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ABSTRACT

Background The relationship between speckle tracking assessed global longitudinal strain (GLS) and Doppler-based echocardiography with basic physiological markers of cardiac function derived from pressure-volume loops is poorly elucidated.

Objective We aimed to describe the association between LS and Doppler-based echocardiography and direct measurements of central haemodynamic parameters from conductance catheter-based pressure-volume loops in an animal model with increasing left ventricular (LV) dysfunction.

Methods 12 Danish landrace female pigs (75–80 kg) were used. All instrumentations were performed percutaneously, including the conductance catheter in the LV. Progressive LV dysfunction was induced by embolisation through the left main coronary artery with microspheres every 3 min until a >50% reduction in cardiac output (CO) or mixed venous saturation (SvO_2), compared with baseline, or SvO_2 <30%. Echocardiography was performed at baseline and 90 s after each injection.

Results With progressive LV dysfunction, mean CO decreased from 5.6±0.9 L/min to 2.1±0.9 L/min, and mean SvO_2 deteriorated from 61.1±7.9% to 35.3±6.1%. Mean LS and LV outflow tract velocity time integral (LVOT VTI) declined from −13.8±3.0% to −6.1±2.0% and 16.9±2.6 cm to 7.8±1.8 cm, respectively. LS and LVOT VTI showed the strongest correlation to stroke work in unadjusted linear regression (r^2=0.53 and r^2=0.49, respectively). LS correlated significantly with stroke volume, end-systolic elastance, systolic blood pressure, ventriculo-arterial coupling and arterial elastance.

Conclusion In an animal model of acute progressive LV dysfunction, echocardiographic and conductance catheter-based measurements changed significantly. LS and LVOT VTI displayed the earliest and the largest alterations with increased myocardial damage and both correlated strongest with stroke work.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ Longitudinal strain (LS) allows the detection of subtle changes in LV function and has shown to be a prognostic marker after acute myocardial infarction (AMI).

WHAT THIS STUDY ADDS

⇒ This study assesses the acute changes observed in LS in a porcine model of AMI and cardiogenic shock. Further, we address LSs correlation with central haemodynamic parameters derived from conductance catheters.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on our findings, LS is a marker of overall LV function, with the strongest correlation with stroke work.

INTRODUCTION

Echocardiography is a cornerstone in the assessment of patients with suspected acute myocardial infarction (AMI), especially in the presence of acute heart failure, where it has a class 1 recommendation in current guidelines.[1 2] Echocardiography provides immediate real-time assessment of left and right ventricular function and valve dysfunction and can detect mechanical complications of AMI. For quantification of left ventricular (LV) systolic function, LV ejection fraction (LVEF) has been the cornerstone for decades, and LVEF assessment is pivotal for risk stratification and selection of patients for certain therapeutic interventions. However, LVEF has several limitations including limited reproducibility and a non-linear association with outcome.[3] Due to these limitations, other imaging modalities complement

the assessment of LV function in acute heart failure, where estimation of stroke volume by LV outflow tract velocity time integral (LVOT VTI) is a valuable tool in critical care to assess cardiac output (CO). Furthermore, the myocardial motion has been quantified using tissue Doppler echocardiography, and finally, the assessment of myocardial deformation by speckle tracking echocardiography (STE) provides a reproducible assessment of LV function and offers the possibility to detect even subtle changes in LV function.[4] The measured global longitudinal strain (GLS) with STE has proven useful in several cardiac disease entities[5] including AMI.[6] The information provided by LVEF and GLS are not interchangeable, and only a few studies have validated these measurements against pressure-volume analysis, which is considered to be the gold standard for basic haemodynamic assessment.[7]

This translational study aimed to evaluate the association between speckle tracking assessed LS and Doppler-based echocardiography with direct measurement of central haemodynamic parameters using conductance catheter-derived pressure-volume loops during increasing severity of LV dysfunction in an experimental animal model of coronary artery embolisation.

METHODS

12 Danish landrace female pigs, weighing 75–80 kg, were studied. The study was approved and conducted in accordance with the current guidelines from the Danish Animal Experiments Expectorate (Study ID number: 2016–15-00951). A detailed description of our animal model has previously been published.[8] In summary, all animals were anaesthetised, mechanically ventilated and treated with a bolus of 300 mg amiodarone to prevent arrhythmias. Animals were given 20.000 IE heparin every 2 hours to avoid blood clotting. Instrumentations were performed using the Seldinger technique with vascular access sheaths ranging from 6 to 14 Fr, as appropriate. A conductance catheter (Ventri-cath 512 PV Loop Catheter, Millar Inc, TX, USA) was placed under fluoroscopic guidance in the left ventricle. A pulmonary artery (PA) catheter was placed (Edwards Lifesciences Corp, Irvine, CA, USA) for monitoring of PA pressure, mixed venous saturation and thermodilution CO measurement. Systemic blood pressure was measured in the femoral artery. At baseline and when CS was present, we drew blood samples for analysis of arterial lactate.

The conductance catheter was calibrated with infusion of hypertonic saline for parallel wall conductance, and the alpha correction was calculated from the thermodilution-derived CO measured with the PA catheter. Preload occlusion of the inferior vena cava was performed for determination of the estimated ventricular volume at zero pressure (V0).[9] The acquired V0 was kept constant throughout the experiment and was used for calculation of end-systolic elastance (EES). The conductance catheter was connected to an MPVS Ultra Pressure-Volume (PV) loop system (Millar Inc). Further, a PowerLab 16/35 (ADInstruments, Dunedin, New Zealand) was used to transfer data to LabChart Pro (ADInstruments, Dunedin) which was used to display and store data for offline analysis.

Echocardiography was performed through a surgically prepared pouch just below the xiphoid process with the placement of the ultrasound probe directly on the diaphragm to optimise image quality. This approach allowed for high-quality five-chamber images including the left and right ventricle. A Vivid E95 (General Electric, Horten, Norway) was used for image acquisition, and all images were stored for offline analysis with EchoPAC (V.204, General Electric). Framerate was kept at a minimum of 60 frames per second. The following images were stored: focused 2D images of the RV and LV, pulsed wave Doppler in the LVOT and colour-coded tissue Doppler images (TDIs). LV LS was measured using the semiautomatic software within EchoPAC. The region of interest was set to cover the whole myocardium, and tracings were manually inspected to ensure correct detection of peak values. With TDIs, we obtained S' with the marker placed in the medial and lateral mitral annulus. LV volumes were calculated by the formula described by Teichholz *et al*.[10]

Myocardial damage was induced with stepwise embolisation in the left main coronary artery, introducing an increasing area of ischaemia and myocardial infarction in the vascular bed of left anterior descending (LAD) and circumflex artery . Each embolus consisted of 1 mL of a mixture of 125 µg polyvinyl alcohol flakes (Contour, Boston Scientific, Marlborough, USA) dissolved in 10 mL saline and 10 mL contrast. Microspheres were injected every 3 min until cardiogenic shock (CS) was present, defined by a sustained reduction in CO of ≥50% and/or a ≥50% reduction in SvO_2 compared with baseline or an absolute $SvO_2 \leq 30\%$. To ensure stabilisation and effect of each embolus, echocardiography was performed between 90 and 120 s after injection.

Haemodynamic measurements

From pressure-volume recordings, the following parameters were measured: stroke work, arterial elastance (EA), LV end-diastolic pressure (LVEDP), LV end-systolic pressure and stroke volume. EES was calculated with the use of the single-beat estimation as described by Senzaki *et al*,[11] and ventriculo-arterial (VA) coupling was calculated as the ratio of EA/EES. CO was calculated as the conductance catheter-derived stroke volume multiplied by heart rate.

End-systolic wall stress was calculated using the following formula[12]:

$$End\ systolic\ wall\ stress = \frac{End\ systolic\ pressure \times \frac{LVIDs}{2}}{2 \times IVSs}$$

where LVIDs is the LV inner diameter in systole and IVSs are the interventricular septum in systole obtained from echocardiographic images. End-diastolic wall stress was calculated with the same formula but with

end-diastolic pressure and diastolic measures of LV inner diameter and interventricular septum thickness.

For non-invasive estimation of EES and EA, we used the following formulas,[13] where EDV is end-diastolic volume derived from the Teichholz formula, as described above:

$$EES_{non-invasive} = \frac{Systolic\ blood\ pressure * 0.9}{EDV_{teich}}$$

$$EA_{non-invasiveve} = \frac{Systolic\ blood\ pressure * 0.9}{strokevolume} = \frac{Systolic\ blood\ pressure * 0.9}{LVOT\ VTI * \left(\frac{LVOT\ diameter}{2}\right)^2 * \pi}$$

For non-invasive VA coupling, the ratio of $EA_{non\text{-}invasive}$ / $EES_{non\text{-}invasive}$ was used.

Statistics

Normally distributed data are presented as the mean and SD. Non-normal distribution data are presented as median and interquartiles. As the number of microsphere injections varied between animals, a percentage of the total number of emboli was calculated with the baseline equal to 0% and CS equal to 100%. For presentation in tables, a mean was calculated for 20%–30%, 45%–55% and 70%–80% of the number of embolisations.

For regression analysis, univariate and multivariate models were used. For both models, standardised coefficient, reflecting the change in SD of the dependent variable per increase in SD of the predictor variable, was calculated. In the multivariate model, backward elimination based on a full model with the following variables, EES, systolic blood pressure, non-invasive VA coupling, LVEDP, and systolic and diastolic wall stress, was performed. To assess multicollinearity, we used the variance inflation factor. The significance level was set to <0.05 for all analyses.

Results

12 pigs underwent CS induction, of which one animal was excluded due to poor quality of conductance-derived data and one due to data loss. In total, 10 animals were included in the study. An average of eight (SD 3) emboli injections was required to induce CS, and three animals required norepinephrine infusion to maintain mean arterial pressure (MAP) >50 mm Hg. The arterial blood pressure, CO and carotid blood flow decreased with increasing levels of myocardial damage, whereas a concomitant increase in central venous pressure was observed. Heart rate and PA pressure remained unchanged. Arterial lactate increased from 1.3 mM/L±0.7 to 2.8 mM/L±1.4. Based on conductance measures, stroke work, end-systolic pressure and EES decreased with increasing severity of LV failure. End-systolic wall stress was overall unchanged (table 1). End-diastolic pressure and EA increased in parallel. Consequently, VA coupling increased from 2.4±1.0 to 10.2±6.1. Non-invasive estimation of VA coupling yielded

Table 1 Haemodynamic data during shock induction

	Baseline		20%–30%		45%–55%		70%–80%		Shock	
Heart rate (beats per min)	74	(10)	73	(10)	72	(7)	72	(10)	72	(8)
MAP (mm Hg)	69	(13)	67	(7)	65	(6)	57	(8)	50	(5)
PAP sys (mm Hg)	33.5	(4.8)	36.9	(4.5)	36.5	(5.0)	36.3	(2.1)	33.8	(3.6)
PAPdia (mm Hg)	21.9	(4.5)	25.1	(5.0)	25.1	(5.8)	27.4	(3.5)	21.9	(5.6)
CVP (mm Hg)	11.5	(3.1)	13.3	(2.8)	13.4	(2.7)	14.4	(2.1)	13.5	(2.7)
Carotid flow (mL/min)	267	(96)	203	(41)	220	(61)	214	(140)	155	(48)
SvO_2	61.1	(7.9)	55.1	(9.2)	49.8	(7.0)	39.0	(6.0)	35.3	(6.1)
CO (mL/min)	5.6	(0.9)	4.1	(0.7)	3.3	(1.1)	2.9	(1.3)	2.1	(0.9)
Pressure-volume area (mm Hg×mL)	13 411	(4678)	11 303	(3695)	11 294	(2613)	10 220	(2636)	8206	(2960)
Stroke work (mm Hg×mL)	5559	(1492)	3185	(890)	2448	(810)	1883	(1015)	976	(559)
Total cardiac work (PVA×HR×10^{-3})	1005	(433)	820	(296)	803	(166)	734	(177)	585	(209)
LVEDP (mm Hg)	19.7	(1.9)	20.7	(2.0)	22.6	(1.7)	22.7	(1.7)	22.9	(2.1)
EA (mm Hg/mL)	1.15	(0.19)	1.34	(0.18)	1.80	(0.67)	2.05	(1.05)	2.31	(1.55)
EES (mm Hg/mL)	0.54	(0.17)	0.38	(0.11)	0.34	(0.08)	0.29	(0.07)	0.22	(0.04)
Ventriculo-arterial coupling	2.4	(1.0)	3.7	(1.2)	5.6	(2.4)	7.8	(4.6)	10.2	(6.1)
EA (non-invasive)	1.8	(0.4)	2.1	(0.6)	2.2	(0.5)	2.4	(0.6)	3.0	(1.0)
EES (non-invasive)	2.0	(1.4)	1.4	(0.4)	1.1	(0.2)	0.9	(0.2)	0.8	(0.1)
Ventriculo-arterial coupling (non-invasive)	1.1	(0.5)	1.6	(0.9)	2.1	(0.7)	2.7	(0.9)	3.9	(1.5)
End-systolic wall stress (kdynes/cm^2)	80.6	(29.5)	76.9	(17.4)	88.5	(13.3)	81.9	(17.8)	73.7	(15.0)
End-diastolic wall stress (kdynes/cm^2)	29.0	(6.8)	29.7	(5.9)	35.6	(7.9)	34.1	(7.3)	39.2	(7.0)

CO, cardiac output; CVP, central venous pressure; EA, arterial elastance ; EES, end-systolic elastance; LVEDP, left ventricular end-diastolic pressure; LVESP, left ventricular end-systolic pressure; MAP, mean arterial pressure; PAP, Pulmonary arterial pressure; SvO_2: CO, cardiac output.

Table 2 Echocardiographic characteristics during shock induction

	Baseline		20%–30%		45%–55%		70%–80%		Shock	
LVIDd (mm)	44.1	(4.1)	45.9	(3.3)	47.4	(3.6)	47.9	(3.9)	47.9	(3.8)
LVIDs (mm)	34.0	(5.3)	37.4	(4.3)	40.1	(3.3)	41.4	(3.2)	42.1	(3.1)
LVEDV (Teich) (mL)	89.2	(19.8)	97.3	(17.6)	105.1	(19.6)	107.7	(21.8)	107.9	(20.8)
LVESV (Teich) (mL)	49.1	(16.8)	60.8	(16.4)	71.1	(14.4)	76.6	(14.0)	79.6	(14.0)
LVEF (Teich) (%)	45.5	(13.9)	37.9	(11.1)	32.0	(8.3)	28.4	(7.0)	25.7	(7.5)
Stroke volume (LVOT) (mL)	49.5	(13.5)	43.2	(13.9)	36.6	(7.6)	31.3	(11.3)	22.9	(7.6)
LVOT VTI (cm)	16.9	(2.6)	13.6	(1.8)	13.6	(2.7)	10.6	(2.5)	7.8	(1.8)
Longitudinal strain (%)	−13.8%	(3.0)	−11.0%	(2.6)	−8.6%	(2.7)	−8.0%	(2.0)	−6.1%	(2.0)
s' lateral (cm/s)	5.6	(1.8)	3.3	(0.8)	3.7	(1.0)	3.1	(0.5)	2.8	(0.5)

LVEDV, Left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, Left ventricular end-systolic volume; LVIDd, Left ventricular internal dimension in end-diastole; LVIDs, Left ventricular internal dimension in end-systole; LVOT VTI, left ventricular outflow tract velocity time integral.

a consistently lower value, but the effect of myocardial damage and magnitude of change was similar (from 1.1±0.5 at baseline to 3.9±1.5 at CS) (table 1).

With echocardiography, extensive changes in LV size and function with increasing severity of myocardial damage were found (table 2). LV chamber dimensions and volume increased in both systole and diastole, and LVEF declined from 45±13.9% at baseline to 26±7.5% at CS. LVOT VTI and the derived stroke volume decreased from 16.9±2.6 cm and 49.5±13.5 mL to 7.8±1.8 cm and 22.9±7.6 mL, respectively (table 2).

LS increased from −13.8±3.0% to −6.1±2.0% at CS (table 2). Relative changes in echocardiographic parameters are displayed in figure 1, and haemodynamic

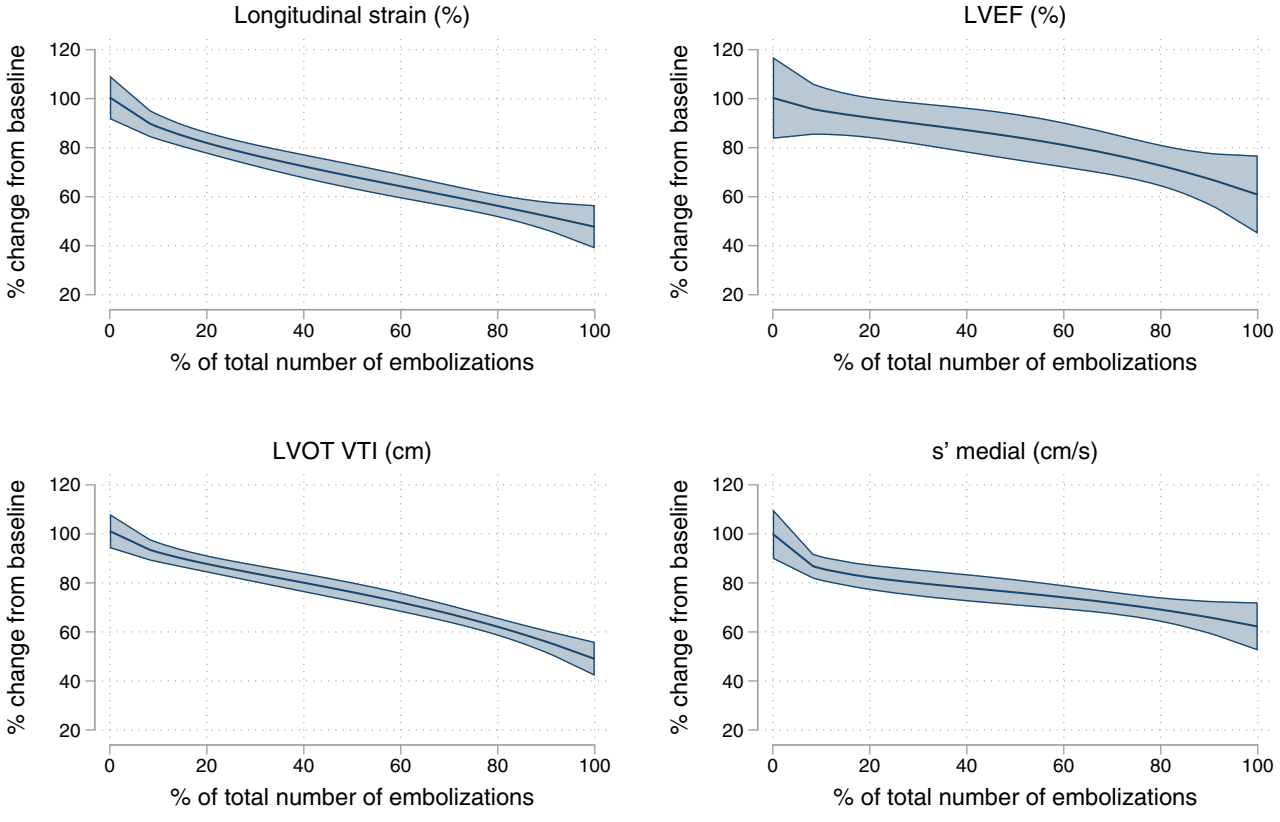

Figure 1 Title Echocardiographic changes. Percentage change in echocardiographic parameters with increasing number of emboli. LVEF, left ventricular ejection fraction; LVOT VTI, left ventricular outflow tract velocity time integral.

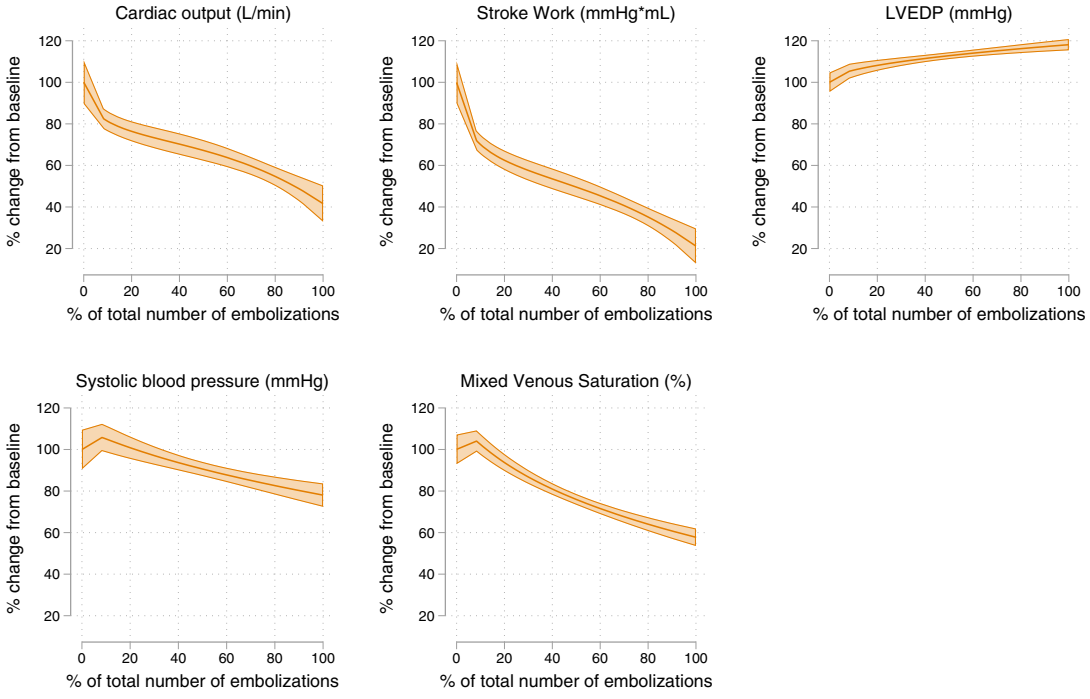

Figure 2 Title: Haemodynamic changes. Percentage change in haemodynamic parameters with increasing number of emboli. LVEDP, left ventricular end-diastolic pressure.

changes are displayed in figure 2. LS and LVOT VTI displayed parallel declines, and both were immediately affected by first embolisations. The observed decrease was slightly more pronounced with LS than LVOT VTI. In comparison with LVEF, the decline in LS was of greater magnitude and with less variation (table 2).

LS demonstrated moderate associations with several haemodynamic measurements. In univariate linear regression, LS correlated with stroke work, stroke volume, contractility (EES), EA, systolic blood pressure, end-diastolic wall stress, VA coupling and LVEDP (table 3, figure 3). There was no correlation with end-systolic wall stress (table 3). The strongest correlation was between LS and stroke work with an r^2 of 0.53 and a standardised coefficient of −0.73. When examining the individual parts of stroke work, both stroke volume and intraventricular pulse pressure were significantly correlated with LS with similar standardised coefficients (−0.38, p<0.000, and −0.43, p<0.000, respectively). With multivariate linear regression, stroke work, systolic blood pressure and end-diastolic wall stress all had a significant influence on LS with an r^2 value of 0.60 for the model (online supplemental table 1). The incremental value of each component is shown in online supplemental table 2. In all multivariate analyses, variation inflation factor was below five for all variables, indicating that the observed findings were not due to multicollinearity.

A significant correlation was found between LVOT VTI and stroke work, stroke volume, EES, EA, end-diastolic wall stress, VA coupling and systolic blood pressure (table 3, figure 4). The strongest association was with stroke work (r^2=0.49).

DISCUSSION

In this animal model of acute myocardial ischaemia induced by left main coronary artery embolisation, we found large alterations in both echocardiographic and conductance catheter-based measures. With echocardiography, measurements based on all four methods for evaluation of LV systolic function, LVEF, Doppler, TDI and speckle tracking were affected with increasing degrees of myocardial damage. However, the magnitude and speed differed between methods with STE-based LS and Doppler-based LVOT VTI being the two modalities that showed the earliest and largest declines.

Two other studies have evaluated the effect of induced myocardial ischaemia on echocardiographic LS in animal models. Moen *et al*[7] used a model with gradually declining perfusion pressure in the LAD artery with a maximum reduction of 60% in perfusion pressure, corresponding to a 54% decline in blood flow. They allowed for 10 min of stabilisation before performing echocardiography. LS was assessed in a part of the anterior wall affected by hypoperfusion, and they reported a gradual increase in strain from −11% at baseline to 2% with maximum reduction in flow. Fistenberg *et al*[14] used complete balloon occlusion of the LAD and observed changes in LS within the first 120 s. With TDI-based strain rate in the septal part of the LV, they noted a 53% reduction in strain rate after 120 s

Table 3 Unadjusted linear regression with longitudinal strain

	Coefficient	Standardised coefficient	95% CI	P value	R squared
Stroke work (mm Hg×mL)	0.00	−0.73	−0.00 to −0.00	0.00	0.53
Stroke volume (mL)	−0.13	−0.68	−0.16 to 0.10	0.00	0.46
EES (mm Hg/mL)	−14.10	−0.56	−18.46 to 9.74	0.00	0.32
End-systolic wall stress (kdynes/cm^2)	0.01	0.07	−0.03 to 0.05	0.51	0.00
End-diastolic wall stress (kdynes/cm^2)	0.16	0.35	0.07 to 0.25	0.00	0.12
Systolic blood pressure (mm Hg)	−0.16	−0.61	−0.20 to 0.11	0.00	0.37
Ventriculo-arterial coupling	0.52	0.58	0.37 to 0.68	0.00	0.34
EA (mm Hg/mL)	1.94	0.48	1.18 to 2.70	0.00	0.23
LVEDP (mm Hg)	0.36	0.24	0.06 to 0.66	0.02	0.06
Unadjusted linear regression with LVOT VTI					
	Coefficient	**Standardised coefficient**	**95% CI**	**P value**	**R-squared**
Stroke work (mm Hg×mL)	0.00	0.70	0.00 to 0.00	0.000	0.49
Stroke volume (mL)	0.11	0.57	0.08 to 0.14	0.000	0.33
EES (mm Hg/mL)	12.13	0.47	7.30 to 16.95	0.000	0.22
End systolic wall stress (kdynes/cm^2)	0.02	0.10	−0.02 to 0.06	0.365	0.01
End diastolic wall stress (kdynes/cm^2)	−0.11	−0.23	−0.21 to 0.01	0.029	0.05
Systolic blood pressure (mm Hg)	0.16	0.62	0.12 to 0.20	0.000	0.38
Ventriculo-arterial coupling	−0.43	−0.48	−0.60 to 0.26	0.000	0.23
EA (mm Hg/mL)	−1.25	−0.30	−2.09 to 0.40	0.004	0.09
LVEDP (mm Hg)	−0.29	−0.19	−0.61 to 0.03	0.078	0.04

EA, arterial elastance; EES, end-systolic elastance; LVEDP, left ventricular end-diastolic pressure; LVOT VTI, left ventricular outflow tract velocity time integral.

of LAD occlusion, as well as significant changes in strain rate after 30 s of occlusion. Despite the different methods in the two studies, their findings are in accordance with our observations of a decline in LS in parallel with LV dysfunction, and these changes occur simultaneously with changes recorded on the conductance catheter.

We observed that LS and LVOT VTI display similar degrees of change from baseline and a response parallel to the decline in LV performance. Further, with an increasing number of emboli, we found an increase in both left ventricular internal dimension in end-diastole (LVIDd) and LVIDs and thereby a corresponding reduction in LVEF. The reduction in LVEF compared with LS and LVOT VTI was less pronounced and with higher variability. Even though LVEF has an unequivocal almost universal role in cardiac disorders, cohort studies of patients with AMI with CS suggest that approximately 1/3 of patients have only mildly or moderately reduced LVEF at presentation.[15] Thus, as a single echocardiographic marker, LVEF may be of limited value in the acute phase of CS.

In our study, we found that LS was associated with several central haemodynamic parameters derived from conductance catheter analysis. However, the correlation coefficients demonstrated only a modest correlation, and with the multivariate analysis, we obtained an r^2 of a maximum 0.6, indicating that there is substantial variance within the applied methodology that is unaccounted for. Stroke work showed the strongest correlation with LS in both univariate and multivariate analyses, and the improvement in the multivariate model with the addition of measures of afterload such as systolic blood pressure and end-diastolic wall stress was limited. Since stroke work is a product of both stroke volume and intraventricular pulse pressure, it seems physiologically meaningful that it correlates well with LV deformation. Strain describes the deformation of an object normalised to its original shape and size. 2D LS describes the movement of greyscale speckles within the myocardium relative to resting length. Thus, LS reflects the longitudinal contraction of the myocardium studied. This contraction induces a volume change. The reduction in volume is preceded by pressure generation during the isovolumetric phase, which is needed to open the aortic valve and the subsequent volume reduction in the LV. This means that LV systolic function is an integrated function of both pressure and volume changes. In agreement, the present study suggests that both stroke volume and pressure generation equally contribute to the association between LS and stroke work. In animal models of chronic pressure and volume overload, LS correlated

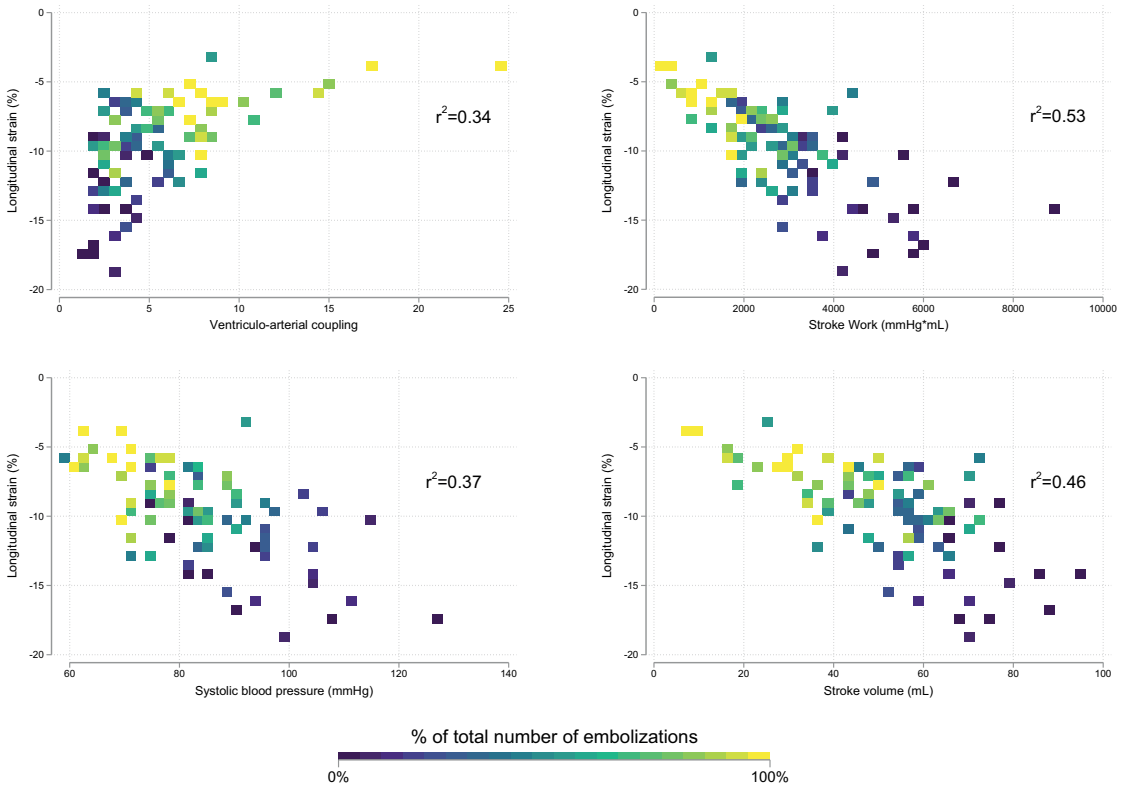

Figure 3 Heatmap of longitudinal strain and conductance catheter-based measures. Scatterplot of longitudinal strain and ventriculo-arterial coupling, stroke work, systolic blood pressure and stroke volume. Colour graded with the percentage of the total number of embolisations.

better with VA coupling and EA, whereas EES was only associated with LS in the volume-overloaded heart.[16] Observations from the present study suggest that LS only had a modest correlation with EA, EES and VA coupling, and this underscores that LS is not a surrogate for a single haemodynamic parameter, such as contractility,

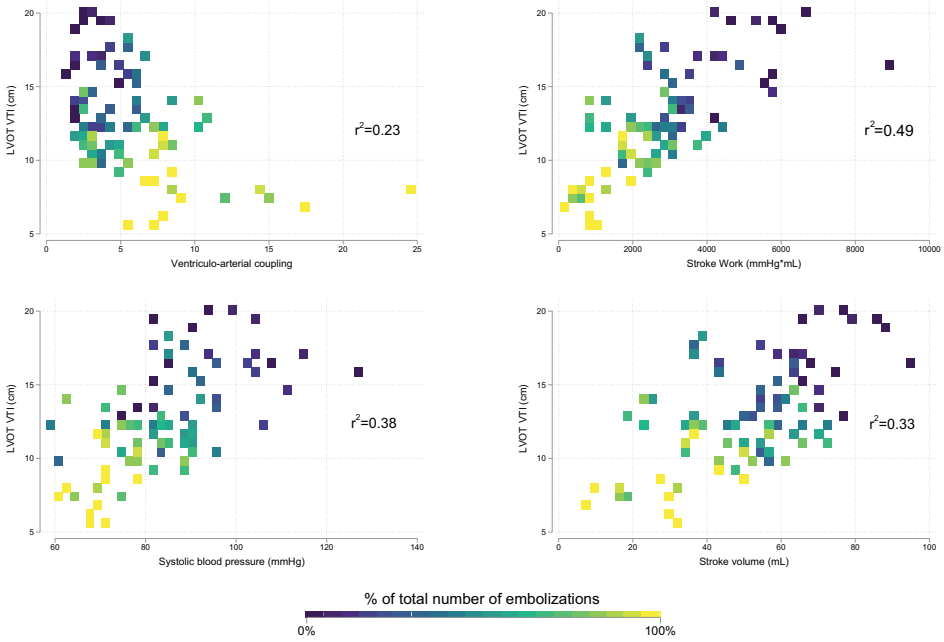

Figure 4 Heatmap of LVOT VTI and conductance catheter-based measures. Scatterplot of LVOT VTI and ventriculo-arterial coupling, stroke work, systolic blood pressure and stroke volume. Colour graded with the percentage of the total number of embolisations. LVOT VTI, left ventricular outflow tract velocity time integral.

but reflects the sum of multiple basic haemodynamic parameters, which should be interpreted in relation to the actual myocardial injury.

In current guidelines for echocardiography as a tool for monitoring, LVOT VTI is highlighted for its ability to detect changes in stroke volume.[17] In our study, we found only a modest correlation with stroke volume but a stronger correlation with stroke work, similar to LS. The observed r^2 of 0.33 corresponds to an r-value of 0.57, which is lower than previously reported. In an experimental animal study of haemorrhagic shock, Markarian *et al* found an r-value of 0.7 for correlation with stroke volume derived from transpulmonary thermodilution.[18] Gaspardone *et al* studied intensive care patients where CO was derived from either thermodilution or indirect Fick method and found a correlation coefficient of 0.8.[19] Our findings could be explained by differences in anatomy, as the LVOT in pigs is shorter and thereby less defined than in humans. This could lead to an underestimation of the forward flow and introduces a substantial bias as the flow is less uniform compared with a longer LVOT.

Limitations

In humans, normal values for LS are well described,[20] although with differences between software vendors. In large animals, normal values are less well established, but both open-chest[7 21] and closed-chest models[22] are available. These studies used smaller pigs (weight approx. 40 kg) with considerable variation in STE LS values ranging from −11%[21] to −21%.[22] We observed an LS of −13.8% at baseline, which is closer to the lower range but higher than expected in comparison with human normal values of GLS.

The number of animals studied is limited, which increases the risk of type II errors. With the dissected subxiphoid approach used for echocardiography, we could only obtain a modified five-chamber image, and LS measures are exclusively based on measurements in a single plane. This limits the ability to extrapolate our findings to studies assessing global LS using all three LV planes. As we have limited visualisation of areas supported by the right coronary artery, our LS values may be lower than the global LS, including all image planes. The method for inducing myocardial damage mimics the clinical situation with no-reflow after coronary occlusion and was designed to create a Society for Cardiovascular Angiography and Interventions class E CS situation[23] with extensive LV damage and severe shock. The pretreatment with amiodarone, to avoid refractory ventricular arrhythmias, caused a relative chronotropic incompetent state seen by the lack of increase in the heart rate with shock induction.

Conclusion

In this large animal model of progressive myocardial damage, both LS and LVOT VTI were affected early, and both variables revealed a prominent decline with progressive myocardial damage. LS correlated with stroke work and demonstrated a modest correlation with contractility, EA and VA coupling, indicating that LS should be seen as a marker of overall LV mechanics.

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