

Relation Between Gd-DTPA Contrast Enhancement and Regional Inotropic Response in the Periphery and Center of Myocardial Infarction

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Background—Gd-DTPA contrast-enhanced (CE) MRI identifies patterns of early hypoenhancement and delayed hyperenhancement in acute myocardial infarction, but their clinical significance for the prediction of myocardial viability remains controversial. Therefore, we closely examined the relationship between these CE patterns and regional inotropic response to low-dose dobutamine infusion at a regional level.

Methods and Results—Thirteen dogs underwent CE and tagged MRI at rest and during $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dobutamine 48 hours after MI. CE patterns and 3D regional strains were measured in 96 segments per animal. Segments were categorized as being normofunctional ($n=828$) if resting circumferential shortening was within the range of remote myocardium, or dysfunctional ($n=420$) if not. Inotropic response in resting dysfunctional segments was assessed according to CE patterns. Significant improvement of radial thickening (from $+12 \pm 1\%$ [mean $\pm$ SEM] to $+22 \pm 2\%$, $P < 0.05$) and circumferential shortening (from $+1 \pm 1\%$ to $-5 \pm 1\%$, $P < 0.05$) strains occurred in dysfunctional myocardium with normal CE pattern but not in myocardium with early hypoenhancement. Delayed hyperenhanced myocardium displayed a more complex behavior. Circumferential stretching improved in the peripheral regions (from $+4 \pm 1\%$ to $-2 \pm 2\%$, $P < 0.05$), where the infarct was nontransmural ($38 \pm 3\%$ transmural), but not in centrally hyperenhanced regions (from $+4 \pm 1\%$ to $+1 \pm 1\%$ $P = \text{NS}$), where the infarct was $66 \pm 3\%$ transmural.

Conclusions—Inotropic reserve was confined to dysfunctional myocardium with normal contrast enhancement but not to myocardium with early hypoenhancement. Inotropic response in delayed hyperenhanced myocardium is influenced by transmural extent of necrosis. These observations support the use of CE MRI for the clinical detection of myocardial viability. (*Circulation*. 2001;104:998-1004.)

Key Words: magnetic resonance imaging ■ contrast media ■ inotropic agents

Two different contrast-enhancement patterns have been described in Gd-DTPA contrast-enhanced (CE) MRI in acutely infarcted myocardium¹: Early hypoenhancement indicates the presence of microvascular obstruction within the infarcted area.^{2,3} Delayed hyperenhancement reflects myocellular necrosis⁴ and results from expansion of extracellular volume due to myocellular membrane disruption and increased capillary permeability.⁵ The extent of both delayed hyperenhancement and early hypoenhancement patterns has been shown to predict clinical outcome and prognosis in patients after acute myocardial infarction (AMI).⁶ Another potential value of CE-MRI after AMI, however, would be the assessment of myocardial viability, ie, the accurate anatomic delineation of areas of necrotic as opposed to reversibly injured myocardium.

The significance of the CE patterns for the delineation of myocardial viability, however, remains controversial. De-

tailed ex vivo studies using ultrathin MRI⁵ have demonstrated that delayed hyperenhancement is a definite indicator of myocardial necrosis at the cellular level, correlating precisely to the area of irreversible tissue injury by pathology.⁵ Yet in vivo studies have found that delayed hyperenhancement overestimates infarct size against 2,3,5-triphenyltetrazolium chloride (TTC) surface staining,^{3,7-10} especially at the borders of infarcted tissue,¹¹ probably because of partial-volume effects caused by slice thickness requirements inherent to in vivo imaging.⁵ Therefore, some authors have suggested that areas of delayed hyperenhancement detected clinically might still contain viable myocardium¹² and improve regional contractile function, either spontaneously or after coronary revascularization. In support of this, recovery of regional contractile function was reported by 2 recent studies in myocardium with delayed hyperenhancement.^{13,14}

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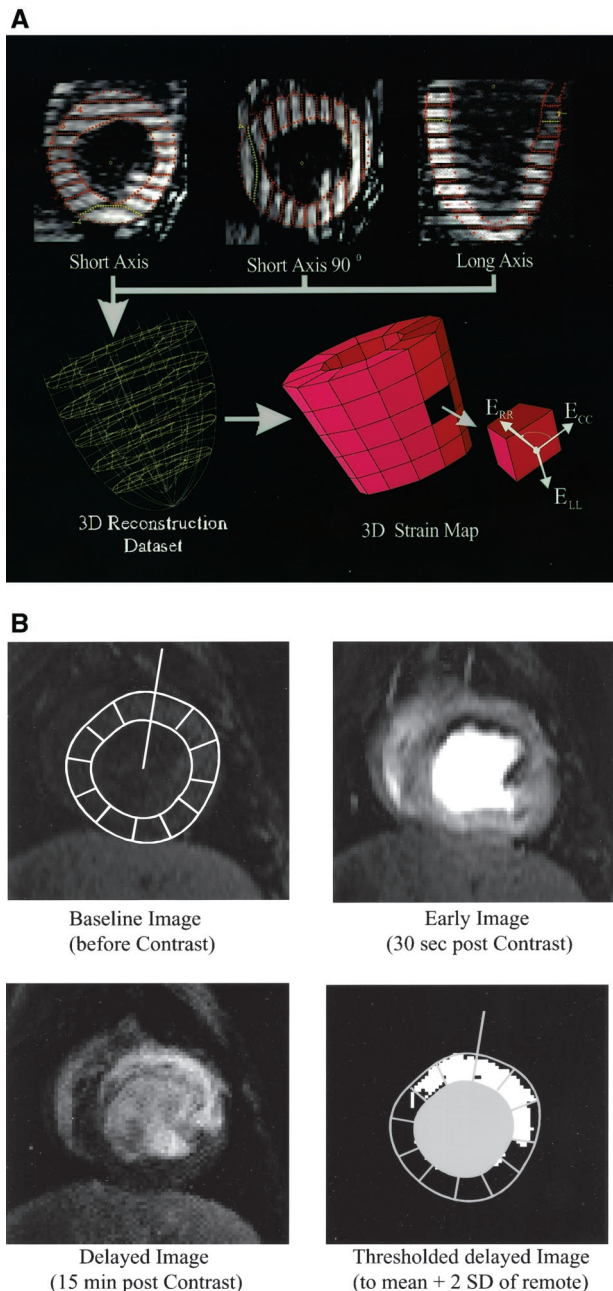


Figure 1. A, Computation of 3D strains. A 3D mesh of taglines is traced on 2 sets of tagged short-axis and 1 set of long-axis images. 3D strain maps are computed with a field-fitting approach and express myocardial deformation in 3 orthogonal normal directions of heart: circumferential shortening (E_{CC}), radial thickening (E_{RR}), and longitudinal shortening (E_{LL}). B, Characterization of CE patterns. Baseline, early (30 seconds to 1 minute after contrast), and late (15 minutes after contrast) images were automatically segmented. Segments were considered to be hypoenhanced if they had less than mean -2 SD PSIC of remote on early images. Segments were defined to be hyperenhanced when they had more than mean $+2$ SD PSIC of remote on late images. Late images were thresholded to compute extent of hyperenhancement in each sector.

These discrepancies, however, question the interpretation of CE MR for clinical detection of myocardial viability. Also, they raise questions about the understanding of the complex relationship between improvement of regional contractility

and myocellular necrosis as detected by Gd-DTPA contrast hyperenhancement at the tissue level. To clarify these issues, this experimental study examined in detail the relationship between Gd-DTPA CE patterns and improvement of regional myocardial contractility in the periphery and center of infarcted regions during low-dose dobutamine infusion.

Methods

Experimental Model

Thirteen adult mongrel dogs of either sex (20 to 25 kg) were anesthetized and underwent 90 minutes of closed-chest occlusion of the proximal left anterior descending coronary artery with an angioplasty balloon to produce anterior AMI. After 90 minutes, the balloon was deflated to allow full reperfusion of the infarcted myocardium. Animals were allowed to recover from anesthesia and were kept alive for 48 hours. The study protocol was approved by the institutional review board of the Johns Hopkins University, and the animals in this study were handled according to the "Position of the American Heart Association on Research Animal Use," adopted November 15, 1984.

MRI Protocol

Forty-eight hours after MI, the animals were reanesthetized and underwent tagged and perfusion MRI in a 1.5-T whole-body magnet (Signa, GE). Tagged images were acquired with an ECG-triggered, segmented k-space spoiled gradient recalled (SPGR) pulse sequence with spatial modulation of magnetization (DANTE-SPAMM) as described previously.¹⁵ Briefly, 3 sets of parallel tagged images, consisting of 2 orthogonal short-axis slices (4 to 5 contiguous slices) and 1 set of 6 radially prescribed long-axis slices, were acquired to allow tracking of 3D LV deformation (Figure 1a). After completion of the rested tagged study, tagging was repeated during constant infusion of $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dobutamine. Imaging was started 10 minutes after the onset of the dobutamine infusion, when hemodynamics had stabilized.

After completion of the tagged imaging sequence, an intravenous bolus (5-second) injection of 0.225 mmol/kg Magnevist (gadopentetate dimeglumine, Berlex) was given. Perfusion images were acquired starting 10 seconds after contrast injection and continued up until 15 minutes thereafter. Images were acquired with a SPGR pulse sequence with nonselective preparatory radiofrequency pulses, as previously described.¹⁰ The same short-axis slice prescription as for the tagged imaging protocol was used.

Pathology

After completion of the MRI study, the animals were euthanized by intraventricular injection of concentrated KCl solution. The hearts were excised, cut into 1-cm-thick short-axis slices, and incubated in a 2% solution of TTC for 20 minutes at 37°C.

MRI Data Analysis

To accurately correlate perfusion and contractile function, images from all data sets were cross-registered with the anteroseptal intersection as anatomic landmark. A mesh consisting of 96 sectors (12 circumferential sectors in 4 longitudinal levels separated radially into endocardial and epicardial layers) was used to compare computed 3D strains and CE patterns.

Tagged data (Figure 1A) were analyzed by a displacement field-fitting method as previously described.¹⁵ 3D strains were computed in the 3 normal orthogonal directions (radial, circumferential, and longitudinal) and expressed as percent fractional change in length between end diastole and end systole. By convention, normal shortening strains (in the circumferential and longitudinal direction) were defined to have a negative sign, and normal thickening strains (in the radial direction) were defined to have a positive sign.

Perfusion data were analyzed quantitatively (Figure 1B). Circumferential profiles of signal intensity were computed on images before

TABLE 1. Strains in Remote Region at Rest and During Dobutamine Infusion

	Radial Thickening, %		Circumferential Shortening, %		Longitudinal Shortening, %	
	Rest	Dobutamine	Rest	Dobutamine	Rest	Dobutamine
Subendocardium	+19±1	+24±1*	-16±1	-20±2†	-6±1	-9±1*
Subepicardium	+26±2	+37±2*	-9±1	-10±1	-8±1	-8±1*

Positive sign indicates thickening deformation of radial strain. Negative sign indicates shortening deformation of circumferential/longitudinal strain.

* $P<0.05$, † $P<0.005$ vs resting strain.

contrast administration, on early images (at the time of peak myocardial contrast enhancement), and on late images (15 minutes after contrast injection). Percent signal intensity increase (PSIC) in each of the 96 segments was computed as follows: $PSIC = [(SI_t - SI_o) / SI_o] \times 100$, where SI_t is the signal intensity at time t and SI_o is the signal intensity before injection of contrast agent. Early hypoenhancement was defined to be present if PSIC was lower than the mean-2 SD of remote normal myocardium at peak myocardial contrast enhancement. Delayed hyperenhancement was defined to be present if PSIC was higher than the mean+2 SD of remote normal myocardium 15 minutes after contrast injection. Images were thresholded to these levels, and the extent of both regions was planimetrically and expressed in percent left ventricular area. For both CE patterns, it was noted whether segments were peripherally (situated within 1 sector of the border of the infarct in either the longitudinal or circumferential direction) or centrally (all other segments) situated within the delayed hyperenhanced and early hypoenhanced regions. Finally, we also computed the transmural extent of delayed hyperenhancement within each segment on thresholded images as the percentage of the segments occupied by pixels having more than the mean+2 SD PSIC of remote myocardium (Figure 1B).

Statistical Analysis

All continuous values are reported as mean±1 SEM. ANOVA with repeated measurements was used to compare strains in remote segments and segments with early hypoenhancement and delayed hyperenhancement. Planned comparisons were made to assess differences in strains in different segments at baseline and also to assess changes of strain in each type of segment between baseline and dobutamine infusion. All tests were 2-tailed, and a value of $P<0.05$ was considered indicative of statistical significance.

Results

Animals and MRI CE Patterns

Anterior infarction identified by negative TTC staining at pathology was present in all 13 dogs 48 hours after coronary occlusion and reperfusion. Early hypoenhancement was identified on early images in the subendocardium of 11 animals and occupied on average $8 \pm 2\%$ of the total LV area. Delayed hyperenhancement was identified on late images in all animals and represented on average $22 \pm 4\%$ of the total LV area. The average size of the region correlated well with the size of the TTC-negative region ($r=0.96$, $P<0.001$), which represented on average $20 \pm 5\%$ ($P=NS$ versus delayed hyperenhanced region).

Baseline Myocardial Strains in Remote and Infarcted Myocardium

3D normal strains at baseline in the remote noninfarcted myocardium (inferoposterior wall) are reported in Table 1. From these normal values in the remote region, we defined normal versus abnormal regional contraction in the other segments of the heart. Segments that were within the mean±2

SD of the circumferential strain of the remote region were considered to be normofunctional ($n=828$); otherwise, segments were considered to be dysfunctional ($n=420$).

Dysfunctional segments presented significant alterations of all 3 normal orthogonal strains at rest compared with the remote region: Radial thickening was severely reduced to $+7 \pm 1\%$ in dysfunctional versus $+24 \pm 2\%$ in remote segments ($P<0.001$). Dysfunctional segments also displayed circumferential ($+3 \pm 1\%$ versus $-13 \pm 1\%$, $P<0.001$) and longitudinal ($+3 \pm 1\%$ versus $-8 \pm 1\%$, $P<0.001$) stretching instead of shortening in remote segments. The 420 dysfunctional segments were classified according to their contrast-enhancement pattern. One hundred seventy-two segments were normoenhanced (no early hypoenhancement or late hyperenhancement); 187 segments displayed only delayed hyperenhancement but no early hypoenhancement; and 61 segments displayed early hypoenhancement: all of these also had delayed hyperenhancement. At baseline, strains were similar in dysfunctional segments with different contrast-enhancement patterns (Table 2).

Regional Contractile Response to Low-Dose Dobutamine Infusion

Infusion of dobutamine resulted in significant increases in heart rate (from 126 ± 5 to 144 ± 4 bpm, $P<0.001$), systolic blood pressure (from 123 ± 5 to 140 ± 7 mm Hg, $P<0.05$), and double product (heart rate×systolic blood pressure, from $15\,683 \pm 1037$ to $20\,165 \pm 1118$ bpm×mm Hg, $P<0.001$).

Inotropic response of 3D strains was correlated with CE patterns, as shown in the example in Figure 2. Alterations of maximal end-systolic normal radial, circumferential, and longitudinal strains during low-dose dobutamine infusion according to their CE patterns are shown in Table 2 and Figures 3 to 5. In remote myocardium, low-dose dobutamine infusion significantly increased strains compared with baseline values. In dysfunctional myocardium, with normal contrast enhancement, both radial thickening and circumferential shortening improved significantly during low-dose dobutamine infusion. Dysfunctional myocardium, which presented early hypoenhancement, was nonresponsive to dobutamine infusion.

The contractile behavior of dysfunctional myocardium, which presented delayed hyperenhancement but no early hypoenhancement, was less homogeneous. When all segments were analyzed, radial thickening and longitudinal shortening strains did not improve during dobutamine infusion. Circumferential strain improved slightly during dobutamine infusion, however (from $+4 \pm 1\%$ to $0 \pm 1\%$, $P=0.05$). As indicated by the positive direction of the strain, this

TABLE 2. Dobutamine Response of Dysfunctional Segments at Baseline According to MRI Perfusion Pattern

	Radial Thickening, %		Circumferential Shortening, %		Longitudinal Shortening, %	
	Baseline	Dobutamine	Baseline	Dobutamine	Baseline	Dobutamine
Normoenhanced (n=172)	+12±1	+22±2*	+1±1	-5±1*	+0±1	-2±1
Delayed Hyperenhancement (but no early hypoenhancement)						
Center (n=116)	+2±1	+11±1	+4±1	+1±1	+5±1	+4±1
Periphery (n=71)	+7±1	+13±2	+4±1	-2±1*	+3±1	+4±1
Early Hypoenhancement (and delayed hyperenhancement)						
Center (n=47)	+0±1	+4±2	+7±2	-2±2	+6±1	+4±2
Periphery (n=14)	+16±6	+9±6	+3±2	+3±3	+0±2	+2±2

Negative sign indicates shortening of tissue (normal direction of circumferential and longitudinal strain). Positive sign indicates thickening of tissue (normal direction of radial strain) or stretching (abnormal direction for circumferential/longitudinal strain), respectively.

* $P<0.05$ vs baseline strain value.

improvement reflected reduction of passive stretching but no increase in active shortening.

Furthermore, improvement of circumferential shortening strain within dysfunctional segments displaying delayed hyperenhancement but no early hypoenhancement varied significantly according to anatomic location. Improvement of circumferential strain (from $+4\pm1\%$ to $-2\pm2\%$, $P=0.05$) was confined to only peripherally hyperenhanced segments (within 1 sector of the border between hyperenhanced and normally enhanced myocardium in either the longitudinal or circumferential direction). Conversely, centrally situated hyperenhanced myocardium (all other sectors) remained unchanged (from $+4\pm1\%$ to $+1\pm1\%$, $P=NS$) during dobutamine infusion. Again, there were no differences in strain response during dobutamine between peripherally and cen-

trally located myocardium for radial thickening and longitudinal shortening strains. Examination of the transmural extent of hyperenhancement in peripherally versus centrally situated hyperenhanced segments revealed that peripherally situated segments had less transmural extension of hyperenhancement ($38\pm3\%$) than centrally situated hyperenhanced segments ($66\pm3\%$ transmural, $P<0.001$). Finally, strain response was also assessed in function of transmural extension of hyperenhancement (Table 3). Only segments with nontransmural extent ($<33\%$) of hyperenhancement were found to improve circumferential shortening and radial thickening during dobutamine, whereas segments with higher ($>33\%$) transmural extent of hyperenhancement had no improvement of strains during inotropic stimulation.

Discussion

The present study attempted to clarify the relationship between patterns of Gd-DTPA contrast enhancement and regional improvement of myocardial strains during dobutamine infusion in a canine model of reperfused infarction. Our results can be summarized as follows.

1. Significant improvement of radial thickening and circumferential shortening occurs in dysfunctional myocardium with normal CE pattern.
2. Infarcted myocardium displaying early hypoenhancement has no contractile response to dobutamine infusion.

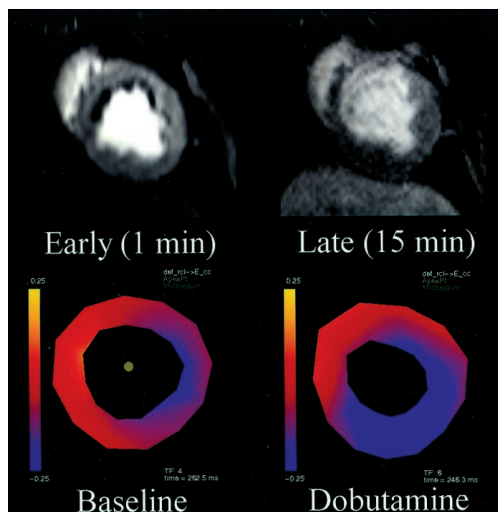


Figure 2. Example illustrating changes of circumferential shortening during low-dose dobutamine infusion in relation to corresponding CE patterns in an apical slice of an animal with AMI. Blue indicates normal shortening; red, absence of shortening; and yellow, stretching. At baseline, regional function is severely altered. During dobutamine infusion, circumferential shortening improves in regions with normal contrast-enhancement pattern but not in regions with early hypoenhancement or delayed hyperenhancement.

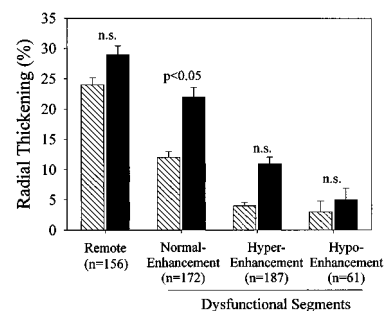


Figure 3. Changes of radial thickening during low-dose dobutamine infusion in remote and dysfunctional myocardium according to CE pattern.

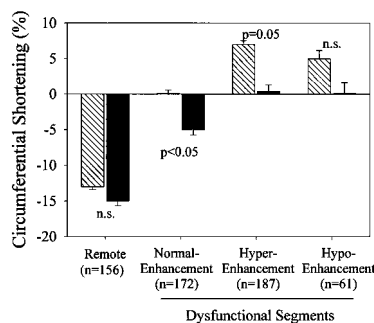


Figure 4. Changes of circumferential shortening during low-dose dobutamine infusion in remote and dysfunctional myocardium according to CE pattern.

3. Central regions with delayed hyperenhancement, where the infarct is transmural, display no inotropic response. By contrast, peripheral hyperenhanced regions, which have non-transmural necrosis, present some degree of improvement in circumferential strain to dobutamine infusion.

CE MRI for Myocardial Viability

There is ongoing debate on the significance of CE MRI for clinical prediction of recovery of contractile function. Recent clinical studies^{14,16,17} demonstrated that normoenhanced dysfunctional myocardium can spontaneously improve contractility after MI, whereas myocardium with early hypoenhancement remains dysfunctional. This is in agreement with pathological findings that indicated that normally enhanced myocardium is noninfarcted,⁵ whereas hypoenhanced myocardium represents necrotic tissue afflicted by microvascular damage and obstruction.² Yet, the significance of delayed hyperenhancement for predicting improvement of contractile function after MI remains debated. Although delayed Gd-DTPA hyperenhancement has been shown to accurately reflect myocellular necrosis and therefore to be a definite marker of absent myocardial viability at a microscopic level on ex vivo imaging,⁵ Dendale et al¹³ reported inotropic response in 41% of hyperenhanced segments, suggesting viability. Also, Rogers et al¹⁴ reported that regions presenting delayed hyperenhancement alone or in combination with early hypoenhancement improve circumferential shortening between 1 and 7 weeks after AMI, suggesting viability. Although other clinical studies^{16,17} found that the majority of hyperenhanced segments remain dysfunctional over time, in

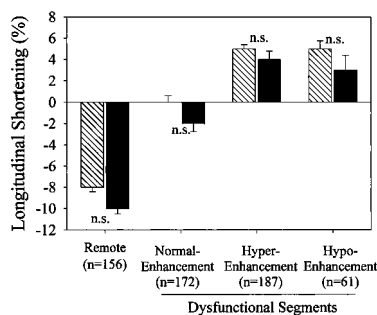


Figure 5. Changes of longitudinal shortening during low-dose dobutamine infusion in remote and dysfunctional myocardium according to CE pattern.

TABLE 3. Influence of Transmural Extent of Delayed Hyperenhancement on Inotropic Strain Response

	Rest	Dobutamine	P
<33% Hyperenhancement (n=46)			
Radial thickening, %			
Subendo	+6±1	+8±2	NS
Subepi	+7±2	+16±3	<0.05
Circumferential shortening, %			
Subendo	0±1	-5±2	<0.05
Subepi	0±1	+1±1	NS
Longitudinal shortening, %			
Subendo	0±1	+3±1	NS
Subepi	+4±1	+3±1	NS
>33% Hyperenhancement (n=202)			
Radial thickening, %			
Subendo	+5±1	-5±1	NS
Subepi	+4±0	+3±1	NS
Circumferential shortening, %			
Subendo	0±1	+8±1	NS
Subepi	+5±1	+14±1	NS
Longitudinal shortening, %			
Subendo	+6±0	+1±0	NS
Subepi	+5±0	+6±1	NS

Subendo indicates subendocardium; subepi, subepicardium. Includes early hypoenhanced segments with delayed hyperenhancement. Negative sign indicates shortening of tissue (normal direction of circumferential and longitudinal strain). Positive sign indicates thickening of tissue (normal direction of radial strain) or stretching (abnormal direction for circumferential/longitudinal strain), respectively.

none of these studies was the presence of hyperenhanced region found to be 100% specific for predicting irreversibly injured myocardium, as expected by the ex vivo studies. This indicates an important discrepancy between metabolic viability at the cellular level, as reflected by hyperenhanced myocardium, and improvement of regional function.

Complex Relationship Between Local Function and Viability in the Infarcted Heart

To better understand the complex relationship between improvement of regional contractility and regional myocellular viability as detected by Gd-DTPA CE MRI, we performed a detailed examination of CE patterns against inotropic response in dogs with AMI. Clinically, inotropic response in previously dysfunctional segments is generally believed to indicate functional improvement in noninfarcted, stunned myocardium. Absence of inotropic response is believed to indicate irreversibly injured myocardium. The findings of the present study, showing presence of inotropic response in normally enhanced dysfunctional myocardium, correlate well with the recovery of function observed in clinical studies^{14,16,17} and are in agreement with pathology findings.^{2,5} The observed complex behavior of inotropic response in hyperenhanced necrotic myocardium, however, merits discussion.

In the present study, we found that this behavior is critically dependent on the anatomic location of the segment.

Some degree of improvement in regional strains occurred in the border zones of the regions with delayed hyperenhancement but not in centrally situated hyperenhanced segments. This might have multiple explanations. Infarct border zones are generally characterized by more patchy and less transmural necrosis than the infarct core. In such nontransmurally infarcted regions, inotropic reserve may be maintained because of contractile improvement of viable cardiomyocytes and interaction with adjacent noninfarcted regions.^{18,19} Indeed, transmission of cross-fiber shortening effects has been conclusively shown to occur between different layers of the myocardium in normal hearts.^{20,21} In accordance with this mechanism, in nontransmurally infarcted regions, the inner infarcted layers might sustain deformation resulting from shortening in the outer noninfarcted layers. Similar interactions might also occur in the circumferential or longitudinal direction: Mechanical interaction or tethering has been shown to cause dysfunction in the noninfarcted rim of the infarct.^{15,22} It is conceivable that the effect applies also in the opposite direction: ie, the inotropic effect of viable myocytes in the rim of the infarct might cause deformation of the border zone of the infarcted myocardium itself. In this respect, it is notable to remark that in our study, no significant shortening occurred in the hyperenhanced regions. Instead, local improvement of circumferential strains was related solely to reduction of passive stretching.

Clinical Implications

This study has important clinical implications. It confirms the usefulness of CE MRI for detection of myocardial viability. Normal CE enhancement was shown to indicate reversibly injured myocardium, whereas early hypoenhanced regions represent necrotic myocardium containing microvascular obstruction. Some improvement of strain occurs in border zones of regions with delayed hyperenhancement, and this has clinical significance. The observed improvement of strain in border zones of the hyperenhanced region relates to reduction of passive stretching and not the development of significant active shortening or thickening in these segments.

More importantly, the study also clearly indicates the limitations of functional improvement as an indicator of myocardial viability by showing that functional improvement can occur in nontransmurally infarcted myocardium through interaction of necrotic endocardial layers with noninfarcted epicardial layers.^{18,19,23} This has also been confirmed by a recent study²⁴ showing that infarct transmural early after MI is directly correlated to wall thickening at late follow-up. These methodological considerations are particularly pertinent to the assessment of myocardial viability as the return of local function¹⁴ or as functional enhancement in response to dobutamine. They also in part explain the observed differences between these techniques and scintigraphic methods for the detection of myocardial viability.²⁵

Conclusions

In conclusion, our study examined the relation between Gd-DTPA CE patterns and presence of myocardial viability. We demonstrate that only dysfunctional myocardium with normal CE exhibits significant inotropic reserve, indicative of

myocardial viability. By opposition, the presence of either early hypoenhancement or delayed hyperenhancement in a transmural pattern correlated with absent contractile reserve to dobutamine infusion. Myocardium displaying such CE patterns must thus be considered to be nonviable. We also found, however, that partial inotropic response may occur in the border zones of hyperenhanced segments, where infarcts are nontransmural, as a result of interaction with neighboring noninfarcted myocardium. These observations clarify and corroborate the value of CE MRI for the clinical detection of myocardial viability in humans.

Acknowledgments

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