Dobutamine induces ineffective work in regional ischaemic myocardium: an experimental strain rate imaging study

Frank WEIDEMANN*†, Jens BROSCHET‡†, Nicole EBERBACH‡, Paul STEENDJIK‡, Wolfram VOELKER*, Clemens GREIM†, Georg ERTL*, Norbert ROEWER† and Jörg M STROTTMANN*

*Medical University Clinic, Josef-Schneider Str. 2, 97080 Würzburg, Germany, †Department of Anesthesiology, University of Würzburg, Josef-Schneider Str. 2, 97080, Würzburg, Germany, and ‡Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, Kamer C5-P, 2333 ZA Leiden, The Netherlands

ABSTRACT

In the present study, we sought to investigate the effects of differing inotropic conditions on regional myocardial function in ischaemic segments. In an experimental pig model (n = 11), the regional deformation parameters peak systolic strain rate [SR SYS (peak velocity of thickening)], systolic strain [ε SYS (systolic wall thickening)] and post-systolic strain [ε PST (ongoing wall thickening after end of systole)] were measured during normal perfusion and regional ischaemia of the posterior wall. These parameters were compared with global contractility [E ES (end-systolic elastance)] measured by a conductance catheter. Ischaemia was induced by an active coronary hypoperfusion in the circumflex coronary artery. Measurements were done at baseline, during dobutamine and during esmolol infusion. In normal perfused hearts, SR SYS (4.8 ± 0.2 s⁻¹ at baseline) increased during dobutamine infusion, decreased during esmolol infusion and correlated significantly with global E ES. In addition, ε SYS averaged 93 ± 3 % at baseline and there was almost no ε PST (4 ± 1 %) in normal myocardium. In ischaemic myocardium, SR SYS and ε SYS were significantly reduced compared with normal myocardium at baseline (SR SYS = 2.8 ± 0.3 s⁻¹, and ε SYS = 43 ± 6 %; P < 0.001 compared with normal perfused hearts), whereas global E ES was unchanged. In contrast, ε PST was significantly increased in regional ischaemic segments compared with the non-ischaemic myocardium (15 ± 2 %; P < 0.001). During the dobutamine infusion, SR SYS remained unchanged. In contrast, ε SYS decreased (25 ± 5 %; P < 0.001) and ε PST increased (25 ± 4 %; P < 0.05) significantly during dobutamine infusion in ischaemic myocardium. In ischaemic segments, an inotropic stimulation with dobutamine resulted in a shift of strain from systole (ε SYS) to post-systole (ε PST). Thus dobutamine induced ineffective myocardial work in ischaemic segments.

INTRODUCTION

In stress echocardiography, dobutamine infusion is considered to have a positive inotropic effect on ischaemic myocardium [1]. During non-invasive imaging, the quantitative approach to measuring the improvement of myocardial function is generally based on the measurement of ejection fraction or fractional shortening, which are parameters of global performance. The impact of dobutamine on regional myocardial function is usually based on the visual interpretation of local radial endocardial excursion combined with the assessment

Key words: contractility, dobutamine, ischaemia, myocardial contraction, strain rate.

Abbreviations: CDMI, colour Doppler myocardial imaging; E ES, end-systolic elastance; ε MAX, maximal strain; ε PST, post-systolic strain; ε SYS, systolic strain; HR, heart rate; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVESP, LV end-systolic pressure; SR SYS, peak systolic strain rate; VEL SYS, peak systolic velocity.

* Both authors contributed equally to this study.

Correspondence: Dr Jörg M. Strotmann (e-mail strotmann.j@medizin.uni-wuerzburg.de).
of local wall thickening/thinning characteristics, which is both subjective and experience-dependent [2]. Various new ultrasound modalities, including endocardial motion detection by colour kinesis [3] or velocity measurements by Doppler myocardial imaging [4, 5], have been developed to provide a quantitative analysis of myocardial function. However, as they detect motion rather than myocardial wall deformation, they are influenced by overall heart motion, cardiac rotation and motion induced by tethering to adjacent myocardial segments [6].

Ultrasound strain rate and strain measurements have been suggested [7, 8] as a new non-invasive method of quantifying regional myocardial function. Strain rate is a measure of the velocity of regional myocardial thickening. Regional strain is the time integral of strain rate and represents the local magnitude of thickening. Ultrasonic-based strain measurements have been validated in experimental sonomicrometric correlative studies and have been shown [9] to be less influenced by the above mentioned tethering effects than regional velocity data. In addition, during post-processing of the strain rate data, it is possible to do a correct timing to distinguish between systolic and post-systolic events [10]. Thus with ultrasonic strain rate imaging it is possible to quantify regional myocardial function in a single segment during the different time periods of the cardiac cycle.

In the regional ischaemic myocardium, it is not known how strain rate and strain and their time course during the heart cycle are influenced by changing contractility conditions. Thus the aim of the present study was to investigate how these parameters of regional myocardial function are influenced by altered states of contractility in normal and ischaemic myocardium in a closed-chest pig model.

METHODS

Animals

Eleven Goettinger minipigs (40 ± 3 kg) were intubated and ventilated with a mixture of air and oxygen (Servo 900; Siemens, Elema, Sweden). Anaesthesia was performed using intravenous infusion of propofol (0.3–0.6 mg/kg of body weight). Midazolam (0.2 mg/kg of body weight) was given every 45 min and pancuronium (0.04 mg/kg of body weight) every 1.5 h. All animals were treated in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Animal preparation

The right carotid artery as well as the right and left femoral arteries were carefully dissected. The right jugular vein and the right and left femoral veins were also prepared. A combined pressure-conductance catheter (Millar® Instruments, Houston, TX, U.S.A.) was inserted via the right carotid artery and placed in the left ventricle to assess pressure–volume loops as described previously [11]. A 5 French catheter, via the left femoral artery, was placed in the descending aorta to measure arterial blood pressure. The left femoral vein was used to insert a three lumen catheter to administer the different medication as described below. A Fogarty catheter was inserted, via the right femoral vein, into the inferior caval vein to allow preload reduction by inflating the balloon of this catheter. After the measurements during normal coronary perfusion were completed, an 8 French sheath was placed in the right femoral artery and a 6 French coronary guiding catheter (AL 2; Cordis, Miami, FL, U.S.A.) was placed in the ostium of the left coronary artery. An active coronary perfusion catheter (Eucatech, Bad Kissingen, Germany) was placed in the proximal third of the circumflex artery and active perfusion was started. Blood for perfusion was withdrawn from the side branch of the 8 French sheath using a high precision roller pump (Copaque®; Mallinckrodt, Berlin, Germany) was given via the perfusion catheter to verify the region of interest where the echocardiographic measurements were done. Afterwards, the animals were killed by injecting 10 ml of T61 (Intervet, Unterschleissheim, Germany) during deep anaesthesia to induce cardiac arrest. Subsequently, 10 ml of Evans Blue was injected, via the perfusion catheter, to stain the perfusion territory. Finally, the heart was removed from the chest, the stained territory (hypoperfused myocardium) was excised, the right ventricle was removed and the stained and non-stained (normal perfused myocardium) left ventricle territories were weighed separately (excluding both atria).

Experimental protocol

After preparation, the animals were allowed to stabilize for 15 min. A set of pressure–volume and echocardiographic measurements was done at baseline. Afterwards, two different interventions were performed, each one followed by a 15 min washout phase: (i) dobutamine (maximum 20 µg·min⁻¹·kg⁻¹) was infused continuously for 5 min; and (ii) esmolol was injected as a bolus injection (1.5 ± 0.4 mg/kg of body weight). For each condition, haemodynamic data were acquired, followed by echocardiographic measurements.
After the measurements were done during normal coronary perfusion, the complete protocol was repeated during active coronary hypoperfusion inducing regional myocardial ischaemia. Subsequently, the intracoronary catheter was removed and circumflex artery patency was verified by contrast injection under fluoroscopy. After 15 min, haemodynamic and echocardiographic data were acquired to verify normal regional and global performance.

**Haemodynamic data acquisition**

Left ventricular (LV) haemodynamics were measured by means of the conductance catheter method [13]. Briefly, a 12-electrode, dual-field, combined pressure–conductance catheter was introduced in the right carotid artery and positioned along the long axis of the left ventricle. The catheter was connected to a Leycom Sigma-5 DF signal processor (CD Leycom, Zoetermeer, The Netherlands) to measure electrical conductances at five levels in the left ventricle from which continuous volume signals were derived. Using this pressure–conductance catheter, the LV pressure and its first derivative (dP/dt) were measured. LV end-diastolic (LVEDP) and end-systolic (LVESP) pressure were determined.

**Maximal end-systolic elastance (EES)**

For the assessment of global LV function, data were acquired during caval occlusion to derive pressure–volume relationships. These pressure–volume relationships were used to extract the end-systolic pressure–volume relationship [14]. End systole was defined as the time point in the cardiac cycle of maximal elastance. Time-varying elastance is calculated as $E(t) = P_{LV}(t)/[V_{LV}(t) - V_0]$, where $P_{LV}(t)$ and $V_{LV}(t)$ are instantaneous LV pressure and volume respectively. $V_0$ was assessed by an iterative approach as described by Kono et al. [15]. The end-systolic pressure–volume points were fitted with a linear function and the slope (which is EES) of this end-systolic pressure–volume relationship was used as an index of global systolic function [11] (Figure 1).

**Ultrasonic data acquisition**

Echocardiographic studies were performed using a Vivid V (GE Vingmed Ultrasound, Horten, Norway) and a 2.5 MHz transducer. B-mode colour Doppler myocardial imaging (CDMI) data were acquired using parasternal short-axis views at a frame rate of 180 frames/s. Pulse repetition frequency was adjusted to avoid aliasing, and three consecutive heart cycles during brief apnoea were recorded.

**Echocardiographic data analysis**

CDMI data were analysed using dedicated software (TVI®; GE Vingmed Ultrasound) as described previously [12] (see Appendix). Briefly, radial strain rate was estimated by measuring the spatial velocity gradient over a computation area of 5 mm. The region of interest was continuously positioned within the basal part of the left ventricle posterior wall and the interventricular septum. A septal myocardial velocity profile was used for the timing of end-diastole (onset of isovolumic contraction) and end-systole (aortic valve closure) [12].

Strain rate profiles were averaged over three consecutive cardiac cycles and integrated over time to derive the natural strain profile using end-diastole as the reference point (SPEQLE®; K.U., Leuven, Belgium) [16]. From the averaged velocity, strain rate and strain profiles, peak systolic velocity (VELSYS), peak systolic strain rate (SRSYS), systolic strain ($\varepsilon_{SYS}$) and maximal strain ($\varepsilon_{MAX}$) were calculated [10] (Figure 2). The amount of thickening after aortic valve closure ($\varepsilon_{PST}$ (post-systolic strain)) was calculated by the following equation:

$$\varepsilon_{PST} = \varepsilon_{MAX} - \varepsilon_{SYS}$$

**Statistical methods**

Data are presented as means ± S.E.M. The difference in values between normal and ischaemic myocardium was tested using Student’s $t$ test for unpaired data. Multiple
RESULTS

In all animals, the complete protocol was performed. The ischaemic region verified by Evans Blue staining averaged 29 ± 2% of the LV mass. In this ischaemic region, the controlled perfusion rate in the circumflex artery was 0.36 ± 0.03 ml · min⁻¹ · g⁻¹ of myocardium.

Complete CDMI data sets (i.e. from all data acquisition points at all stages) were obtained from all animals (n = 11). However, 2% of the data subsequently had to be excluded due to the presence of either excessive reverberation artefacts or a poor signal to clutter ratio. The contrast injection at the end of the study confirmed that the segment of the posterior wall interrogated during the ultrasound study was within the ‘area at risk’ in all 11 animals.

Haemodynamic data

The haemodynamic data for normal and ischaemic hearts are shown in Table 1. In normal myocardium during dobutamine infusion, heart rate (HR) and EES increased significantly, whereas esmolol infusion induced a significant increase in LVEDP and a decrease in EES. Regional ischaemia did not affect global EES at any condition, except during dobutamine infusion: EES still increased significantly during dobutamine infusion, although the increase was less pronounced than during normal perfusion. Thus EES during dobutamine infusion in ischaemia was significantly lower compared with the non-ischaemic conditions. In contrast with the effect during normal perfusion, esmolol did not change EES during ischaemia.

Echocardiography data

VELSYS of the posterior wall

In non-ischaemic myocardium, VELSYS of the posterior wall at baseline was 3.9 ± 0.2 cm/s. VELSYS increased significantly during dobutamine infusion (8.0 ± 0.7 cm/s) and showed a decay during esmolol infusion. Induced ischaemia in the posterior wall resulted in a significant reduction in VELSYS compared with normal myocardium (2.9 ± 0.3 cm/s; P < 0.05). Furthermore, in ischaemic myocardium, VELSYS increased significantly during

### Table 1 Haemodynamic data during normal perfusion and induced regional ischaemia

*P < 0.05 compared with baseline, and #P < 0.05 compared with normal perfused hearts at the same experimental status.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal perfusion</th>
<th>Induced regional ischaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Dobutamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>64 ± 2</td>
<td>107 ± 8*</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>11 ± 1</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>LVESP (mmHg)</td>
<td>107 ± 6</td>
<td>123 ± 10</td>
</tr>
<tr>
<td>EES (mmHg/ml)</td>
<td>8.0 ± 0.7</td>
<td>20.5 ± 2.0*</td>
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</table>
Regional myocardial function

Figure 3  Regional SR<sub>sys</sub>, ε<sub>sys</sub> and VEL<sub>sys</sub> at baseline and during dobutamine and esmolol infusion in normal perfused hearts and in hearts during circumflex hypoperfusion

SR, strain rate; VEL, velocity. * P < 0.05 compared with baseline, and # P < 0.05 compared with normal perfused hearts (same experimental status and same myocardial region). Base, baseline; Dobu., dobutamine; Esmo., esmolol.

dobutamine infusion (4.9 ± 0.3 cm/s) and decreased significantly during esmolol infusion (1.7 ± 0.2 cm/s) (Figure 3).

SR<sub>sys</sub> of the posterior wall

In normal myocardium, regional SR<sub>sys</sub> of the posterior wall at baseline was 4.8 ± 0.2 s<sup>-1</sup>. SR<sub>sys</sub> increased significantly during dobutamine infusion (9.1 ± 0.7 s<sup>-1</sup>) and decreased significantly during esmolol infusion (2.9 ± 0.2 s<sup>-1</sup>). During ischaemia of the posterior wall there was a significant reduction in SR<sub>sys</sub> compared with normal myocardium (2.8 ± 0.3 s<sup>-1</sup>; P < 0.001). Compared with the baseline values in ischaemic myocardium, SR<sub>sys</sub> remained unchanged during dobutamine infusion, but decreased significantly during esmolol infusion (1.8 ± 0.2 s<sup>-1</sup>) (Figure 3).

ε<sub>sys</sub> of the posterior wall

In non-ischaemic myocardium, regional ε<sub>sys</sub> of the posterior wall at baseline was 93 ± 3 %. Dobutamine infusion did not alter ε<sub>sys</sub>. In contrast, ε<sub>sys</sub> decreased significantly during esmolol infusion (52 ± 5 %). During ischaemia, ε<sub>sys</sub> was significantly reduced compared with non-ischaemic myocardium (43 ± 6 %; P < 0.0001). In ischaemic myocardium ε<sub>sys</sub> decreased significantly during dobutamine infusion (25 ± 5 %) compared with the ischaemic baseline values (Figure 3).

ε<sub>pst</sub> of the posterior wall

In non-ischaemic myocardium there was almost no ε<sub>pst</sub> at baseline (4 ± 1 %) and during the different pharmacological interventions. In ischaemic myocardium, ε<sub>pst</sub> was significantly increased at baseline (15 ± 2 %; P < 0.001) compared with normal myocardium. In comparison with the baseline values during ischaemia, ε<sub>pst</sub> increased significantly during dobutamine infusion (25 ± 4 %) and decreased significantly during esmolol infusion (5 ± 1 %) (Figure 4).

VEL<sub>sys</sub>, SR<sub>sys</sub>, ε<sub>sys</sub> and ε<sub>pst</sub> of the remote septal region

During normal perfusion, all parameters of the remote septum were significantly lower than in the non-ischaemic posterior wall (VEL<sub>sys</sub>, −2.4 ± 0.3 cm/s; SR<sub>sys</sub>, 1.7 ± 0.1 s<sup>-1</sup>; and ε<sub>sys</sub>, 32 ± 2 %; P < 0.001). During dobutamine infusion, septal VEL<sub>sys</sub> and SR<sub>sys</sub> increased significantly (VEL<sub>sys</sub>, −8.2 ± 1.1 cm/s; and SR<sub>sys</sub>, 5.8 ± 0.9 s<sup>-1</sup>; P < 0.001). Compared with baseline values, esmolol infusion did not significantly change these parameters in the normally perfused septum. However, after circumflex hypoperfusion, VEL<sub>sys</sub>, SR<sub>sys</sub> and ε<sub>sys</sub> of the non-ischaemic septum were significantly increased compared with the septal values of the normal perfused hearts at baseline (VEL<sub>sys</sub>, −3.7 ± 0.5 cm/s; SR<sub>sys</sub>, 2.6 ± 0.3 s<sup>-1</sup>; and ε<sub>sys</sub>, 45 ± 3 %; P < 0.05). During ischaemia of the posterior wall, dobutamine infusion resulted in a significant increase in VEL<sub>sys</sub> and SR<sub>sys</sub> of the non-ischaemic septum (VEL<sub>sys</sub>, −8.1 ± 0.4 cm/s; and SR<sub>sys</sub>, 6.7 ± 0.5 s<sup>-1</sup>; P < 0.001) (Figure 3). During normal perfusion and induced ischaemia of the posterior wall, there was almost no ε<sub>pst</sub> at baseline (2 ± 1 %) and during the different pharmacological interventions in the septum (Figure 4).
Correlation of regional motion and deformation with global elastance

VelSYS of the posterior wall correlated significantly with the EES as a global contractility parameter during both normal perfusion \((r = 0.71, P < 0.0001)\) and regional ischaemia \((r = 0.62, P < 0.0001)\). In contrast, SRSYS of the posterior wall correlated well with the global EES in non-ischaemic hearts \((r = 0.81, P < 0.0001)\), but not in ischaemic hearts \((r = 0.07, P = 0.65)\). In addition, VelSYS did not correlate with the global EES in normally perfused hearts \((r = 0.09, P = 0.5)\) and in ischaemic hearts \((r = -0.21, P = 0.16)\).

**DISCUSSION**

The findings in the present study, conducted in well-controlled experimental settings, indicate the diverging influence of altered states of contractility on regional and global LV function in normal and ischaemic myocardium. These observations may carry important clinical implications as a hypoperfusion of 30% of the LV myocardium has a significant impact on regional myocardial function but not necessarily on global ventricular contractility.

**Ischaemic myocardium during changing contractility**

As in previous studies on stunned myocardium [12] and acute ischaemia [17], ischaemic myocardium of the posterior wall was induced by controlled hypoperfusion in the circumflex artery. As expected, both strain rate and strain were significantly reduced in the region of interest. In addition to this reduction, the complete time course of strain in the ischaemic myocardium was changed. Thus hypoperfusion resulted in a decreased magnitude of VelSYS in the region of interest. After aortic valve closure, the ischaemic myocardium continued to thicken during the isovolumic relaxation period, resulting in a delayed thickening peak. This 'ischaemia-related' VelPST has been well known for many years [18] and has been documented in experimental echocardiographic studies on acute ischaemia [17,19,20], stunned myocardium [12] and in patients with chronic ischaemia [21]. In general, dobutamine is considered to have a positive inotropic effect. The present study showed that, during the dobutamine challenge, VelSYS decreased significantly in ischaemic myocardium compared with the ischaemic baseline values. In contrast, VelPST significantly increased and contributed to half of the total amount of thickening. This 'ischaemia-related' VelPST has been well known for many years [18] and has been documented in experimental echocardiographic studies on acute ischaemia [17,19,20], stunned myocardium [12] and in patients with chronic ischaemia [21]. In general, dobutamine is considered to have a positive inotropic effect. The present study showed that, during the dobutamine challenge, VelSYS decreased significantly in ischaemic myocardium compared with the ischaemic baseline values. In contrast, VelPST significantly increased and contributed to half of the total amount of thickening. This 'ischaemia-related' VelPST has been well known for many years [18] and has been documented in experimental echocardiographic studies on acute ischaemia [17,19,20], stunned myocardium [12] and in patients with chronic ischaemia [21].
In contrast, negative inotropic stimulation by esmolol infusion resulted in an expected decrease in $\varepsilon_{\text{SYS}}$ in the ischaemic segments, but also in a decrease in $\varepsilon_{\text{PST}}$. Thus esmolol infusion reduces the ineffective work in the ischaemic segments. This might be due to a decrease in afterload during the esmolol infusion (i.e. LVESP was reduced) but, as regional myocardial wall stress could not be measured in our model, we can only speculate on this.

As normal individuals can only reliably detect motion at a temporal resolution of more than 90 ms [22], it is not possible to distinguish between $\varepsilon_{\text{SYS}}$ and $\varepsilon_{\text{PST}}$ during clinical stress echocardiography. This also emphasizes the importance of exact timing and the comparison of regional compared with global cardiac mechanical events when analysing regional function in ischaemic myocardium, especially during a dobutamine stress test.

### Regional compared with global function

In non-ischaemic myocardium, $\varepsilon_{\text{SYS}}$ reflects the changes in global myocardial contractility, which is in agreement with previous studies [23,24]. In contrast, the present study shows that $\varepsilon_{\text{SYS}}$, which is influenced both by HR [24,25] and stroke volume [9,24,26], does not correctly reflect the inotropic status of the myocardium. For instance, dobutamine infusion resulted in a non-significant decrease in $\varepsilon_{\text{SYS}}$ in the normal perfused posterior wall, because of the shortened time for ventricular filling secondary to the dobutamine-induced increase in HR. This means that a decrease in $\varepsilon_{\text{SYS}}$ during inotropic stimulation might not necessarily indicate an induced abnormality in contractility and should be interpreted with caution for the identification of stress-induced regional ischaemia. In contrast, in the ischaemic hearts, $\varepsilon_{\text{SYS}}$ in the normal perfused septum tended to increase, which clearly indicates the compensatory increase in myocardial function in the remote region. Thus, in normal myocardium, the quantitative evaluation of strain rate and not only strain as assessed by the human eye might be of clinical value for the accurate quantification of changes in contractile function.

In a left ventricle with 30% of the myocardium subjected to ischaemia, global contractility assessed by $E_{\varepsilon}$ was unchanged at rest. This is because global contractility during regional ischaemia is mainly influenced by three different factors: (i) the decrease in regional myocardial function in the hypoperfused region; (ii) the compensatory increase in regional myocardial function in the remote region; and (iii) the increase of LVEDP, which results in an intrinsic increase of contraction due to the Frank-Starling mechanism. Thus the measurement of global contractility by $E_{\varepsilon}$ would not assess that 30% of the myocardium was subjected to graded ischaemia. This highlights the importance of exact monitoring of regional myocardial function for the detection of hypoperfused myocardium.

### Motion compared with deformation

Our present findings, using $\text{VEL}_{\text{SYS}}$ and $\text{SR}_{\text{SYS}}$ to measure regional myocardial function, are consistent with the known pharmacological effects of dobutamine and high-dose $\beta$-blockade on both regional contractile function and global systolic LV function in normal myocardium [4,24,27,28]. During changing contractility conditions in ischaemic myocardium, the motion parameter $\text{VEL}_{\text{SYS}}$, but not the deformation parameter $\text{SR}_{\text{SYS}}$, paralleled parameters of global contractility. As velocity measurements are influenced by overall heart motion and motion induced by contraction in adjacent myocardial segments [6,9], the positive and negative inotropic stimulation of the non-ischaemic myocardium results in subsequent changes of $\text{VEL}_{\text{SYS}}$ in the ischaemic myocardium. Thus, for normal myocardium, motion measurement might be a sufficient parameter to assess regional myocardial function. In contrast, in ischaemic myocardium, it is mandatory to extract the strain rate and strain for the quantification of regional myocardial function.

### Clinical implications

The non-invasive evaluation of patients with suspected acute coronary syndromes still remains a clinical challenge, especially during clinical stress echocardiography and in the operating theatre during heart surgery where continued surveillance of regional myocardial function is warranted. The present study has demonstrated that the quantification of regional myocardial function, as derived by non-invasive strain rate imaging, is very sensitive to acute myocardial ischaemia and detects the ineffective work in the ischaemic segments during a dobutamine challenge. These data suggest that in normal myocardium $\text{SR}_{\text{SYS}}$ should be used to quantify the inotropic status. In contrast, for the assessment of regional ischaemia, $\varepsilon_{\text{PST}}$ and not $\text{SR}_{\text{SYS}}$ might be the better quantitative parameter. However, further studies are needed to determine whether these data can be applied to patients in clinical practice.

### Limitations

In the present study, we measured $\text{VEL}_{\text{SYS}}$, $\text{SR}_{\text{SYS}}$, $\varepsilon_{\text{SYS}}$ and $\varepsilon_{\text{PST}}$ only in the radial direction as, in closed chest pigs, only parasternal views (and not apical views for longitudinal function) can be obtained.

All Doppler techniques are angle-dependent. This is also applicable to myocardial Doppler velocities and deformation indices [4]. This limitation was minimized in the present study by a careful alignment of the ultrasound beam with the radial contraction of the region of interest.
As we tried to imitate the conditions of clinical echocardiography as closely as possible, we did not use sonomicrometry validation techniques in our porcine model, as such an approach requires opening of the chest and pericardium, both of which may influence systolic and diastolic deformation indices [29,30]. Thus regional contractility and regional myocardial wall stress were not measured.

Conclusions
In ischaemic myocardium, the combined use of SRSYS, \( \varepsilon_{SYS} \) and \( \varepsilon_{PET} \) provide complementary information on regional myocardial performance and are very sensitive for detection of acute ischaemic myocardium. Thus ultrasonic strain rate imaging has potential clinical implications both in detecting ischaemic myocardium and in evaluating the impact of differing pharmacological interventions on regional myocardial function.

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APPENDIX
This appendix describes the concepts of regional strain rate and strain measurements and how these parameters are derived from myocardial velocities measured with the CDMI technique.

Strain rate
This corresponds to the rate of the deformation of an object. Local myocardial strain rate (SR, expressed in s\(^{-1}\)) can be calculated from the spatial gradient in velocities recorded between two neighbouring points in the tissue (points 1 and 2 with velocities \( v_1 \) and \( v_2 \)):

\[
SR = \frac{v_1 - v_2}{L}
\]

with \( L \) reflecting the distance between points 1 and 2 [16]. When a segment is thickening in the radial direction, strain rate is defined to be positive. When a segment thins in the radial direction, it is characterized by a negative value (see Figure 1).

Strain
Regional strain values can be obtained by integrating the regional strain rate curve over time. Strain defines the relative amount of local deformation caused by an applied force [16]. Myocardial radial strain increases during myocardial thickening and decreases during thinning. Both thickening and thinning can be measured over time throughout the cardiac cycle. The ultrasound technique, as currently formatted, estimates the instantaneous change in segment length. This is the natural strain value [16], which is expressed as a percentage and is described by the equation:

\[
\text{Strain}_{\text{r}} = \frac{1}{t_{2}} \int_{t_{2}}^{t_{1}} \text{SR} \, dt
\]

where \( t_2 \) is a reference time point, \( t \) is the instant time point and \( dz \) is an infinitesimally small time interval.

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