Relationship of Elevated $^{23}\text{Na}$ Magnetic Resonance Image Intensity to Infarct Size After Acute Reperfused Myocardial Infarction

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**Background**—Elevated $^{23}\text{Na}$ MR image intensity after acute myocardial infarction has previously been shown to correspond to high tissue $[\text{Na}^+]$ and loss of myocardial viability. In this study, we explored the potential of in vivo $^{23}\text{Na}$ MRI to assess infarct size and investigated possible mechanisms for elevated $^{23}\text{Na}$ image intensity.

**Methods and Results**—Thirteen dogs and 8 rabbits underwent in situ coronary artery occlusion and reperfusion and were imaged by $^{23}\text{Na}$ MRI. For anatomically matched left ventricular short-axis cross sections ($n=46$), infarct size measured by in vivo $^{23}\text{Na}$ MRI correlated well with triphenyltetrazolium chloride staining ($r=0.87$, $y=0.92x+3.37$, $P<0.001$). Elevated $^{23}\text{Na}$ image intensity was observed in infarcted myocardium (206±37% of remote in dogs, $P<0.001$; 215±58% in rabbits, $P<0.002$) but was not observed after severe but reversible ischemic injury (101±11% of baseline, $P=\text{NS}$). High-resolution ex vivo imaging revealed that regions of elevated $^{23}\text{Na}$ image intensity appeared to be identical to those of infarcted regions ($r=0.97$, $y=0.92x+1.52$, $P<0.001$). In infarcted regions, total tissue $[\text{Na}^+]$ was elevated (89±12 versus 37±9 mmol/L in control tissue, 156±60% increase, $P<0.001$) and was associated with increased intracellular sodium (254±68% of control, $P<0.005$) and an increased intracellular sodium/potassium ratio (868±512% of control, $P<0.002$). Morphometric analysis demonstrated only a minor increase in extracellular volume (17±8% versus 14±5%, $P<0.05$) in the infarcted territory.

**Conclusions**—Elevated $^{23}\text{Na}$ MR image intensity in vivo measures infarct size after reperfused infarction in both a large and a small animal model. The mechanism of elevated $^{23}\text{Na}$ image intensity is probably intracellular sodium accumulation secondary to loss of myocyte ionic homeostasis. (*Circulation*. 1999;100:185-192.)

**Key Words:** magnetic resonance imaging ■ sodium ■ radiography ■ myocardial infarction

Assessment of the extent and location of nonviable myocardium is important clinically in both acute and chronic syndromes of ischemic heart disease. For example, it is known that the quantity of necrotic myocardium is one of the most important prognostic indicators of both short- and long-term outcome after acute myocardial infarction (AMI)1,2. In addition, it is recognized that coronary revascularization in patients with chronic coronary artery disease and left ventricular (LV) dysfunction best improves symptoms and prognosis if the dysfunctional myocardium is viable.3,4 In this situation, a noninvasive imaging examination that verifies the absence of infarcted myocardium in regions with impaired contractility could be vital in the decision to undergo a revascularization procedure, with its attendant morbidity and mortality.

Although the presence of nonviable myocardium can be inferred by use of a variety of techniques, it has been suggested that the loss of cell membrane integrity as evidenced by the loss of intracellular–extracellular ionic gradients is perhaps the best criterion to identify myocyte death.5,6 In the case of $\text{Na}^+$, absence of the intracellular–extracellular ionic gradient would result in a large increase in total tissue $\text{Na}^+$ content for 2 reasons: 1, because extracellular $[\text{Na}^+]$ (≈145 mmol/L) is so much larger than intracellular $[\text{Na}^+]$ (≈15 mmol/L),7 and 2, because myocardial tissue volume is primarily intracellular (≈75% of the water space8). Detection of this increase in myocardial $[\text{Na}^+]$ could be a direct indication of tissue death, and Cannon et al8 showed evidence for elevated $^{23}\text{Na}$ image intensity in myocardial regions subject to infarction and reperfusion in an MRI study of ex vivo canine hearts.

To explore the potential of this approach in assessing myocardial viability, we previously evaluated the ability of MRI to obtain in vivo $^{23}\text{Na}$ images of the heart in animals on a high-field (4.7-T) research magnet9 and in human volunteers on a clinical scanner (1.5 T).10 Application of fast...
gradient-echo techniques reduced $^{23}\text{Na}$ imaging times to a few minutes (15 minutes in humans) even though the in vivo $^{23}\text{Na}$ myocardial signal is $\approx 22,000$ times smaller than the standard $^1\text{H}$ signal. In addition, we demonstrated in rabbits that nonviable myocardium after acute reperfused infarction results in a nearly 100% elevation in $^{23}\text{Na}$ image intensity in vivo and that this is associated with $\geq 140\%$ increase in tissue $^{23}\text{Na}$ content measured by MR spectroscopy (MRS).

The purpose of the present study was 2-fold. First, we wished to test the hypothesis that elevated $^{23}\text{Na}$ MR image intensity correlates with the histochemical measurement of infarct size after AMI in both a large and a small animal model. Second, we investigated possible mechanisms for increased tissue [Na$^+$] on a cellular level because the clinical utility of this technique will ultimately depend on the physiological information available in the $^{23}\text{Na}$ MR images.

**Methods**

In vivo $^{23}\text{Na}$ MRI was performed after infarction and reperfusion in 7 dogs and 8 rabbits and was performed before, during, and after severe but reversible ischemic injury in 4 dogs. High-resolution ex vivo $^{23}\text{Na}$ MRI was performed in 2 dogs. Image intensity was compared with regional sodium content by postmortem $^{23}\text{Na}$ MRS on tissue samples from all 8 rabbit hearts. To determine tissue sodium distribution on a cellular level, electron probe x-ray microanalysis (EPXMA) was performed in 6 additional rabbit hearts subjected to the same infarction and reperfusion protocol. Morphometric assessment of the extracellular space was also performed in this latter group of 6 rabbits to determine whether extracellular edema alone could significantly increase tissue sodium content within the infarcted territory.

**Experimental Preparation**

The care and treatment of all animals involved in this study was in accordance with the “Position of the American Heart Association on Research Animal Use,” adopted November 15, 1984.

**Dogs**

A closed-chest, in vivo dog model was used as previously described, with minor modifications. Briefly, animals were anesthetized (sodium pentobarbital 30 mg/kg IV), intubated, and ventilated. A 7F right Judkins 3.5-cm guiding catheter was placed near the left main coronary ostium, and an angioplasty catheter with a 3.0-mm balloon was positioned in the left anterior descending coronary artery. In animals subjected to infarction, the balloon was inflated for 90 minutes and then deflated to allow 4 hours of reperfusion. In animals subjected to severe but reversible ischemic injury as established by previous studies, the balloon was transiently inflated for 15 minutes.

**Rabbits**

An in vivo rabbit model was used as previously described. Briefly, 3.0- to 4.0-kg rabbits were anesthetized with ketamine 50 mg/kg IM and xylazine 5 mg/kg IM, intubated, and mechanically ventilated. An anterior branch of the left coronary artery was occluded for 40 minutes, followed by 60 minutes of reperfusion.

**MRI and Experimental Protocol**

Images were acquired on GE/Bruker 4.7-T Omega systems, with different gradient sets used for dog and rabbit imaging. A 15- or 5-cm-diameter double-resonant $^{23}\text{Na}$-$^1\text{H}$ surface radiofrequency coil was used to image dogs and rabbits, respectively.

**In Vivo MRI**

The techniques used for in vivo $^{23}\text{Na}$ MRI have been described in detail elsewhere. In brief, 2- or 3-dimensional (2D or 3D) cardiac gated gradient echo imaging was performed with short repetition and echo times. For dogs, voxel sizes were $2\times4\times15$ or $3\times3\times3$ mm and imaging times were 10 or 20 minutes for 2D and 3D images, respectively. For rabbits, voxel sizes were $1.25\times2.5\times6$ or $1.5\times3\times3$ mm and imaging times were 11 or 20 minutes for 2D and 3D images, respectively. In all animals, standard proton MR images were acquired for comparison.

**TTC Staining**

After MR imaging, the animals were euthanized, the hearts were excised, and the LV was sectioned into 2 to 5 short-axis slices at the same distances from the LV apex as the MRI short-axis images. The slices were then incubated in a 2% triphenyltetrazolium chloride (TTC) solution for 20 minutes at 37°C. Regions that failed to stain brick-red were considered to represent infarcted myocardium. The TTC-stained slices were photographed, and the resultant 35-mm slides were digitally scanned for subsequent analysis.

**Ex Vivo MRI**

Infarcted hearts from 2 dogs were subjected to detailed comparison of ex vivo MRI with histology over the entire LV. The hearts were quickly immersed in cold ($4^\circ$C) saline and rinsed, and the ventricular cavities were blotted dry. Balloons containing 99.9% deuterated water ($D_2$O) were placed in the ventricular cavities. To facilitate future registration of the ex vivo MR images with histology, 3 markers defining the short axis of the heart were glued to the epicardium near the base. The hearts were then suspended vertically in a 10-cm-diameter $^{23}\text{Na}$ coll, and images were acquired with a spatial resolution of 1×1×1 mm. The hearts were then cooled and made partially stiff by short, repeated immersions in 95% ethanol precooled to $\approx 80^\circ$C and sectioned into 2-mm-thick short-axis slices from base to apex with a commercial rotating meat slicer. The cutting plane used for sectioning in the commercial slicer was defined by use of the 3 epicardial markers glued to the base of the heart. All slices were then stained with 2% TTC and photographed.

**In Vivo Image Analysis**

The LV endocardial and epicardial borders were traced by use of the software package NIH Image on the higher-resolution $^1\text{H}$ images. Two independent observers blinded to the histochemical results were instructed to trace myocardial regions with elevated $^{23}\text{Na}$ image intensity on each short-axis slice. The spatial extent of regions with elevated $^{23}\text{Na}$ image intensity was expressed as percent LV myocardium on a slice-by-slice basis. The results for the 2 independent observers were averaged (interobserver variability was 6.5%) and then compared with the histochemical measurement of infarct size planimetered by a third independent observer using the digitized TTC images.

**Magnetic Resonance Spectroscopy**

The sodium contents of the tissue samples were determined spectroscopically as previously described. Briefly, $^{23}\text{Na}$ spectra were acquired and compared with $^{23}\text{Na}$ signal from a test tube with known Na$^+$ content. The results were expressed in mmol Na$^+$/L.

**Electron Probe X-Ray Microanalysis**

Intracellular Na concentrations were examined by EPXMA techniques similar to those described in detail and validated by other groups. In brief, hearts were excised, and tissue samples (500 to 1500 mg) were flash-frozen between highly polished copper blocks precooled in liquid nitrogen. Frozen, freeze-dried sections 1 to 2 µm thick were examined in a Hitachi S-4500-II cold field emission scanning electron microscope equipped with EPXMA (Voyager, Noran Instruments Inc). A total of 72 spectra were collected from 5×5-µm intracellular regions over the range of 0 to 10 keV with 500-second live-time acquisitions. The sizes of each peak in the spectra were expressed as a peak-to-background (P/B) ratio similar to that described by Hall et al.
Morphometric Analysis

Frozen tissue sections (1 to 3 μm) adjacent to those analyzed by EPXMA were placed on glass slides, fixed in 95% ethanol, and stained with hematoxylin and eosin. Four to 6 representative microscopic fields within each tissue section were photographed under light microscopy at ×400 magnification and scanned into a computer. The digital images were thresholded in Adobe Photoshop to produce a binary image in which extracellular regions were white and the extracellular space was calculated as the percentage of white pixels.

Statistical Analysis

All results were expressed as mean±SD. Infarcted and control myocardial differences in \(^{23}\text{Na}\) image intensity, tissue \([\text{Na}^+]\) content, intracellular \([\text{Na}^+]\), intracellular \([\text{Na}^+]/[\text{K}^+]\) ratios, and intracellular and extracellular space were assessed with paired \(t\) tests. The correlation between extent of infarction determined histologically and by MRI was determined by least-squares linear regression analysis. Values of \(P<0.05\) were considered significant.

Results

In Vivo \(^{23}\text{Na}\) MRI

Figure 1 shows typical in vivo \(^{23}\text{Na}\) MR images of 3 different dogs that have undergone acute reperfused myocardial infarction. The leftmost column demonstrates \(^{23}\text{Na}\) MRI on a red-yellow color scale on which increasing yellow is higher \(^{23}\text{Na}\) image intensity. The corresponding \(^1\text{H}\) MRI images are shown in the next column. The third column shows a composite \(^{23}\text{Na}\)-\(^1\text{H}\) image, in which endocardial and epicardial borders of LV myocardium were defined on \(^1\text{H}\) images and used to directly superimpose myocardial \(^{23}\text{Na}\) image intensities over \(^1\text{H}\) images (see text). The fourth column shows postmortem TTC-stained slice (right ventricles removed before staining) of same base-apex level. Note visual correlation of myocardial regions with elevated \(^{23}\text{Na}\) image intensity with infarcted regions (green arrows).

![Figure 1: LV short-axis cross sections of 3 different dog hearts (rows). Left column shows in vivo \(^{23}\text{Na}\) MRI using a red-yellow color scale on which increasing yellow is higher \(^{23}\text{Na}\) image intensity. Next column shows \(^1\text{H}\) MRI of same location to delineate anatomy. Third column shows composite \(^{23}\text{Na}\)-\(^1\text{H}\) image, in which endocardial and epicardial borders of LV myocardium were defined on \(^1\text{H}\) images and used to directly superimpose myocardial \(^{23}\text{Na}\) image intensities over \(^1\text{H}\) images (see text). Right column shows postmortem TTC-stained slice (right ventricles removed before staining) of same base-apex level. Note visual correlation of myocardial regions with elevated \(^{23}\text{Na}\) image intensity with infarcted regions (green arrows).](image-url)
in the same region that showed no change in image intensity after the 15-minute occlusion.

Figure 3A summarizes the imaging results in 4 animals before, during, and after a 15-minute coronary occlusion. Image intensity after severe but reversible ischemic injury was not changed compared with baseline (101 ± 11% of baseline, P = NS). The success of coronary occlusion (19 ± 13% of remote) and reperfusion (113 ± 43% of remote) was documented by radioactive microspheres.

Tissue Sodium Distribution

MR Spectroscopy
Total tissue [Na⁺] (intracellular plus extracellular) was measured by MRS from postmortem tissue samples from viable and infarcted myocardium (8 rabbits). As in the imaging results, sodium content was elevated in myocardial samples from the infarcted region (89 ± 12 mmol/L) compared with remote, noninfarcted tissue (37 ± 9 mmol/L, 156 ± 60% increase, P < 0.001).

EPXMA
Figure 4A and 4B shows representative EPXMA spectra from control and infarcted myocytes. The sodium peak along with peaks for silicon, phosphorus, sulfur, chlorine, and potassium are clearly visible. Note the marked increase in intracellular sodium and decrease in intracellular potassium for the infarcted myocyte. Figure 4C and 4D summarizes the EPXMA results (n = 72). There were significant increases in intracellular sodium (2.38 ± 0.72 versus 0.93 ± 0.08, [Na P/B], 254 ± 68% of control, P < 0.005) as well as intracellular sodium/potassium ratios in infarcted compared with normal myocytes (2.51 ± 1.13 versus 0.33 ± 0.10, [Na P/B]/[K P/B], 868 ± 512% of control, P < 0.002).

Light Microscopy
Morphometric analysis of control myocardium (31 microscope fields) quantified the extracellular space as 14.3 ± 5.3% of total tissue volume. The extracellular space of infarcted myocardium (31 microscope fields) was on average 20% larger (17.2 ± 7.6%, P < 0.05).

High-Resolution Ex Vivo ²³Na MRI
Figure 5 shows a comparison of high-resolution ²³Na MR images with the corresponding TTC-stained histological...
slices in 1 animal after acute reperfused infarction. Throughout the entire LV, the location and spatial extent of elevated $^{23}$Na image intensity matched the infarcted region defined by TTC.

Figure 6 shows the spatial extent of $^{23}$Na MRI–derived infarct size plotted against the spatial extent of TTC-negative regions for in vivo (A) and ex vivo (B) MRI. In vivo MRI correlated well with histology in both the dog (22 slices: $r=0.92$, $y=0.73x+5.76$, SEE=3.98, $P<0.001$) and rabbit (24 slices: $r=0.89$, $y=1.07x+2.45$, SEE=8.68, $P<0.001$) models of acute reperfused infarction, as well as in a pooled analysis of all animals (46 slices: $r=0.87$, $y=0.92x+3.37$, SEE=7.31, $P<0.001$). High-resolution ex vivo MRI correlated better with histology (48 slices: $r=0.98$, $y=0.92x+1.41$, SEE=2.07, $P<0.001$) and did not consistently overestimate or underestimate infarct size compared with histology ($P=NS$; range, 0% to 40.8% versus 0% to 40.9%).

**Discussion**

We found that elevated $^{23}$Na image intensity correlated well with the histochemical measurement of infarct size and that severe but reversible ischemic injury did not result in elevated $^{23}$Na image intensity. To the best of our knowledge, this is the first study to demonstrate that elevated $^{23}$Na image intensity on in vivo $^{23}$Na MR images can be used to measure infarct size after acute reperfused infarction.

**Pathophysiological Basis of Elevated $^{23}$Na Image Intensity**

**Total Tissue Sodium**

Our results showed that $^{23}$Na image intensity was $\sim 110\%$ higher in the infarct zone than in adjacent noninfarcted myocardium and that this elevation in image intensity was associated with a $>150\%$ increase in tissue $[Na^+]$ measured by MRS. These results are similar to data from our previous study in which we evaluated $^{23}$Na image intensity unblinded in infarcted rabbits by use of superimposed TTC-guided outlines to define the infarcted territory. Non-NMR techniques, such as flame emission photometry and atomic absorption spectroscopy, have also shown increased tissue $[Na^+]$ after AMI with reperfusion. This increase can result from either elevated intracellular sodium concentration ($[Na^+]_i$), expansion of the extracellular space, or a combination of the 2 mechanisms. In our study, significant elevations in $[Na^+]_i$, long after reperfusion strongly implies loss of cellular membrane integrity and myocyte death. Although ischemia in viable myocytes can raise $[Na^+]_i$, cellular levels should return to baseline within minutes on reperfusion, unless irreversible injury occurs, in which case $[Na^+]_i$ ultimately equilibrates with extracellular sodium ($[Na^+]_o$). Conversely, expansion of the extracellular space due to tissue edema does not imply irreversible cellular injury. Because $[Na^+]_i$ is normally much greater than $[Na^+]_o$, expansion of the extracellular space alone could significantly raise total tissue $[Na^+]$ and thus $^{23}$Na image intensity. This topic is further discussed below (see Extracellular Sodium).

**Intracellular Sodium**

EPXMA was used to evaluate intracellular sodium rather than MRS with a paramagnetic shift reagent such as dysprosium. The latter method depends on intact sarcolemmal membranes to compartmentalize the shift reagent and thereby discriminate between intracellular and extracellular sodium. In fact, because sarcolemmal membrane rupture is common

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**Figure 4.** A and B, Representative EPXMA spectra from control and infarcted myocardium, respectively. Sodium (Na), silicon (Si), phosphorus (P), sulfur (S), chlorine (Cl), and potassium (K) peaks are clearly visible. Note that sodium peak is markedly higher and potassium peak markedly lower in infarcted tissue than in control. C and D summarize EPXMA results and show a significant increase in intracellular sodium P/B ratio and intracellular sodium (P/B)–to–potassium (P/B) ratio in infarcted tissue compared with control.
after reperfused infarction, separation of intracellular and extracellular spaces may be physiologically artificial. Nonetheless, EPXMA was performed in this study to test the hypothesis that the observed elevation in $^{23}\text{Na}$ image intensity was due to loss of cellular electrochemical gradients.

Intracellular Na P/B was measured to be 254% higher in infarcted tissue than in control. This increase was similar to the EPXMA results of Buja et al., who found that $[\text{Na}^+]_i$ increased from 343.4 to 546.2 mmol·L$^{-1}$·kg dry wt$^{-1}$ (159% of control) in myocytes of isolated perfused interventricular rabbit septum under hypoxic conditions. These results were in myocytes with electron-dense mitochondrial inclusions and with presumably severe ischemic injury. As in this previous study, our increase in $[\text{Na}^+]_i$ may have been attenuated by several factors, including sampling tissue with heterogeneous ischemic injury, partial depolarization of control myocytes after excision of the heart and before flash freezing, and other factors related to x-ray microanalysis, which measures total elemental content rather than just the free (ionized) component. Our cellular sodium-to-potassium ratio in control specimens was 0.33, as opposed to the 0.19 measured by Walsh and Tormey, also by EPXMA in isolated perfused rabbit right ventricular wall. Although this result suggests mild cellular depolarization in our control specimens, our finding that myocyte Na/K ratios in infarcted tissue were 868% of control values adds to evidence for severe impairment of sarcolemmal function in regions with elevated $^{23}\text{Na}$ image intensity.

**Figure 5.** High-resolution ex vivo $^{23}\text{Na}$ MR images compared with histology. Size and shape of regions of elevated $^{23}\text{Na}$ image intensity appeared to correspond to those of irreversible injury defined histologically throughout entire LV.

**Figure 6.** Relationship between size of myocardial regions with elevated $^{23}\text{Na}$ image intensity plotted against infarct size (TTC-negative). Spatial extents of all measurements are given as a percentage of LV myocardial area on a slice-by-slice basis. Dashed line represents identity relationship.
**Extracellular Sodium**

In the present study, the extracellular space of control myocardium was measured to be 14.3±2.0% of the total tissue space. Morphometric analysis was used to measure the extracellular space rather than the use of tracer molecules, such as radioactively labeled inulin or sucrose, because the latter technique requires intact sarcolemmal membranes for the tracer molecule to be excluded from the intracellular space.7,31 In addition, the extracellular space was purposely defined not to include extracellular structures, such as blood cells or vascular walls, because our primary goal was to measure changes, if any, in the extracellular water space after infarction with reperfusion. Nevertheless, our extracellular space measurement in control myocardium is similar to the 11.8% measured by Barclay et al32 in LV myocardium of perfused rabbit hearts with inulin as the extracellular marker and to the 18.4% measured by Polimeni7 in rat LV with [35S]SO4 as the extracellular marker.

After reperfused infarction, the extracellular space increased from 14.3% to 17.2% of the total tissue volume. Thus, because of the extracellular contribution alone, tissue [Na+] would increase 4.2 mmol/L (ie, (0.172–0.143)×145=4.2) in a voxel of infarcted myocardium. Our experimental measurements, however, showed a 52-mmol/L (ie, 89–37=52) difference between infarcted and control myocardium. Our results therefore suggest that <10% of the increase in tissue [Na+] was due to extracellular volume expansion and consequently point to cellular accumulation of sodium as the primary mechanism for elevated tissue [Na+] in acutely infarcted myocardium.

Our small increase in the extracellular space should not imply that tissue edema is minimal in reperfused infarction. Several studies have clearly shown that total tissue water increases 20% to 30% after acute reperfused infarction.12,21,29 However, Kloner et al33 found that the marked tissue edema found after reflow was due primarily to massive cellular swelling rather than interstitial edema. This distinction is important because, as noted previously, [Na+]i, is normally much greater than [Na+], and cellular edema, by limiting expansion or actually decreasing the extracellular space,33,34 may also limit elevations in total tissue sodium unless irreversible cellular injury occurs, with loss of sarcolemmal integrity. In fact, Jennings et al, using canine models of myocardial ischemic injury, showed that tissue [Na+] markedly increases after reperfusion of irreversibly injured myocardium6,21 but found only a 13% increase in total tissue [Na+] after a period of severe ischemia just short of irreversible injury.13 In addition, they found only mild tissue edema (9% increase in tissue water) and essentially normal myocardial ultrastructure after severe reversible ischemic injury and 20 minutes of reflow.13 These results are consistent with our finding that [Na] image intensities were not elevated after severe but reversible ischemic injury (Figure 3) and our finding that MRI did not overestimate infarct size compared with histology (Figure 6) despite the likelihood that a border region of viable myocytes surrounding the infarct zone had experienced reversible levels of ischemic injury (“at risk but not infarcted region”).11,35

**Sodium Delivery**

Jennings et al21 showed that tissue [Na+] increases from 22.3 to 86.3 mmol·L−1·100 g fat-free dry wt−1 after 20 minutes of reflow in a canine model of AMI. Nonreperfused infarction, however, required more than 24 hours to reach similar tissue [Na+] values. Increases in tissue [Na+], therefore, probably depend on tissue perfusion to the infarct zone and therefore sodium delivery. Even with epicardial coronary reflow, ischemic injury to the microvasculature could result in “no-reflow”34,35 zones in the core of the infarct, which would also limit Na+ delivery to infarcted myocardium. Nonetheless, the results of Jennings et al suggest that in the absence of tissue perfusion, electrolyte delivery from slow ion diffusion will allow equilibration of tissue [Na+] in 1 to 2 days.

**Clinical Potential**

Full volumetric imaging techniques, such as single photon emission CT (SPECT) with 201Tl or 99mTc sestamibi or PET with tracers such as fluorodeoxyglucose or 82Rb can be used to localize myocardial infarction and determine myocardial viability. It is important, however, to note that neither SPECT nor PET imaging has sufficient voxel resolution to show transmural gradients in radionuclide distribution. As a point of comparison, if SPECT or PET imaging allows an average voxel resolution of 12×12×12 mm (detector width at half-maximum height), the raw uninterpolated spatial resolution for in vivo 3D 23Na MRI in dogs in this study was 3×3×3 mm (Figure 2), an ≈64-fold reduction in voxel size compared with tomographic radionuclide imaging. It is possible that precise information about the transmural extent of infarction will be useful to quantify myocardial salvage after reperfusion therapy or other interventions designed to limit myocardial necrosis.

Our studies were performed on large and small animals at high magnetic field; however, we have recently demonstrated the feasibility of obtaining cardiac 23Na MR images of humans at 1.5 T.10 Fast 3D imaging techniques, along with optimization of pulse sequences specifically for the 23Na nucleus, reduced imaging times to 15 minutes. Clinical feasibility, however, does not imply clinical utility, and we have attempted in this study to determine whether 23Na MRI can provide knowledge of the extent and location of nonviable myocardium after AMI. Although myocyte death is signaled by changes in intracellular rather than extracellular electrolytes, the potential increase in [Na+]i from loss of myocyte membrane integrity along with the disproportionately large intracellular space allows a significant (>150%) increase in total tissue [Na+]i. This large increase in tissue [Na+]i in reperfused infarction probably forms the pathophysiological basis for the utility of 23Na MRI to assess myocardial necrosis.

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