BASIC RESEARCH

Real time magnetic resonance guided endomyocardial local delivery

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Objective: To investigate the feasibility of targeting various areas of left ventricle myocardium under real time magnetic resonance (MR) imaging with a customised injection catheter equipped with a miniaturised coil.

Design: A needle injection catheter with a mounted resonant solenoid circuit (coil) at its tip was designed and constructed. A 1.5 T MR scanner with customised real time sequence combined with in-room scan running capabilities was used. With this system, various myocardial areas within the left ventricle were targeted and injected with a gadolinium-diethylenetriaminepentaacetic acid (DTPA) and Indian ink mixture.

Results: Real time sequencing at 10 frames/s allowed clear visualisation of the moving catheter and its transit through the aorta into the ventricle, as well as targeting of all ventricle wall segments without further image enhancement techniques. All injections were visualised by real time MR imaging and verified by gross pathology.

Conclusion: The tracking device allowed real time in vivo visualisation of catheters in the aorta and left ventricle as well as precise targeting of myocardial areas. The use of this real time catheter tracking may enable precise and adequate delivery of agents for tissue regeneration.

Despite recent treatment advances, cardiovascular disease is still the leading cause of death. The socioeconomic impact of cardiovascular diseases will increase in the future because of treatment advances that convert acute events into chronic disease states. These trends, combined with a longer lifespan, are the causes of rising incidences of congestive heart failure, arrhythmias, and valvar disease. The need for curative, rather than palliative, interventions to meet these trends is evident. As such, novel attempts to alter favourably the balance of myocardial perfusion and demand in patients with coronary artery disease and chronic refractory ischemic states have included local application of laser energy[1 2] and growth factors.[3] Other means are being tested for tissue regeneration, such as injecting embryonic cardiomyocytes,[4] skeletal myoblasts,[5 6] and bone marrow cells,[7] to repair terminally injured myocardium, although the effectiveness of these approaches has yet to be proved.

Local tissue delivery of pharmacological, genetic, or cellular material may offer a level of treatment not possible with systemic delivery techniques. The success of myocardial tissue regeneration techniques will probably depend on the precision and accuracy of the delivery of probes to the regions of interest. An even distribution of treatment agents throughout diseased tissue is desirable for most treatment strategies. This principle is especially pertinent to agents that are delivered locally. When hypodermic needles are used as delivery tools, precision is required to distinguish sites previously injected from those sites not yet injected. This is a simple matter when materials are injected under direct visualisation, but becomes a considerable challenge when internal tissues are targeted and alternative imaging modalities are used. For any imaging method used, it is crucial to localise the needle (or delivery device) tip and to establish its position continuously with respect to both target tissue and surrounding structures. Fluoroscopic imaging, normally used during interventional cardiac procedures, does not provide optimal visualisation of myocardial target areas or enable the precise navigation of delivery devices.

Recently, several groups have used the infarct related artery as the delivery route for stem cells with the goal of myocardial regeneration. This technique appears particularly appealing in the immediate period after myocardial infarction, whereas its potential appears limited for region directed treatment of the chronically diseased ventricle, in which fibrosis may be the dominant tissue type. It is conceivable that treatment combining multiple delivery techniques, such as local needle based and intracoronary non-needle based techniques, may offer even greater therapeutic efficacy.

Advances in magnetic resonance (MR) imaging have greatly improved the evaluation of cardiac structure and function. MR imaging provides excellent contrast that differentiates soft tissue components on the basis of biophysical and biochemical parameters such as chemical composition and concentration, water content, physical state, molecular motion, and diffusion. MR can also be used to detect and assess the extent of infarcted myocardium because of the delayed absorption and release kinetics of gadolinium in such tissue when compared with that of normal myocardium.[8] Additionally, progress in materials technology has furthered the ability to track medical devices under MR guidance.[9] Therefore, by coupling advances in image processing and catheter development, the performance of cardiac interventional procedures under real time MR guidance has become feasible. Reports of its use in vascular intervention,[10] atrial septal closure,[11] and electrophysiological procedures[12] illustrate the potential of real time MR imaging during cardiovascular procedures.

Abbreviations: DTPA, diethylenetriaminepentaacetic acid; FIESTA, fast imaging employing steady state acquisition; MR, magnetic resonance

This study aimed at testing the feasibility of combining real time myocardial visualisation and catheter tracking to enable local endoventricular delivery.

METHODS

Real time MR imaging protocol

A clinical MR imager (Signa CV/i 1.5 T, gradient 40 mT/m, SR150; General Electric, Milwaukee, Wisconsin, USA) with customised real time steady state free precession pulse sequence (real time fast imaging employing steady state acquisition (FIESTA)) combined with in-room scan running capabilities was used. The pulse sequence allowed an acquisition rate of 10 frames/s when interfaced to the real time control and display program (iDrive, General Electric). Arbitrary slice orientation and offset were controlled interactively through the user interface.

The real time images were obtained with the following parameters: echo time 1.4 ms, repetition time 2.9 ms, field of view 30 × 20 cm, slice thickness 10 mm, matrix 128 × 64, fractional number of excitations and partial phase field of view, flip angle 30°, and receive bandwidth 125 kHz. The acquisition per slice rate with these parameters was (2.9 ms) × (32 + 8 views) × (0.85 partial phase field of view) = 98.6 ms, the equivalent of 10 complete images in one second. Spatial resolution was 2.3 × 3.1 mm^2 in plane. With the sequence and the field of view selected, wrapping was not observed.

Catheter and tracking coil design

A percutaneous microimplant delivery catheter (SR200 MyoCath; Bioheart, Inc, Santa Rosa, California, USA) was modified for MR compatibility. It is a 7 French intramyocardial injection system containing a protruding 25 gauge needle and deflectable tip. Controls for needle extension, injection, and tip deflection are contained in the proximal handle.

The susceptibility based passive visualisation of the catheter shaft was sufficient to determine device position and to facilitate image plane selection. However, to distinguish the catheter shaft from its tip, a more distinct marker was required. For this purpose, a miniaturised resonant circuit composed of a multiturn solenoid inductor of Teflon coated silver wire (diameter 0.25 mm) connected in parallel to a miniature chip capacitor (ATC 700A; American Technical Ceramics, Huntington Station, New York, USA) was applied to the catheter tip (fig 1). The resonant circuit was tuned to

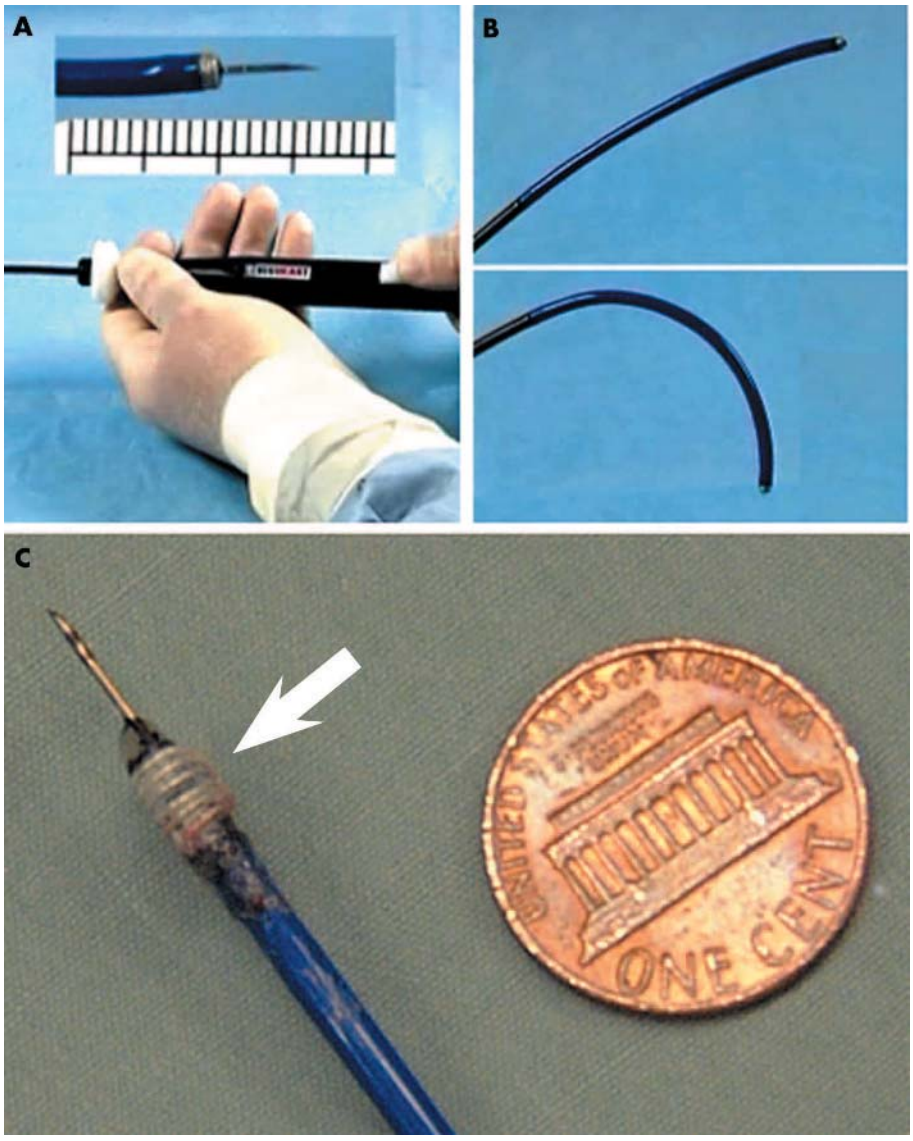

Figure 1 Delivery catheter equipped with a miniaturised resonant circuit to serve as a tracking marker (white arrow). The shaft and active deflection system of the catheter were modified to be magnetic resonance (MR) compatible and free of imaging artefact. All conducting structures were removed to minimise potential hazardous heating of the catheter and surrounding structures.

63.85 MHz. For mechanical protection and electrical isolation the tuned circuits were covered with heat shrink tubing and clear polyethylene glue.

In vitro experiments

To test the visibility of the tracking coil in various orientations of the catheter tip in the magnetic field (B0) the MR compatible catheter was immersed in a copper sulphate doped saline phantom and rotated by 360° in the B0 during real time imaging. The device was similarly manipulated and evaluated in the left ventricular chamber of explanted porcine hearts filled with either normal saline or whole blood.

In vivo experiments

Yorkshire albino swine (n = 6, 30–40 kg) were selected for this study. The pigs were anaesthetised and prepared for surgical arterial sheath placement as previously described.[13] In brief, the pigs were premedicated with ketamine 15 mg/kg intramuscularly and anaesthesia was induced with intravenous propofol 10 mg/kg followed by continuous infusion of propofol 10–15 mg/kg/h. Animals were intubated, mechanically ventilated with an MR compatible ventilator (Pneupac, Broomall, Pennsylvania, USA), and placed supine in the magnet. A customised two element phased array surface coil was placed on the chest. The catheter was introduced under MR conditions in the left ventricle through a 14 French introducer sheath placed in the right common carotid artery.

Intramyocardial injections were composed of diluted gadolinium and Indian ink to enable visualisation of injected myocardial tissue sites during real time MR imaging and during gross pathological evaluations. After each experiment, animals were killed and the hearts were harvested, inspected for trauma, and sectioned to identify sites of injection.

The handling, maintenance, and care of the animals, as well as all the procedures performed in this protocol, were approved by the Mount Sinai School of Medicine animal management program and followed American Heart Association guidelines for animal research.

RESULTS

The tracking coil gave a distinct bright signal, even in least favourable B0 to B1 angles, allowing uninterrupted visualisation of the moving catheter tip within the phantom, as captured by the still frame images in fig 2.

The image quality of the real time FIESTA pulse sequence enabled visualisation of the moving aortic valve. When this sequence was coupled with the bright signal of the tracking coil and the discrete susceptibility artefact of the catheter shaft, the ability to position the catheter at and across the aortic valve and then within the left ventricle was greatly facilitated (fig 3).

Near continuous visualisation of the moving catheter was made possible by a rapid image update rate, thereby avoiding jagged (stop and go) interaction between image and operator. There was no delay between acquisition and frame display. Precise placement of the catheter tip within the left ventricle was made possible by using the basic functions for the device (rotation and tip deflection). Figures 3 and 4 depict an example of apical positioning and injection. Once the catheter was visually confirmed to be in apposition to the endocardium, the needle was advanced and the gadolinium-Indian ink mixture was injected. Injections were immediately visualised as bright focal intramural deposits with a dark rim (halo) and were administered in 1–2 myocardial sites in each animal. Visualisation of injections did not require adjustment of imaging parameters or the use of a saturation preparation pulse. The energy delivery was within the acceptable specific absorption rate. In addition, our scanner is automatically set to stop at specific absorption rate of 100. With the sequence and the field of view selected for these studies, wrapping was not observed.

In these experiments, the operator was positioned along the right side of the table opposite from the in-room monitor and within 1–2 m of the magnet. Noise levels during the procedures were not measured. Basic communication between in-room operators or between operators and control room personnel were impaired but not disabled by noise levels.

Correlation with gross pathology

Deposits of Indian ink were identified and corresponded to each injection site as documented on real time MR imaging. Figure 4 shows the apical injection displayed in fig 3. No signs of myocardial perforation were observed.

DISCUSSION

We report the feasibility of administering materials intramyocardially under real time MR imaging guidance through a catheter equipped with a resonant microcoil. This study

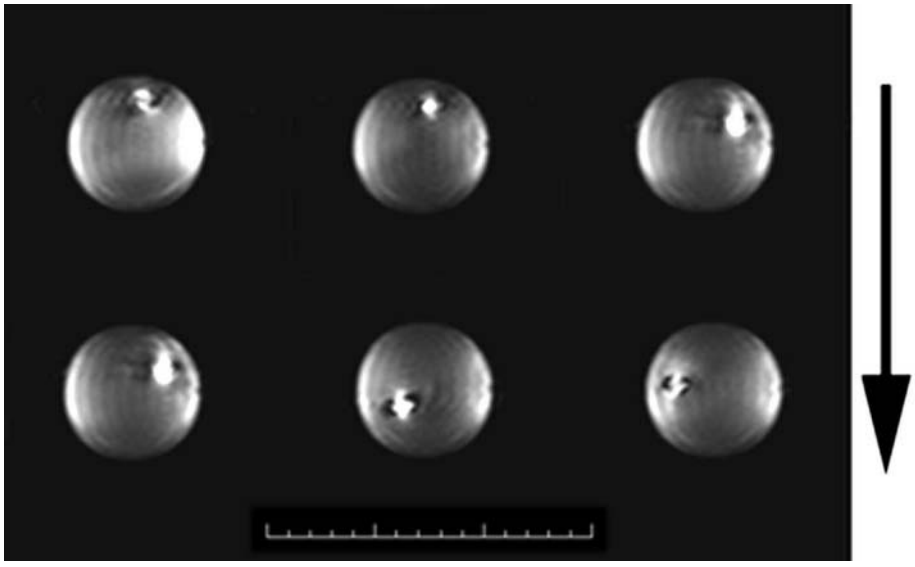

Figure 2 In an ex vivo experiment the visibility of the tracking coil by various orientations of the catheter tip was tested by rotating the catheter in a phantom containing copper sulphate. The miniaturised resonant circuit gave a bright signal that was visible through the 360° rotation.

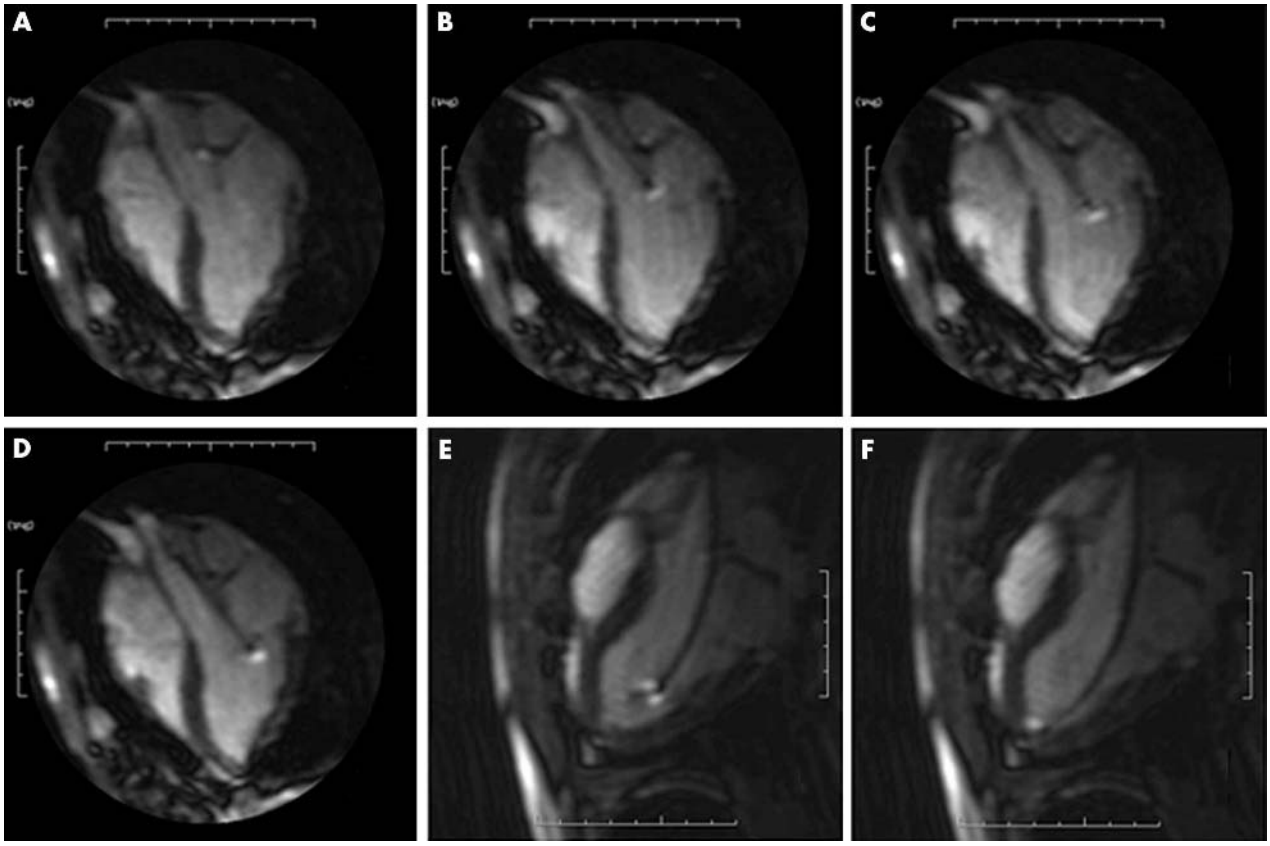

Figure 3 Serial MR images acquired in real time showing the entry of the catheter into and movement within the left ventricle. (A–D) The image plane across the valve was a modified two chamber view, displaying the left ventricular outflow tract and apex. (E, F) Images taken in long axis view, during which the catheter tip was deflected and rotated towards the apex.

shows the in vivo feasibility and user friendliness of this technique, which is unique in its imaging and injection system characteristics. The availability of this injection method may significantly facilitate the successful, accurate, and controlled local delivery of various agents for myocardial and vascular regeneration.

Treatments targeted at specific anatomical locations have immense appeal, especially in disease states with regional manifestations, such as left ventricular dysfunction secondary to coronary artery disease. The local delivery of cellular material for ventricular repair by transcatheter techniques has reached phase I clinical trials. While safety and effectiveness end points for human studies can be easily set, procedure related success is less well defined. For catheter based cell implantation studies procedure related success is characterised by the absence of complications, rather than by evidence of effective tissue delivery.

Conceptually, an optimal delivery method requires the meticulous delineation of target tissue and the ability to show deposition of the treatment agent within that tissue, both in real time. For deposition to be shown with catheter delivery systems, both the targeted tissue and the catheter tip must be clearly and distinctly visualised in three dimensions. Such is not the case with existing catheter delivery systems. All depend on either fluoroscopic or other imaging methods, and none can display the physical changes that occur in targeted tissue after implantation.

Our imaging system has shown this ability to overcome these deficiencies. High resolution tissue imaging with real time display at 10 frames/s was routinely achievable. Catheter tip recognition and tracking were exquisitely visible and the entry of injectate into myocardial tissue was clearly seen.

MR is recognised as a highly sophisticated technique to image soft tissue. It can distinguish soft tissues of different molecular composition, physical state, and water content. These differences may be taken advantage of in real time conditions, allowing a unique opportunity to monitor intramyocardial delivery of drugs, genes, or cells, especially if the injectate is enhanced by the addition of contrast agents. In our study we used a gadolinium-diethylenetriaminepentaacetic acid (DTPA) solution that allowed visualisation and monitoring of each single injection. In the future, specific molecular enhancers may provide the visualisation only of vital cells to monitor the success of cardiomyoplasty over time.

The catheter delivery system used in our study has several features that are key in enabling MR guided cardiac treatments. The resonant coil that was mounted at the catheter tip permitted localisation with real time FIESTA imaging during the entire procedure. The imaging characteristics imparted to the tip by the coil were distinctive from surrounding structures, including tissue, blood, and adjacent segments of the catheter itself. The solenoid microcoil was not orientation insensitive but its visualisation was sufficient for tracking purposes. In fact, the MR signal of the resonant coil was detected even in the less favourable angle to B0. The susceptibility based artefact of the catheter shaft created a distinct signal void, resulting in clear visualisation within bright appearing blood. Eggers and colleagues[9] recently reported a simple and robust tracking technique with optically de-tunable parallel resonant circuits. They showed

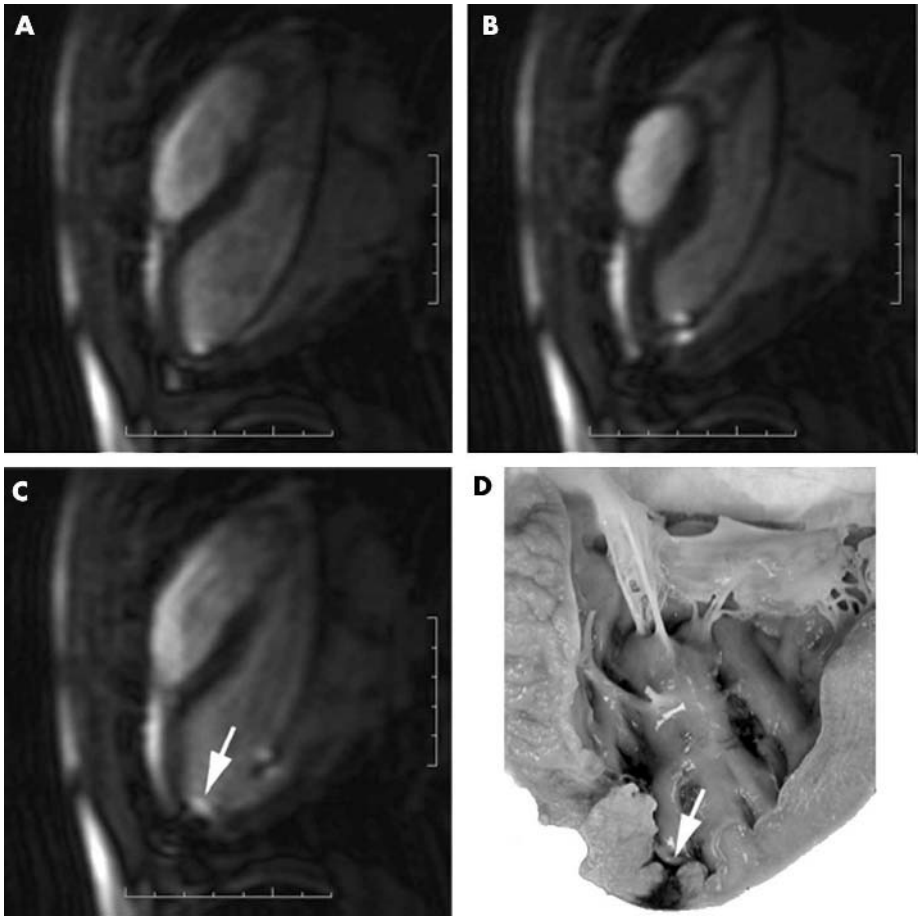

Figure 4 The tip of the catheter was placed at the apex of the left ventricle (A), the needle was advanced (B), and 0.5 ml of Gd-DTPA/Indian ink solution was injected. The injectate was promptly detected as a bright spot in the myocardium (arrow in C). Localisation of the injectate correlated well with the macropathology (arrow in D).

that this promising strategy eliminates most of the drawbacks usually associated with image based tracking.

Other intrinsic physical properties of the catheter used in our study, including its deflectable distal segment and its torque responsiveness, led to the simple manoeuvrability to virtually all reaches of the ventricle. The adjustable needle depth feature enhanced the deliverability of injections by the online evaluation of wall thickness and tissue penetration. With this system, the detection of imprecise or incomplete delivery would then lead to modification of needle depth settings or other variables, thereby maximising the effectiveness of subsequent injections and minimising the possibility of intracavitary injection and myocardial perforation.

Compared with previously reported techniques, our method eliminates complex user interfaces, enabling manipulation of the catheter, unencumbered by cable connections to the MR system. Additionally, neither extraprocessing power nor superimposed road mapping images[14 15] are required to use our system.

By utilising the advantages of the real time imaging sequence as well as the inherent simplicity of the single resonant structure on the catheter tip, we have shown a feasible, simple approach to in vivo catheter tracking.

Catheter heating as a potential hazard was not addressed in this preliminary feasibility study. We are working on the miniaturisation of a simple add-on circuit that would provide sufficient detuning during the transmitting phase, further reducing the risk of dangerous heating of the structures adjacent the coil. Possible performance improvements are array sensitive encoding technique parallel imaging to double or triple the temporal resolution (to 20 or 30 frames/s), view sharing techniques to double the frame rate, and the use of ramped pulses to approach more quickly a steady state condition on scan plane orientation or location changes. Other aspects of the procedure, such as effects on the operators of their proximity to the bore, are undefined at this time.

Conclusion

We have developed a method for MR guided endomyocardial delivery that may have important clinical applications. By utilising the advantages of real time imaging and a single resonant structure at the catheter tip, we have established a simple approach to in vivo device tracking. Given its abilities to visualise catheters in the aorta and left ventricle and to target regions of myocardium precisely, entire procedures are feasible with this system. The local delivery, through MR guidance, of substances with therapeutic potential into diseased myocardium is the subject of ongoing investigations.

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IMAGES IN CARDIOLOGY

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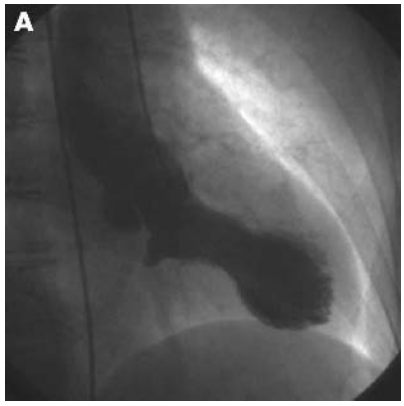
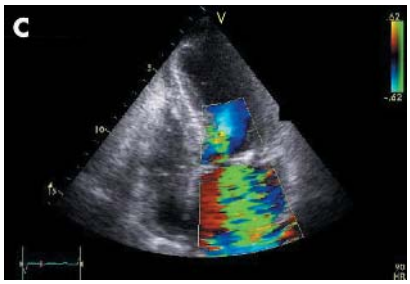
Dobutamine induced severe midventricular obstruction and mitral regurgitation in left ventricular apical ballooning syndrome

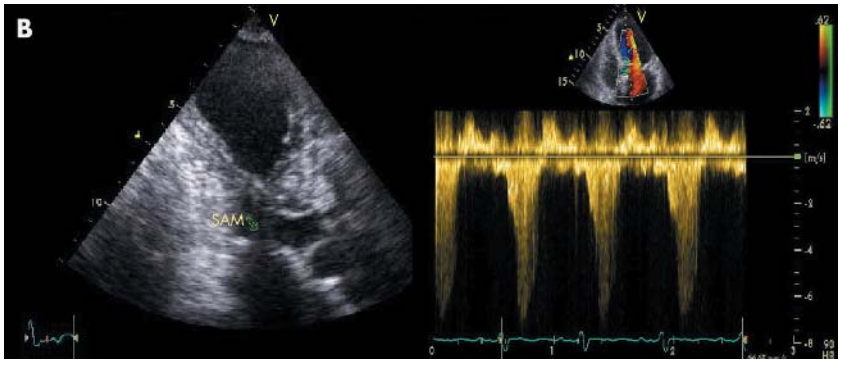
A 73 year old woman with no history of cardiac disease was admitted for chest pain of 12 hours duration not related to physical or emotional stress. Admission ECG showed a 1 mm ST segment elevation from V1–V3 with negative T waves in V4–V6. Creatine kinase MB (CK-MB) mass and troponin I were significantly raised (28 ng/ml and 2.5 ng/ml, respectively). The patient underwent emergency coronary angiography. This showed no significant coronary lesions with slow distal run-off of the left anterior descending and right coronary artery. At left ventricular angiography a systolic apical ballooning was evident (panel A), with normal contraction of the basal segments and no significant mitral regurgitation. After treatment with intravenous glyceryl trinitrate the patient's chest pain subsided and negative T waves developed in all precordial leads .

Five days later the patient underwent a dobutamine stress echocardiography to evaluate the presence of stunned myocardium. Baseline echocardiogram showed an akinesia of the distal septum and the apex and no intraventricular pressure gradient. At a dose of 10 μg/kg/min the akinetic area showed no significant recovery; a mid ventricular obstruction caused by the systolic anterior motion of the anterior mitral leaflet and the juxtaposition of the septum to the mitral chordal apparatus developed (panel B, left); at the site of the obstruction a late peaking flow with a pressure gradient of 150 mm Hg was recorded by continuous wave Doppler (panel B, right). Obstruction was associated with the development of a severe mitral regurgitation (panel C) and an increase in pulmonary systolic pressure from 25 mm Hg to 50 mm Hg. After propranolol administration both intraventricular obstruction and mitral regurgitation resolved.

Left ventricular apical ballooning is an acute syndrome mimicking acute myocardial infarction associated with significant







intraventricular pressure gradient in 10–20% of cases. In this patient severe intraventricular obstruction and mitral regurgitation with increased pulmonary artery pressure was induced by sympathetic stimulation with dobutamine. This mechanism may be implicated in the pathogenesis of the syndrome and may be responsible for the acute pulmonary oedema and cardiogenic shock observed in 15–20% of these patients.

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