86$, $P = 0.00$ and $r^2 = 0.19$, $P = 0.04$, respectively, c–e). $d\sigma^*/dt_{max}$: s^{-1}; E_{max}: mmHg/m; dP/dt_{max}: mmHg/s; PAMP: $w.mL^{-2}.10^{-4}$; E_a: mmHg/mL. All values were normalized by dividing the absolute value by baseline value. (A color version of this figure is available in the online journal)

state conditions after load change while they targeted the short, transient state. IVCO can result in short-term alterations in sympathetic tone, LV pericardial constraints and ventricular interaction, all of which can influence the P–V relationship.[35] It also changes the volume offset of the conductance catheter.[35] All these variables may affect the relationship between $d\sigma^*/dt_{max}$ and EDV. Second, drastic preload change as presented in that study is supra-physiological. Our index is load-independent within a certain preload decrease (21.7↓) by IVCO, but is load-dependent beyond this range (>21.7%↓ to 70%↓). In Black *et al.*, EDV decreased by 32% ($d\sigma^*/dt_{max}$ values varied from $0.5\,s^{-1}$ to $6\,s^{-1}$ in normal canine) with IVCO where the index was deemed preload-dependent. Furthermore, our study is more comprehensive in evaluation of preload dependence. We not only tested preload change by IVC, but also preload change with saline infusion (49%↑ of EDV).

Other studies have criticized the load-dependence of maximal velocity V_{peak}.[15,36,37] It is noted that $dV/dt_{max} = V_{peak} \times A$, where V_{peak} is peak velocity and A is measured either at aorta location or the LV outflow tract (LVOT). This has been controversial as some studies have shown that peak velocity (V_{peak}) measured at the aorta location is load-dependent,[15,36,37] whereas V_{peak} measured at LVOT is load-independent.[14] These discrepancies can be explained as follows. Although conservation of mass requires that dV/dt_{max} at LVOT to be equal to that at the aorta (product of velocity and area), clearly the velocities are not equal since the areas of the LVOT and aorta are different, and the former can change significantly throughout the cardiac cycle. dV/dt_{max} is equal to the product of V_{peak} and area of the LVOT but is not equivalent to V_{peak} at the aorta (it is proportional to it but the area of LVOT can also change). Our present swine results demonstrate that $d\sigma^*/dt_{max}$ is both preload and afterload independent and are in agreement with Bauer *et al.*[14] in sheep and with Zhong *et al.*[16] in patients.

The variations in preload and afterload in the present study were equal to or significantly greater than those reported in the literature. Reports of preload increase from 6% to 24% by saline infusion and preload decrease from 10% to 32% by IVCO have been made[14,34,36,38,39] as compared to 49% and 30% in our study, respectively. Similarly, afterload increases varied from 16% to 70% by aorta occlusion (as compared to 70% in this study), while afterload decreases varied from 13% to 29% by nitroprusside or nitroglycerin (NTG) in the literature.[14,34,36,38,39] Although the loading conditions were varied very widely, the load-independence was found for a physiologically significant subset of the range (as listed in Tables 1–4).

In the present study, we found that E_{max} was independent of preload and afterload changes within the maximum range tested (−30% to +50% preload changes and 0–100% afterload changes), confirming the relative superiority of this invasive index. However, when studied over wider loading conditions (preload decrease of 44% and afterload increase of up to 240%), E_{es} has been previously found to be load-dependent.[40] Hence, no contractility index is completely load-independent beyond a certain range and the clinical impact of such limitation is questionable.

In this study, the interventions to manipulate preload and afterload were selective (i.e. IVCO and saline infusion to alter preload and intra-aortic occlusion to alter afterload). We did not use pharmacological intervention since norepinephrine not only increase afterload via α-adrenergic vasoconstriction but also stimulate cardiac β-adrenergic receptors, thereby potentially influencing the contractile state of the LV.[41] Similarly, NTG not only dilates arteries (affecting afterload) but also dilates veins which may result in preload reduction.[42]

The effect of HR on contractility is also controversial. While some studies support that HR can affect the measurement of dP/dt_{max} and E_{max},[9–11,43] other studies have questioned the importance of HR on contractility *in vivo*.[11,44–46] For example, Kavaler *et al.*[45] showed that the effect was not statistically significant in non-excised, canine papillary muscle *in situ*. Suga *et al.*[11] showed that an increase in HR caused very little change in the end-systolic PV relationship in a denervated, paced heart. Maughan *et al.*[46] reported a staircase phenomenon in an isolated canine LV, where the influence of HR on the contractility depends on the range over which the HR was varied. It should be noted that all the above-mentioned studies were performed on fibres or isolated heart. We found no significant effect of HR during all the procedures in the present study.

Non-invasive utility of $d\sigma^*/dt_{max}$

Non-invasive determination of $d\sigma^*/dt_{max}$ depends on techniques for measuring volume flow and myocardial volume. Flow can be assessed either by echocardiography[16,17] or MRI.[19,20] Previous studies found that LV volume data obtained from echocardiography are highly correlated with the conductance catheter measurements in sheep,[47] mice,[26] and in patients.[48] Furthermore, echocardiography-derived peak velocity correlated strongly with maximal flow from the conductance catheter in animal studies ($r = 0.96$).[15] In clinical application, non-invasive methods that can be used longitudinally are highly desirable because both the disease and its treatment are chronic processes. Our contractility index may permit comparison between individuals with various cardiac disease, as demonstrated in our previous clinical studies.[17–19,49] Cardiac disease of various origins contributes to different LV remodelling, and causes different changes in LV outflow rate and myocardial mass. Our index, based on outflow rate and LV mass, represents an integrated assessment of LV contractility.

Limitations

There are a number of limitations in this study. We did not denervate the heart, excise the heart, or fix the load state mechanically to better maintain constancy of variables. Rather, we gradually changed the loading state in order to eliminate the baroreceptor reflex interference, which induced slight preload–afterload interaction during each intervention. Although HR was consistent before and after each intervention, the change of beat by beat Ca^{2+} influx should be taken into account. Pacing the heart can maintain a constant HR, but it can induce an abnormal

myocardial contraction sequence, which may influence contractility. Although HR exerts little effect on the load-dependence of myocardial properties,[11,44] its effect on $d\sigma^*/dt_{max}$ requires further study. Finally, future non-invasive measurements of the index with echocardiography during hemodynamic alterations in swine will further substantiate the index clinically.

Clinical utility

Assessment of global LV systolic function is a standard practice in the clinic and typically includes measurement of EF which is load-dependent (as confirmed in our study). Conductance-based measurements (e.g. end-systolic elastance; E_{es}) which are independent of loading conditions in the range of interest, are cumbersome and have not been used routinely.[50] $d\sigma^*/dt_{max}$ is a potential index of LV contractile function that is independent of load in a wide range of interest and that can be determined non-invasively (i.e. using echocardiography, MRI, etc.). We have validated the utility of this index in patients with cardiac disease of various origins, such as in HF with normal EF[17]; ischaemic cardiomyopathy before and after surgery,[19,20] and hypertrophic cardiomyopathy.[49] Although no index is truly load-independent, the more relevant issue is the range of load-independence. We confirmed that our index is load-independent within a relatively wide range of physiological loading conditions. The range of load variation is clearly beyond what would be observed in patients under steady state conditions.

Author contributions: XJ carried out experiments, acquired and analyzed the data and wrote first draft of paper. JSC, ZZ and MS assisted with experiments. LZ and RST assisted with study design. GSK conceived, designed and coordinated the study. All authors read and approved the final manuscript.

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