

iSTORY

HISTORICAL PERSPECTIVE

Early Use of Contrast in Cardiac Magnetic Resonance

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Computed tomography (CT) was developed for medical diagnosis more than a decade before the introduction of magnetic resonance (MR) imaging. Contrast media for CT and MR imaging have identical tissue distribution and plasma kinetics. So the story of the early history of contrast media for cardiac magnetic resonance (CMR) actually starts with early experimental work with iodinated contrast media and prototype cardiac CT scanners in the 1970s.

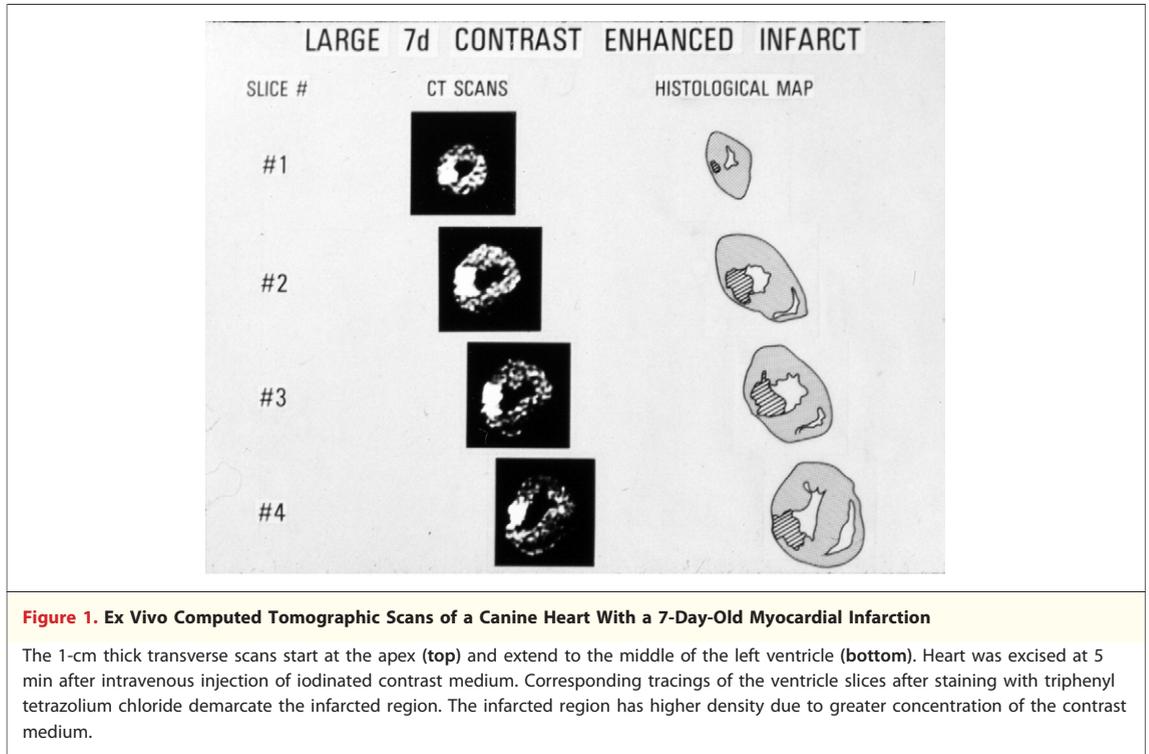
CT and MR imaging were rapidly accepted to diagnose diseases of the brain and spine. Indeed, within a few years after their introduction, these tomographic imaging techniques had already revolutionized precision in diagnosis of neurologic diseases. On the other hand, widespread adoption of these techniques for cardiac diagnosis has required about 25 years. Some of this delay in clinical application was related to delays in technologic advances necessary for overcoming the motion of breathing and cardiac contraction. Additionally, there was a prevailing perception in the 1970s and 1980s that echocardiography and nuclear imaging provided most information required from noninvasive cardiac imaging. The promise of tissue characterization using CT and, especially, MR imaging was considered either unimportant for clinical cardiology or practically unattainable.

In 1977 to 1978, our research group at the University of California, San Diego, was

awarded research grants from the National Institutes of Health and the American Heart Association to explore the use of contrast-enhanced CT for tissue characterization of the severity of ischemic myocardial injury. At that time, we were aware that available iodinated contrast media distributed rapidly in the extracellular space and were excluded from viable cells in most organs, including the heart. Our hypothesis was that ischemic injury would cause loss of cellular membrane integrity and permit entrance of contrast media into damaged myocardial cells. The initial research involved extirpation of canine hearts with acute and chronic myocardial infarctions at 5 to 30 min after intravenous injection of iodinated contrast media. Ex vivo CT imaging (electrocardiography [ECG] gating of CT scanners was not available in 1977 to 1978) of the hearts with acute infarction demonstrated dramatically higher density of the infarcted tissue compared with normal myocardium (1) (Fig. 1). The hyperenhanced myocardial region conformed to the site of increased uptake of technetium pyrophosphate (infarct-avid radionuclide) and the regional deficit of 201-thallium distribution (2). The hyperenhanced region showed close correspondence with the spatial extent of myocardial infarction as demarcated by histochemical morphometry (triphenyl tetrazolium chloride [TTC]). Subsequently, the intracellular distribution of iodine in infarcted tissue was confirmed using scanning electron microscopy with X-ray dispersive analysis (3). Tissue samples obtained from animals with reperfused infarcts showed a similar myocardial spatial distribution of iodine

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(iodinated contrast media) and technetium-99m pyrophosphate; thallium-201 had a diametric distribution. Iodine and technetium-99m pyrophosphate had the greatest concentration in the center of the infarct; a lower concentration at the periphery suggested a border zone of ischemic injury (2). The

hyperenhancement of acute infarctions was shown later in the in situ beating heart using a prototype electrocardiographic (retrospective)-gated CT scanner in the late 1970s (4).

The paucity of ECG-gated CT scanners (<10 in the world) capable of imaging the beating heart at this time caused this information to have little clinical applicability. Indeed, the notion that persistent enhancement of myocardial infarctions on tomographic imaging could be used to assess myocardial viability was not universally recognized until several years after the introduction of CMR.

MR imaging had a more favorable early history for potential cardiovascular applications. Early ECG-gated MR imaging were produced within a few years after the introduction of MR imaging for neurologic diagnoses. The first CMR images were published in the early 1980s (5,6). Around the same time, the concept of preferential and persistent enhancement of myocardial infarctions using gadolinium chelates was established using MRI of canine hearts extirpated at 5 min after administration of gadolinium contrast media (Fig. 2) (7,8). Shortly thereafter, the phenomenon of delayed contrast enhancement of acute myocardial infarctions was demonstrated in the in situ canine heart using ECG-gated T1-weighted images (Fig. 3) (9). Using ECG-gated MRI of the intact animals, it



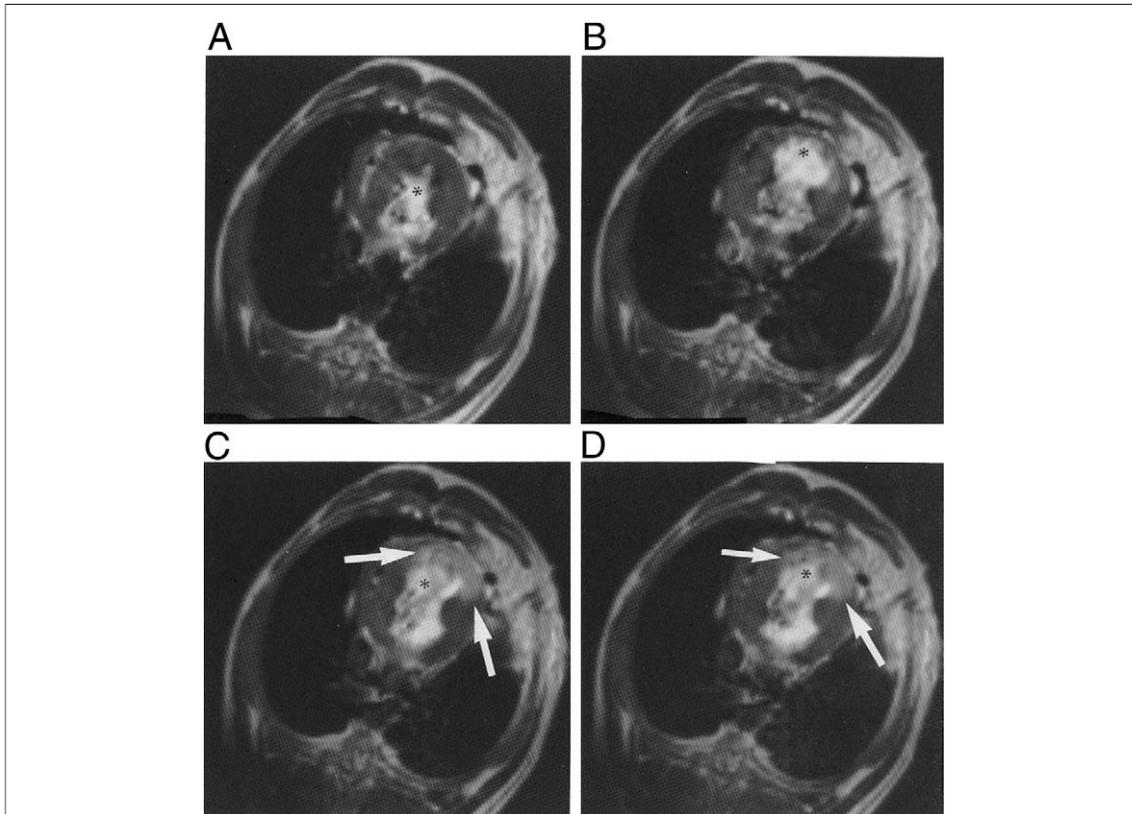


Figure 3. Electrocardiography-Gated In Vivo T1-Weighted Magnetic Resonance Images of a Heart

Two adjacent levels are shown: before (A and B) and after 5 min post-intravenous injection of gadolinium-diethylenetriaminepentaacetic acid (C and D). The 48-h-old myocardial infarction is demarcated on the contrast-enhanced images (arrows). *Indicates the high signal in the left ventricular cavity due to slowly flowing blood. Reprinted, with permission, from Tscholakoff et al. (9). Abbreviation as in Figure 2.

was also shown that differential distribution of gadolinium contrast media could distinguish between reperfused and nonreperfused myocardial infarction (9); this method could identify a no reflow zone (microvascular obstruction). Early animal studies using varying durations of ischemia showed no delayed enhancement of reversibly injured myocardium (ischemia of <15 to 20 min), but delayed enhancement only of irreversibly injured myocardium (10,11).

Gadolinium-enhanced CMR imaging of ischemically injured myocardium was shown to be effective for estimating the severity of ischemic myocardial injury (12,13). Using increasing durations of regional ischemia, the distribution volume of the gadolinium chelate in the myocardium increased. The distribution volume in normal myocardium corresponded roughly to the extracellular space (approximately 20%); with complete necrosis, the distribution volume approached 100% of the myocardium in the infarcted region. By quantifying

the intensity of delayed gadolinium enhancement and estimating the regional myocardial distribution volume, a gradient of necrosis could be discerned from the center to the periphery of the ischemic zone (14). This gradient matched the distribution of technetium-99m diethylenetriaminepentaacetic acid (DTPA), a radioactive surrogate of gadolinium-DTPA, on autoradiographic images of 20- μ m-thick cross-sectional slices of the rat heart.

The initial report documenting the occurrence of differential gadolinium enhancement of myocardial infarctions in patients was reported in 1989 by de Roos et al. (15). The group also showed the different enhancement patterns in patients with presumed occlusive compared with reperfused infarctions (16).

Improvements in CMR technology along with the development of a sequence to greatly improve contrast between normal myocardium and infarctions contributed greatly to clinical acceptance of the use of gadolinium-enhanced CMR for demon-

strating the presence, transmural extent, and size of myocardial infarctions. This sequence of inversion recovery gradient echocardiographic imaging in order to null normal myocardial signal provided enormous contrast between the infarct and adjacent normal myocardium, increasing the ease and reliability of image interpretation (17).

Several studies established the concept that this technique was a reliable one for distinguishing necrotic or scarred myocardium from viable myocardium (18). Moreover, the concept of using the transmural extent of delayed gadolinium enhance-

ment of dysfunctional myocardial segments to predict late recovery of regional contractile function in the follow-up of acute infarctions (19) or in response to revascularization (20) has become one of the most important applications of CMR in the past decade and remains so today.

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Key Words: cardiac magnetic resonance ■ computed tomography ■ contrast enhancement ■ delayed contrast enhancement ■ magnetic resonance ■ myocardial infarction.