Defining the Transmurality of a Chronic Myocardial Infarction by Ultrasonic Strain-Rate Imaging

Implications for Identifying Intramural Viability

An Experimental Study

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Background—In a correlative functional/histopathologic study, we investigated the regional deformation characteristics of both chronic nontransmural and transmural infarctions before and after a dobutamine challenge.

Methods and Results—After stenosing copper-coated stent implantation to produce circumflex artery endothelial proliferation, 18 pigs were followed up for 5 weeks. Posteuthanasia histology showed 10 to have a nontransmural and 8 a transmural infarction. Eight nonstented animals served as controls. Regional radial function was monitored by measuring ultrasound-derived peak systolic strain rates (SRSYS) and systolic strains (εSYS) before stent implantation and at 5 weeks, at baseline (bs) and during an incremental dobutamine infusion. In controls, dobutamine induced a linear decrease in SRSYS (dobutamine: bs, 4.8±0.4 s⁻¹; 20 µg·kg⁻¹·min⁻¹, 9.9±0.7 s⁻¹, P<0.0001) and an initial increase of εSYS at low dose (bs, 58±5%; at 5 µg·kg⁻¹·min⁻¹, 78±6%; P<0.05) but a subsequent decrease during higher infusion rates. In the nontransmural group, bs SRSYS and εSYS were significantly lower than prestent values (SRSYS, 2.9±0.5 s⁻¹ and εSYS, 32±6%, P<0.05 versus prestent). During dobutamine infusion, SRSYS increased slightly at 5 µg·kg⁻¹·min⁻¹ (4.7±0.6 s⁻¹, P<0.05) but fell during higher infusion rates, whereas εSYS showed no change. For nontransmural infarctions, transmural scar extension correlated closely with εSYS at bs (r=0.88). For transmural infarctions, SRSYS at bs was significantly reduced and εSYS was almost not measurable (SRSYS, 1.8±0.3 s⁻¹, εSYS, 3±4%). Both deformation parameters showed no further change during the incremental dobutamine infusion.

Conclusions—Ultrasonic deformation values could clearly differentiate chronic nontransmural from transmural myocardial infarction. The transmural extension of the scar could be defined by the regional deformation response.
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Key Words: infarction ▪ ultrasonics ▪ contractility

The noninvasive differentiation of ischemic (but viable) from infarcted myocardium is important in clinical practice. Ultrasonic strain-rate imaging has been introduced as a new noninvasive method of quantifying regional myocardial deformation.¹ Myocardial strain measurements have been validated in correlative experimental sonomicrometric studies.² A series of experimental and clinical strain-rate imaging studies have suggested that this approach may be an improvement in the noninvasive quantification of regional function by ultrasound.¹⁻⁴ With ultrasonic strain-rate imaging, both the amount of deformation (strain) and the rate of local deformation (strain rate) can be quantified.⁵

The aim of the present study was to compare the deformation properties of chronic nontransmural and transmural infarcted myocardium both at rest and during a dobutamine challenge in a closed-chest animal model and to determine whether the induced changes could reliably distinguish viable from infarcted myocardium.

Methods

Experimental Protocol
A copper-coated stent was implanted to induce either severe coronary stenosis or vessel occlusion by reactive intima hyperplasia in a series of animals. The chronically ischemic animals were then followed up for 5 weeks. Regional radial deformation was quantified noninvasively (under anesthesia) by ultrasonic strain-rate imaging both before stent implantation (prestent) and 5 weeks after implantation. Postimplantation data were collected at baseline (bs) and
during an incremental dobutamine infusion (2.5, 5, 10, and 20 μg · kg⁻¹ · min⁻¹ for 5 minutes each). During each step of the dobutamine protocol, left ventricular pressure and its first derivative (dP/dt) were measured by a Millar catheter. After the dobutamine challenge, control angiography was performed to quantify stented vessel stenosis. One day later, a correlative positron emission tomography (PET) study was performed to quantify myocardial flow. All studies were followed by euthanasia with an overdose of pentobarbital. Hearts were then excised for histopathology.

**Stent Coating**

The stents used induce severe stenosis/occlusion were constructed of a single stainless steel wire (0.127 mm in diameter) and were coated with copper by use of an electroplating technique. Stent implantation typically induced either severe nonthrombotic stenosis or vessel occlusion.

**Animal Instrumentation**

Eighteen crossbred pigs (27 to 32 kg, Animalium Ku Leuven, Leuven, Belgium) were anesthetized with intravenous propofol (0.3 mg · kg⁻¹ · min⁻¹) and fentanyl (0.5 μg · kg⁻¹ · min⁻¹), intubated, and then ventilated with an air/oxygen mixture. All animals were treated in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. A copper-coated stent was placed in the proximal segment of the left circumflex coronary artery by use of standard catheterization techniques. Eight additional animals without stent implantation were used as controls.

**Echocardiographic Data Acquisition**

Transesophageal echocardiography was performed with a Vingmed System 5 (GE Ultrasound). B-mode color Doppler myocardial velocity data were acquired during brief apnea in parasternal short-axis views. Data were acquired at 180 frames per second by use of a previously described methodology.

**Echocardiographic Data Analysis**

Myocardial end-diastolic wall thickness was measured by the M-mode technique. Color Doppler myocardial imaging data were analyzed with dedicated software (TVI, GE Ultrasound). In summary, radial strain rate was estimated by measuring the spatial velocity gradient over a computation area of 3 to 5 mm (the area used being dependent on the wall thickness). A septal myocardial velocity profile was used to time end diastole (onset of isovolumic contraction) and end systole (aortic valve closure). Strain-rate profiles were averaged over 3 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). From the averaged strain-rate and strain data, peak systolic strain rate (SR SYS ), systolic strain (ε SYS ), and maximal strain (ε MAX ) were calculated (Figure 1).

ε SYS was defined to be the magnitude of deformation measured from end diastole to end systole. ε MAX was defined to be the magnitude of deformation from end diastole to maximal thickening. From these 2 measurements, a postsystolic strain index (PSI) was calculated by use of the following equation: PSI=(ε MAX −ε SYS )/ε SYS .

**PET Measurements**

Correlative perfusion studies were performed with a PET camera (CTI Siemens) as previously described. Myocardial flow was calculated in both the region of interest and the remote region.

**Histopathologic Studies**

After euthanasia, hearts were perfusion-fixed, and the left ventricular inferolateral region of interest was identified. Histological sections were taken and examined for ischemic cells, scarring, and the extension of scar (expressed as percentage, 100% being transmural).

**Statistical Methods**

Data are presented as mean±SEM. Multiple comparisons between different groups were performed by use of ANOVA with post hoc Duncan’s test. Within each of the 3 groups, the comparison between the different stages was performed by 2-way ANOVA for repeated measurements. A linear Pearson correlation was used to compare regional deformation parameter with the extension of transmural scar distribution. Statistical significance was inferred for a value of P<0.05.

**Results**

At death, 10 stented pigs had developed a histologically confirmed nontransmural infarction and 8 stented pigs a transmural infarction. In the nontransmural group, the transmurality of the scar averaged 62±8% (range, 20% to 90%). In nontransmural infarct epicardial layers, staining documented increased glycogen storage within cells, indicating typical chronic ischemic changes. In the 8 nonstented controls, histology was normal. Typical examples of the pathologic findings for both nontransmural and transmural infarcts are shown in Figure 2.

Left ventricular inferolateral wall thickness was significantly reduced in transmural (3.5±0.4) but not in nontransmural infarcts (4.6±0.4) compared with controls (5.1±0.1; P<0.05 versus transmural infarctions). The degree of stenosis in the circumflex artery in the nontransmural infarction group was 93±3%.
Hemodynamic Data
The findings with regard to heart rate and \( +\mathrm{dP}/\mathrm{dt}_{\text{max}} \) are summarized in Table 1. Heart rate and \( +\mathrm{dP}/\mathrm{dt}_{\text{max}} \) increased gradually in all 3 groups during the incremental dobutamine infusion.

Myocardial Perfusion
Correlative PET studies were performed in a subset of 3 controls and 7 nontransmural infarction pigs. In controls, myocardial perfusion was \( 1.08 \pm 0.14 \) mL \( \cdot \) g\(^{-1}\) \( \cdot \) min\(^{-1}\) in the inferolateral wall and \( 1.05 \pm 0.1 \) mL \( \cdot \) g\(^{-1}\) \( \cdot \) min\(^{-1}\) in the septum. In the nontransmural infarction pigs, perfusion in the region of interest was significantly lower than in the remote region (inferolateral, \( 0.55 \pm 0.07 \) mL \( \cdot \) g\(^{-1}\) \( \cdot \) min\(^{-1}\); septum, \( 0.9 \pm 0.07 \) mL \( \cdot \) g\(^{-1}\) \( \cdot \) min\(^{-1}\); \( P<0.01 \)).

Echocardiographic Data
Deformation in the Control Group
At baseline, \( S_{\text{sys}} \) and \( \epsilon_{\text{sys}} \) in the inferolateral wall averaged \( 5 \pm 0.2 \) s\(^{-1}\) and \( 60 \pm 2\% \), respectively. \( S_{\text{sys}} \) increased linearly with incremental dobutamine infusion and returned to near baseline levels at recovery (at \( 2.5 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), \( 6.5 \pm 0.05 \) s\(^{-1}\); \( P<0.05 \) versus dobutamine bs; at \( 20 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), \( 9.9 \pm 0.7 \) s\(^{-1}\); \( P<0.0001 \) versus dobutamine bs; recovery, 4.7 \pm 0.8 \) s\(^{-1}\), \( P=\text{NS} \) versus dobutamine bs). In contrast, during dobutamine infusion, \( \epsilon_{\text{sys}} \) values initially increased (at \( 5 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), \( 78 \pm 6\% \), \( P<0.05 \)), but with further dobutamine infusion (10 and \( 20 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)), \( \epsilon_{\text{sys}} \) values decreased and were not significantly different from baseline values at \( 20 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) (Figure 3). There was almost no PSI in the normally perfused inferolateral wall either at study entry or during the incremental dobutamine infusion (PSI at pretest, \( 3 \pm 1\% \)) (Figure 4).

Deformation in the Nontransmural Infarction Group
Figure 5 shows the typical radial strain profile response recorded from a nontransmurally infarcted inferolateral wall during the incremental dobutamine infusion. At baseline, the magnitude of systolic thickening was slightly reduced compared with controls, and myocardial thickening continued after aortic valve closure (postsystolic thickening). This resulted in a delay in peak thickening. During dobutamine infusion, the systolic thickening of the inferolateral wall decreased incrementally, whereas postsystolic thickening increased progressively. By \( 20 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), most myocardial thickening occurred after end ejection.

At study entry, inferolateral wall \( S_{\text{sys}} \) and \( \epsilon_{\text{sys}} \) values averaged \( 5 \pm 0.5 \) s\(^{-1}\) and \( 59 \pm 3\% \), respectively. They were comparable to baseline values in the controls (\( P=\text{NS} \)). Five weeks after stent implantation, \( S_{\text{sys}} \) was significantly lower in the nontransmurally infarcted inferolateral wall compared with pretest values (\( 5 \pm 0.5 \) versus \( 2.9 \pm 0.5 \) s\(^{-1}\); \( P<0.05 \) (Figure 3). In this group, the dobutamine infusion induced a biphasic \( S_{\text{sys}} \) response with an initial
increase at 5 μg · kg⁻¹ · min⁻¹ (4.7 ± 0.6 s⁻¹; P<0.05 versus dobutamine bs). With a further increase in dobutamine infusion rates (10 and 20 μg · kg⁻¹ · min⁻¹), εSYS values decreased and were not significantly different from baseline values at 20 μg · kg⁻¹ · min⁻¹; εSYS decreased to 32±6% in the nontransmurally infarcted inferolateral wall (P<0.001 versus prestent). During the incremental dobutamine infusion, εSYS remained at this abnormally low level. The PSI increased significantly in the nontransmurally infarcted inferolateral wall compared with prestent values (42% versus 40±6%; P<0.01). During the dobutamine challenge, PSI increased further and was highest at 20 μg · kg⁻¹ · min⁻¹ (121±20%; P<0.01 versus dobutamine bs) (Figure 4). For each dobutamine stage, SRSYS and εSYS were significantly lower and PSI was significantly higher (P<0.05) than in controls.

In nontransmural infarcts, there was a significant correlation between the transmural extension of scar and εSYS in the inferolateral wall at dobutamine baseline (r=0.88, P<0.001) (Figure 6). A weaker correlation was found between the transmural scar extension and SRSYS (r=0.76, P<0.01).
Deformation in the Transmural Infarction Group
Figure 5 shows a typical example of the radial strain profile response during an incremental dobutamine infusion derived from the transmural infarctions. At baseline, there was almost no deformation in the infarcted wall during the cardiac cycle. During the dobutamine infusion, deformation did not change in the infarct zone.

At study entry (ie, before stent implantation), inferolateral wall SRSYS and εSYS in animals that subsequently developed a transmural infarction averaged 4.8±0.4 s⁻¹ and 58±2%, respectively. These were comparable to control values (P=NS). Five weeks after stenting, SRSYS was significantly reduced, with almost no εSYS in the infarcted inferolateral wall before the dobutamine challenge (SRSYS, 1.8±0.3 s⁻¹; εSYS, 3±4%; P<0.01 versus prestenst) (Figure 3). Both deformation parameters showed no change during the dobutamine infusion (at 20 µg·kg⁻¹·min⁻¹: SRSYS, 2.1±0.4 s⁻¹ and εSYS, 3±3%; P=NS versus dobutamine bs). For each dobutamine stage, SRSYS and εSYS were significantly lower and PSI was significantly higher (P<0.01) than in controls.

Deformation in the Remote Region
At baseline and during each dobutamine stage, SRSYS, εSYS, and PSI in the remote region (septum) were not significantly different from those in controls or in nontransmural or transmural infarcts. At baseline, the SRSYS, εSYS, and PSI in the septum averaged 3.5±0.2 s⁻¹, 28±1%, and 4±1%, respectively. In all 3 groups, the remote region response was similar and corresponded to normal myocardium, with SRSYS increasing linearly with incremental dobutamine infusion (at 20 µg·kg⁻¹·min⁻¹: SRSYS, 10.8±0.5 s⁻¹; P<0.0001 versus dobutamine bs). The septal εSYS showed a normal biphasic response, with the highest value occurring at an infusion rate of 10 µg·kg⁻¹·min⁻¹ (52±3% P<0.0001 versus dobutamine bs).

Discussion
The fact that contractile function is reduced in either infarcted or ischemic myocardium is well established.³,⁸,¹⁰–¹³ However, for the first time, this study has demonstrated that the measurement of regional deformation by strain-rate imaging can accurately differentiate between nontransmural and transmural infarction in a closed-chest chronic animal model that closely mimics the clinical setting.

This finding is a logical extension of the work of Derumeaux et al.¹¹ who had previously shown that in an open-chest, open-pericardium acute infarct model, Doppler myocardial imaging, by determining the radial transmural velocity gradient, could differentiate nontransmural from transmural infarction.

Our results are consistent with their acute infarct findings and show that in the different setting of chronic infarction, the noninvasive measurement of deformation properties can characterize both the functional and pathological changes in the underlying tissue. In addition, the chronic experimental closed-chest model used in this study better mimics the clinical setting, because opening and closing the pericardium can induce important changes in regional deformation.¹⁴

For chronic nontransmural infarctions, the local deformation indices SRSYS and εSYS were reduced at rest. This decrease was probably related to the combination of changes induced by the presence of nondeforming scar tissue in the endocardium together with reduced thickening in the chronically ischemic myocardium in the outer wall. This study also showed that the transmural extension of scar distribution in the infarct zone was proportionally related to the measured reduction in systolic function. During a dobutamine challenge, the typical response pattern of the nontransmural infarct zone was similar to that previously described in our work for acute ischemia.⁸ This “ischemic” response is characterized by a dose-dependent increase in postsystolic thickening that is associated with either a reduction or no change in εSYS.⁵ In the present study, the “ischemic” response of the nontransmural infarct zone would suggest that myocardial perfusion to the midmyocardial and epicardial layers via the severely stenotic circumflex artery was inadequate and that any collaterals that had developed were insufficient to support the increased oxygen demand during the dobutamine challenge. This postulate was supported by histological studies of the epicardial layer of the nontransmural infarction, which showed the typical histological changes associated with chronic ischemia. The presence of “ischemia-related” postsystolic thickening after 5 weeks of chronic ischemia would again suggest that this may be a marker of segmental viability.₁⁵,₁⁶ It also emphasizes the importance of the precise timing of regional deformation when analyzing function in complex ischemic substrates.

In all transmural infarcts, histology confirmed the transmurality of the scar in the region of interest. Such transmural scar distribution was characterized by no measurable systolic thickening either at rest or during the graded dobutamine infusion. Because the calculated PSI is related to the amount of systolic deformation, we extracted high values of PSI in the transmural myocardial infarction group. Thus, when assessing ischemic myocardium, it is the measurement of systolic deformation and not maximal deformation that is necessary to distinguish between viable versus nonviable myocardium.

For both nontransmural infarcts and stunned myocardium, regional deformation is reduced at rest. For both ischemic substrates, the myocardium will continue to thicken during the isovolumic relaxation period (this phenomenon has been called postsystolic thickening).⁴ However, in contrast to nontransmural infarcts (which show an ischemic dobutamine response), stunned myocardium is characterized by a normalization of the strain curve with a progressive decrease in postsystolic thickening during a dobutamine challenge.⁴ Thus, to distinguish between these different ischemic substrates, it is necessary to measure both systolic and postsystolic deformation both at rest and during a graded dobutamine infusion (Table 2).
TABLE 2. Summary of Deformation Characteristics at Rest and During Dobutamine Stress for Each Ischemic Substrate

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<th>Rest</th>
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<td>ε&lt;sub&gt;SYS&lt;/sub&gt;</td>
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<td>Control</td>
<td>5/s</td>
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<td>Stunning</td>
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<td>Acute ischemia</td>
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<td>Nontransmural MI</td>
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<tr>
<td>Transmural MI</td>
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MI indicates myocardial infarction; ↓, lower vs controls; ↑, higher vs controls; →, no change vs rest values; ↗, increase vs rest values; ↘, decrease vs rest values; and ↗, initial increase at low-dose dobutamine and a further decrease with higher dobutamine dose.

The responses included in the Stunning and Acute ischemia rows are taken from our prior work on stunning and acute ischemia. See Jamal et al.4,8

**Clinical Implications**

In an attempt to overcome the limitations inherent in the visual scoring of wall motion in hearts with regional ischemia, several noninvasive quantitative imaging methods have been developed.4,8,17–19 Motion-based techniques, such as Doppler myocardial velocity measurement17 or endocardial border detection by color kinesis,18 are influenced by tethering effects and thus may seem to be closely related to the transmural distribution of both at rest and during a graded dobutamine infusion (Table 2).

The methodology used does not allow quantification of deformation properties of the transmurally infarcted wall. However, to distinguish between the differing ischemic substrates,4,8,20 the use of only 1 deformation parameter is insufficient. To do this, it is necessary to measure SR<sub>SYS</sub>, ε<sub>SYS</sub>, and PSI both at rest and during a graded dobutamine infusion (Table 2).

In addition, in nontransmural infarcts, deformation would seem to be closely related to the transmural distribution of scar. Thus, the lower the systolic deformation, the greater the regional transmural extension of the scar.

**Study Limitations**

The methodology used does not allow quantification of deformation in differing myocardial layers but does measure averaged deformation across the whole wall.

Another potential limitation is that no correlative PET data could be acquired in transmural infarctions. However, histological studies in this group confirmed a transmural scar distribution. Thus, information on perfusion in the region of interest in this group was not essential to the understanding of the deformation properties of the transmurally infarcted wall.

**Conclusions**

This study shows that in an experimental setting, the quantification and timing of regional deformation can differentiate chronic nontransmural from transmurally infarcted myocardium.

**References**

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