Catheter-Based Endomyocardial Injection With Real-Time Magnetic Resonance Imaging

Robert J. Lederman, MD; Michael A. Guttman, MSc; Dana C. Peters, PhD; Richard B. Thompson, PhD; Jonathan M. Sorger, BS; Alexander J. Dick, MD; Venkatesh K. Raman, MD; Elliot R. McVeigh, PhD

Background—We tested the feasibility of targeted left ventricular (LV) mural injection using real-time MRI (rtMRI).

Methods and Results—A 1.5T MRI scanner was customized with a fast reconstruction engine, transfemoral guiding catheter–receiver coil (GCC), MRI-compatible needle, and tabletop consoles. Commercial real-time imaging software was customized to facilitate catheter navigation and visualization of injections at 4 completely refreshed frames per second. The aorta was traversed and the left ventricular cavity was entered under direct rtMRI guidance. Pigs underwent multiple injections with dilute gadolinium-DTPA. All myocardial segments were readily accessed. The active GCC and the passive Stiletto needle injector were readily visualized. More than 50 endomyocardial injections were performed with the aid of rtMRI; 81% were successful with this first-generation prototype.

Conclusion—Percutaneous endomyocardial drug delivery is feasible with the aid of rtMRI, which permits precise 3-dimensional localization of injection within the LV wall. (Circulation. 2002;105:1282-1284.)

Key Words: magnetic resonance imaging ■ drugs ■ ischemia ■ radiography ■ catheterization

X-ray fluoroscopy provides outstanding guidance for a transcatheter therapy, including coronary intervention, but is limited when imaging soft tissue compared with contrast-filled blood lumen or bone. MRI provides excellent tissue contrast, even without exogenous contrast agents, and is free of radiation exposure. Although fluoroscopic MRI is not a new concept, technology advances now permit rapid image acquisition and display. We tested the ability of in vivo real-time MRI (rtMRI) to guide catheter-based cardiac injection in swine. This technology may enable a new class of therapeutic cardiovascular procedures.

Methods

MRI Technology

We used a General Electric Signa CV/i 1.5T scanner with a custom reconstruction engine.2 Raw data were transferred to a workstation (Onyx2; Silicon Graphics) for real-time reconstruction and display at tabletop consoles.

The GE i-Drive real-time slice navigation interface was modified to add steady-state free precession (SSFP; also known as FISP) imaging3 and additional real-time controls: nonselective saturation preparation to enhance gadolinium injections; ECG gating to reduce cardiac motion; individual channel gain adjustment and color highlighting to enhance the catheter signal; and multislice acquisition and interactive volume rendering of multislice datasets as described below. An x-ray fluoroscope was available but not used.

Animals

The National Heart, Lung and Blood Institute Animal Care and Use Committee approved the protocols. Farm swine (n=6; weight, 40 to 50 kg; National Institutes of Health, Bethesda, Md) received telazol/ xylazine, continuous isoflurane, and heparin. Femoral artery sheaths (9F) were placed. The explanted heart from 1 animal was fixed with unpressurized formalin.

Catheters and Injections

Custom transfemoral LV guiding catheters (Boston Scientific) were modified to serve as intravascular receiver coils (GCCs). Independently steerable coaxial 9F and 7F guiding catheters directed a needle in the LV cavity. These first-generation devices had no special adaptation to attenuate potential catheter heating. The GCC was used in parallel with a custom high-impedance phased array of 3 flexible surface coils (Nova Medical). The spring-loaded 27G injection needle (Stiletto; Boston Scientific) was modified for MRI compatibility but not as a receiver coil. The actuated Stiletto needle extends 3.5 mm.

Gadolinium-DTPA (Magnevist) was diluted with NaCl solution to achieve a concentration of 30 mmol/L and physiological osmolarity for 1-mL injections. In one animal, brilliant green dye was admixed with gadolinium injectate for postmortem inspection of injection sites. Injection depth was measured off-line (Medical Image Processing, Analysis, and Visualization; National Institutes of Health). Data are reported as mean±SD.

Results

Technical Details of MRI

Catheter manipulations were guided by SSFP sequences. These were highly sensitive to appropriate center-frequency and shim adjustment. At heart rates of 60 to 100 bpm, an acceptable balance of cardiac motion, signal-to-noise ratio,
and spatial and temporal resolution was obtained with the following parameters: 128×96 pixel matrix, 7-mm slice thickness, 32×24-cm field of view, 60° flip angle, 125- or 62.5-kHz bandwidth, 1.8-ms echo time, 4.4-ms repetition time, and three-fourths k-space acquisition. These parameters yielded 4 completely refreshed frames per second.

Nonselective saturation preparation, with a 90° flip-angle and an effective inversion time of 120 ms, suppressed blood and myocardial signal to enhance gadolinium visualization. For most injections, intramyocardial gadolinium was clearly visible even without saturation preparation.

**Catheter Tracking and Visualization**

The transfemoral guiding catheter traversed the aorta entirely with rtMRI (SSFP sequences) guidance, navigating away from the cephalic vessels and across the aortic valve, using intrinsic blood and tissue contrast, and without superimposed roadmap images or subtraction masks. Coloring the catheter channel red often helped to identify catheter-related components, such as nitinol guidewires (which demonstrated inductive coupling), that were not readily visualized in some configurations with pure grayscale imaging.

The tip of the catheter appeared as a signal void and was visualized only when located within the selected imaging slice, so entry into the left ventricle was better tracked using volumerendered multislice imaging (ie, combining multiple slices).

Scan planes were dynamically selected to show the aortic arch (for LV entry) or rotated along the long axis of the left ventricular catheter (for injection site selection). The catheter was easily manipulated into any selected scan plane; similarly, scan planes were easily manipulated to determine catheter position. The preformed coaxial catheters needed to be aligned in-plane for complete visualization within single thin slices.

The active GCC was well visualized against the white-blood SSFP sequences as a black central stripe (along the catheter lumen) surrounded by a region of enhanced local signal (Figure 1B). Catheter position could easily be demonstrated in relation to endocardial and epicardial surfaces and papillary and valvar structures. The passive Stiletto device was well visualized as a black magnetic susceptibility–induced signal void during SSFP sequences, distinct from blood and myocardium (Figure 1C). Both devices also could be seen, weakly, to provide spatial context during T₁-weighted imaging with saturation preparation intended to suppress background and enhance visualization of the myocardial gadolinium injectate (Figure 1D and 1E).

The Stiletto device could be tracked as it exited and straightened the GCC until it made contact with the targeted endocardial injection site (Figure 1C). The first-generation units tested in this study sometimes moved out of plane, although visualization of endocardial contact usually could be restored by adjusting the scan plane position. Endocardial contact usually could be maintained without significant ventricular ectopy.

**Endomyocardial Injections**

A total of 53 injections were attempted, 43 of which were visualized as myocardial accumulation of gadolinium (81%). A representative endomyocardial injection sequence is shown in Figure 1. Figure 1A includes an overlay to identify the 4 cardiac chambers and pulmonary artery, as well as the intracardiac GCC. Figure 1B shows the GCC directed toward the interventricular septum without making contact. In Figure 1C, the Stiletto is extended from the guiding catheter and engages the apical left ventricular septum. Figure 1D shows the GCC as it exits and straightens the GCC until it makes contact with the targeted endocardial injection site (Figure 1C). Both devices were visible within the myocardial wall. Injections typically remained visible for >10 minutes.

The morphology of each injection was variable. Injections had an average depth of 4.0±1.4 mm, compared with the Stiletto needle length of 3.5 mm and an average wall thickness of 10.0±1.4 mm. In the long axis, injections had an average maximum diameter of 8.3±2.5 mm and an average minimum diameter of 5.7±1.5 mm. Figure 2 illustrates the
close relationship between rtMRI and pathology when gadolinium was admixed with tissue-fast dye.

Discussion
We have demonstrated feasibility of rtMRI guidance of catheter-based endomyocardial injection in pigs. This technique afforded good spatial localization and detail. All myocardial segments were readily accessible, and intramuscular accumulation of injectate was imaged in vivo and in real-time.

We intend to apply rtMRI-guided catheter injection to targeted local myocardial drug delivery. Potential applications include protein or gene formulations for therapeutic angiogenesis in the treatment of myocardial ischemia, myoblast or stem cell preparations to repair failing or infarcted myocardium, and ablation of conduction tissue in rhythm disorders or of outflow tissue in hypertrophic cardiomyopathy. Treatment could be tailored, for example, according to regional MRI perfusion or functional characteristics. Successful targeting and injection can be observed directly by including dilute gadolinium or other metal chelates, as in our present experiments.

Tracking catheters is challenging in rtMRI. Passive catheters can be difficult to visualize because the signal void created by the catheter may be nonuniform, obscured by volume-averaging with surrounding bright tissues (especially in thick slabs), or invisible against surrounding dark regions. Signal-enhancing passive catheters may overcome some of these obstacles but do not allow independent manipulation of the catheter signal for enhanced visualization during navigation, nor do they help obtain high-resolution images of the surrounding tissue. We addressed these challenges in several ways. First, we converted the guiding catheter to an active receiver coil, which provides a bright signal.5 Second, we used thin-slab images to reduce volume-averaging. Third, we intermittently employed multislice imaging, in which multiple parallel slabs were rapidly acquired in sequence. Although multislice imaging reduced overall temporal resolution (by the number of slices—typically 3), thinner slabs reduce volume-averaging for better detection of catheter signal and anatomic detail. Catheters could be tracked across multiple slices, which could be combined into a single image.

In this experience, thin slabs reduced volume-averaging sufficiently so that even the passive Stiletto needle was clearly visualized using bright-blood pulse sequences. Both single- and multislice rtMRI afforded easy tracking of active catheters. We found it convenient to rotate the imaging plane along the LV long-axis for either catheter tracking or myocardial targeting. When projection-like images were desired, as during aortic valve traversal, multislice imaging proved useful. Other teams have described rapid thick-slab (projection) myocardial MRI using spoiled gradient echo techniques4,6,7 or they have superimposed contextual road maps9,10 to guide catheters.

Limitations
This is a proof-of-concept experience with first-generation catheters and exploratory imaging techniques. Catheters could be improved, for example, by placing receiver coils in the injection needle, by increasing coil sensitivity, and designing guiding catheters that remain in a single imaging plane. In addition, precautions must be taken to attenuate potentially dangerous catheter heating during rtMRI. Several approaches are being tested currently.11–13 Commercial MRI scanners could be improved with faster image reconstruction capability and the ability to switch rapidly between different imaging sequences. For example, it would be helpful to alternate between rapid sequences for catheter manipulation and high-resolution sequences for careful tissue inspection. Nevertheless, in our laboratory, contemporary gradient systems and a custom reconstruction engine permitted multiple completely refreshed frames to be acquired and displayed each second with satisfactory latency, signal-to-noise ratio, and spatial resolution to guide catheter manipulation, orientation, and myocardial injection from within the LV cavity.

Conclusion
Percutaneous endomyocardial drug delivery is feasible using rtMRI and permits precise three-dimensional localization of injections within the left ventricular wall. We believe rtMRI therapeutic procedures involving direct visualization of the full thickness of the myocardium and valves will soon be possible in humans. Combined with on-line observation of functional, perfusion, and spectroscopic characteristics, rtMRI may offer a new cardiovascular therapeutic modality. In our preliminary experience, images are readily demonstrated that are not attainable even by surgical exposure, and these images are obtained without exogenous contrast agents and without regard to plane orientation or interposed air or bone.

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