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Review Article

Direct Therapeutic Agents Delivery in Ischemic Myocardium: Emphasis on the Role of MRI

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Abstract

Angiogenic growth factors, genes and stem cells have been delivered, during coronary artery bypass grafting, as an alternative treatment, to restore myocytes and blood vessels in end stage patients. It is vital to carefully design, develop, and optimize minimally invasive devices and to use noninvasive diagnostic methods before attempting to apply these devices to clinical routine. Accurate local delivery of therapeutic agents has been recently introduced using endoscopic- and MRI-guidance in experimental animals. Investigators found that local intra-myocardial delivery can be achieved using endoscopic- and MRI-guidance.

Minimally invasive methods have the following advantages: 1) it provides direct visual control of the devices in vivo, 2) it allows visualization of infarcted myocardium and precise needle placement in peri-infarct zones during therapeutic cells/gene administration, 3) it provides high retention profile compared to intravenous or intra-arterial routes and 4) it allows intervention lists to avoid damaging coronary arteries/veins or major blood vessels. Furthermore, clinical and preclinical studies have indicated that noninvasive.

MR imaging provides quantitative data on myocardial perfusion, function and viability. Doping of therapeutic agents with MR contrast media is useful for monitoring their distribution in the targets. These capabilities have positioned MR imaging as an important approach to pursue for assessing the benefits of locally delivered therapies. This mini-review addresses our experience and others in delivering local therapeutic agents in ischemic heart disease with special emphasis on the role of MRI in assessing therapies.

Keywords: MR imaging; MRI; Therapeutic agents; Myocardium

Introduction

Ischemic heart disease is a major public and economic health problem. Due to its epidemiologic importance, it became imperative to develop minimally invasive techniques to treat this disease and improve non-invasive diagnostic methods to monitor the efficacy of the treatment. Coronary angioplasty, bypass surgery and thrombolytic therapy are routinely applied to restore blood flow to ischemic myocardium, which has resulted in improvement of Left Ventricular (LV) function. However, many patients with end stage coronary artery disease continue to suffer from disabling angina, risk of LV remodeling, and heart failure. The beneficial effects genes and/or steam cells has been demonstrated in patients with ischemic heart disease [1,2].

A variety of routes have been used and compared after delivery of genes and/or steam cells therapies (Table 1) [3-7]. The major limitations of these routes are: degradation by blood enzymes, lung entrapment of cells, the need for extremely high doses and poor tissue uptake [8].

Unlike direct intramyocardial therapy, selective intracoronary infusion enables delivery of therapeutic agents to specific coronary perfusion territory, but this technique provides inefficient retention of drugs in the myocardium. Similarly, genes and cells utilizing large molecules have limited capacity to diffuse into hypoperfused myocardium. It was demonstrated that nano-formulated anti-inflammatory drugs in combination with gene product offers a clinical solution to enhance the distribution of drugs in myocardium [9].

In the last decade, investigators focused on the feasibility and effectiveness of direct intramyocardial cell therapy in open chest patients [10-14]. Rosengart et al. indicated that direct intramyocardial therapy is safe and reliable [15]. Several experimental animals explored the direct delivery of therapies and found that direct transfer of angiogenic growth factors, genes and stem cells provides high concentration of therapies in the needed ischemic regions and minimizes the spread of these therapeutic agents to other organ [16-32]. Vrtovec et al compared the efficacy of transendocardial (n=20 patients) and intracoronary (n=20 patients) delivery of CD34+ cells in non-ischemic dilated cardiomyopathy patients [33]. Investigators found that transendocardial CD34+ cell transplantation is associated with higher myocardial retention rates and greater improvement in ventricular function, and exercise capacity compared with intracoronary route. Others used combined delivery approach (intramyocardial and intracoronary) of bone marrow mononuclear cells at 3-6 weeks and 3-4 months after myocardial infarction in 60 patients using endocardial mapping systems (NOGA-STAR˚) [34].

Table 1: Approaches for direct myocardial therapies.

Previous Approaches	Recent Approaches
Systemic injection (rare)	MR-guided catheter-based technique
Intra-operative injection during bypass surgery; direct intramyocardial injection (common)	Transthoracic endoscopic technique
Pericardial	
Per-adventitial	
Percutaneous image-guided catheters;	
Transesophageal echocardiography (2D)	
Electromechanical mapping technology (NOGA) (scar tissue)	

Table 2: Applications of MRI in assessing local myocardial therapies.

Tissue characterization
Assessing LV function and perfusion
Molecular imaging
Guiding and monitoring local therapies; genes, stem cells and ablation

Table 3: MRI sequences for assessing local myocardial therapies.

MR fluoroscopy using fast gradient echo sequences offers a near real-time feedback
Cine MRI for measuring LV volumes, mass and radial strain.
Tagging cine MRI for measuring circumferential stain
Velocity encoded phase contrast cine MRI for measuring longitudinal strain.
First pass MRI perfusion for measuring relative myocardial blood flow.
Delayed contrast enhancement for measuring infarct size.
T1, T2 and T2* mapping
Extracellular volume measurements.

Noninvasive biomedical imaging (positon emission tomography, single-photon emission computed tomography, Magnetic Resonance Imaging (MRI), optical imaging and echocardiography) played an important role in tracking, monitoring and evaluation of the efficacy of cardiac therapies. Cardiologists focused on MRI because it has the potential to chronologically assess left/right ventricular function, myocardial perfusion and viability in treated patients [35,36] (Table 2). MR sequences are also useful for measuring cardiac mass and ventricles geometry, which are used as surrogate endpoints in clinical trials. It can also delineate the complex repair process of infarcted myocardium (edema, necrosis, inflammation and collagen formation [37]. Furthermore, delayed contrast enhanced MRI (DE-MRI) sequences can reliably characterize tissues and measure the size and transmurality of acute and chronic myocardial infarct (Figure 1). After drug delivery, non-invasive MRI provides accurate information on the time course of infarct healing. Summary of MRI sequences used in cardiac imaging are shown in Table 3. Bengel et al. indicated that MRI may be the most suitable noninvasive technique for chronologically monitoring myocardial repair [38].

The ability to label cells/genes with MR contrast media/tracers prior to local delivery also enhanced the potential to localize and monitor the distribution of administered therapies. The feasibility of endoscopic delivery and MR-guided transendocardial systems for direct transfer of therapies have been demonstrated in experimental animals [39,40]. The advantages of these devices over x-ray-guided intervention procedures are avoidance of radiation, reduction of the incidence of renal damage and allergic reaction induced by iodinated contrast media. Fast MRI-guided acquisition also offers 3-dimential images and functional information in almost real time, thereby, allows interventionist to control the intervention procedures.

Methods of Therapeutic Delivery

Intracoronary delivery

Selective intracoronary infusion enables delivery of therapeutic agents to specific coronary perfusion territory [41,42]. This technique, however, is also limited by inefficient retention of drugs in the myocardium. Thus, investigator introduced coronary vasodilation and vascular/cellular permeability enhancement for dense regional gene transfer [43,44]. Another issue is that genes and cells utilize large molecules that have limited capacity to diffuse throughout the myocardium. It was demonstrated that nano-formulated anti-inflammatory drugs in combination with gene product may offer a clinical solution to enhance the distribution of drugs in myocardium [9]. Available data on adeno-associated viruses suggest that vasodilation, vascular permeability enhancement, and avoidance of inhibitors to infection are still relevant variables. Investigators have suggested that slow infusion of a mixture of the adeno-associated viruses, antibodies and contrast media into coronary arteries is an effective means of delivery. However, the recent study by Greenberg et al call into question the efficacy of this open-artery AAV slow infusion approach [45].

Endoscopic-guided device

The configuration of the epicardial injection cannula is shown in Figures 2 and 3. Figure 2 shows an endoscope residing in the lumen of the cannula that contains a specialized distal viewing tip. The transparent asymmetrically conical viewing tip possesses a linear ventral surface. An operating channel resides in the ventral wall of the viewing tip, and this channel accommodates the needle used for intra-myocardial injection. The ventral aspect of the epicardial injection cannula also contains a suction pod that may be used to stabilize the cannula on the epicardial surface of the beating heart, if necessary, during gene injection. Viewing of epicardial morphology occurs as the viewing tip is placed in apposition with the epicardial surface of the heart. The linear configuration of the ventral surface of the viewing tip provides adequate contact with the epicardium to ensure a clear view of the heart. The tissue contact length of the viewing tip against the heart translates into the depth of field of view of the corresponding endoscopic image (Figure 3).

The following surgical technique has been used in our laboratory, where a 2cm skin incision was made in the 4th intercostal space at the anterior axillary line to enter the left pleural cavity in swine
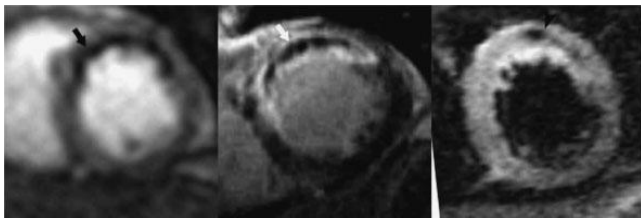
Figure 1: MR images show a reperfused myocardial infarct in the atrio-septal LV wall of a patient. The territory of perfusion deficit is demonstrated on the first pass perfusion sequence as a hypoenhanced zone (arrow, left image). Microvascular zone is also seen as hypoenhanced region on delayed contrast-enhanced MR image (arrow, center image). On STIR T2-weighted imaging, the infarct appears bright with hypoenhanced zone (arrow, right image), suggesting the presence of intramyocardial hemorrhage due to the damage in microvessels.
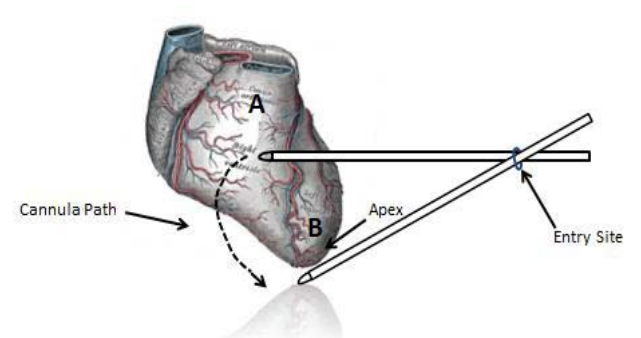

Figure 2: Schematic presentation of two views of the epicardial injection cannula and port of drug injection. The injection needle length (a) is adjusted to 7mm.

Figure 3: The configuration of the epicardial injection cannula and port of drug injection. The injection needle length (a) is adjusted to 7mm.

Figure 4: Schematic description of the cannula movement around the heart. The cannula may access the anterior (A), lateral and around the apex (B) to the posterior wall of the left ventricle.
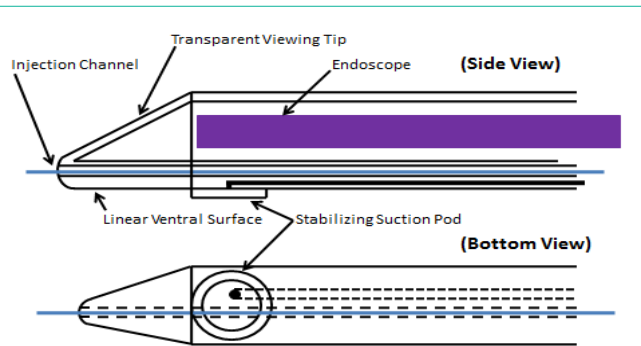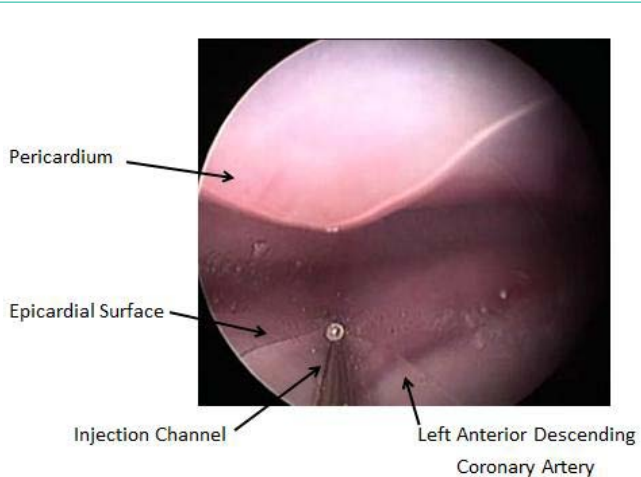

Figure 5: An endoscopic view allows an appreciation of the pericardium and epicardial surface, including the outline of the left anterior descending coronary artery.
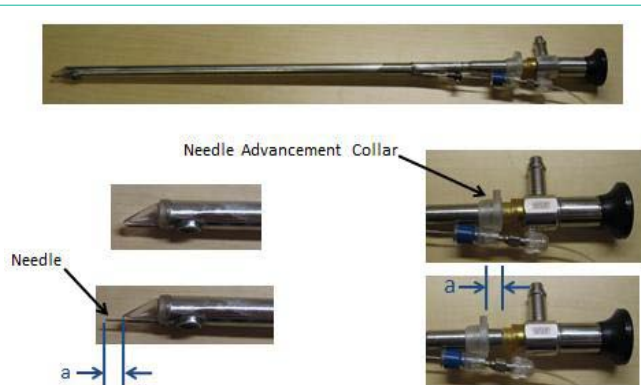
(n=24). The endoscopic epicardial cannula was advanced towards the mediastinum. The endoscopic epicardial cannula was advanced further to puncture through the left pleural and pericardial layers at a point midway between the anterior surface of the heart and the posterior aspect of the sternum. Once pericardial entry has been achieved, access is available to both the anterior and posterior aspects of the heart (Figure 4). The endoscopic cannula is initially positioned on the anterior epicardial surface. By moving the cannula inferiorly, the apex of the heart can be visualized. Continued movement of the endoscopic cannula past the apex will position the device on the posterior aspect of the heart. Thus, both anterior and posterior infarcts may be addressed via a single intercostal entry incision. Positioning of the operating channel on the linear ventral surface of the viewing tip provides an unobstructed view of the vast majority of the anatomic field.

As shown in Figure 5, the endoscopic view allows an appreciation of the pericardial sac superiorly, and the epicardial surface, including the outline of the left anterior descending coronary artery. Injection needle exit from the viewing tip occurs at the white dot observed at the distal end of the injection channel.

The main advantages of the endoscopic device are: 1) the endoscopic epicardial injection cannula provides direct visual control of the pericardial entry process; and once the pericardium has been traversed, it imparts guidance for epicardial navigation and myocardial intervention, 2) the epicardial endoscopy allows visualization of infarcted myocardium and precise needle placement in peri-infarct zones during therapeutic cell/gene delivery, 3) this approach eliminates the use of fluoroscopy and 4) direct anatomical viewing assists the clinician in avoiding major coronary artery/vein injury during myocardial injection and minimizes surgical invasiveness.
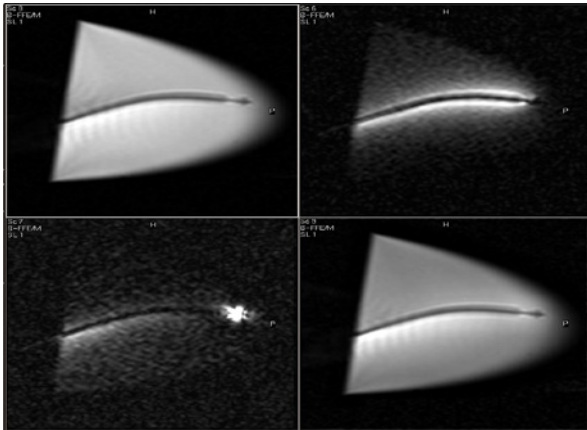
Figure 6: Long-axis MR images acquired in a water bath with different catheter and external coil elements active. The same acquisition (FOV=240mm, matrix=160x160, slice=8 mm, TR/TE/flip=4.0ms/2.0ms/70^0, 2 frames/s) was used in all cases. The top left image shows the activity of external coils elements, while top right image shows the activity catheter coil. In the bottom left image, the catheter tip microcoil is active. Bottom right image demonstrates the activity of all coils elements.
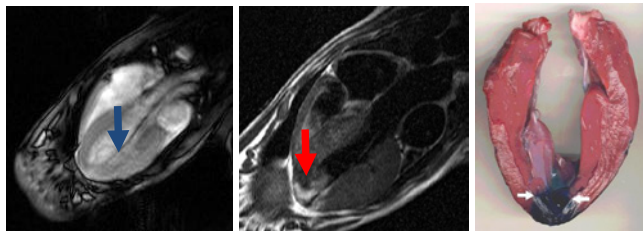

Figure 7: Electrocardiographically gated dual-inversion-recovery T1-weighted contrast-enhanced MR image (oblique-coronal view, 500/40) shows the catheter in the LV (arrow, left) and transmural enhancement at the heart apex (arrow, middle) after administration of 2 mL of a mixture of gadodiamide and blue dye. MRI of the middle slice shows the close correspondence of the stained tissue (arrows right) with the enhanced region on MRI.

The other application of endoscopic device is for ventricular ablation. Ablation of ventricular tachycardia remains a challenge due to the inaccessibility of the epicardial wall from the left ventricular chamber. Schweikert et al found 40% of the patients with ventricular tachycardia require additional epicardial ablation [46]. Zenati et al found that peri-cardioscopic approach is suitable for epicardial ablation and interventions [40].

MR-guided endovascular catheter

Standard MRI sequences are considered a state-of-the-art technique for simultaneously measuring infarct size, regional/global LV function and perfusion in patients. Real-time MRI imaging (A steady state free percession sequence, bFFE) has opened the road toward MRI-guided catheter navigation for delivering local therapies. The endovascular MR-guided catheters were developed by Karmarker et al. [39]. These catheters are equipped with embedded antennae and coils. The properties of an active catheter were tested in vitro using 1.5T XMR scanner (Figure 6) [19]. The bright signal surrounding the catheter allowed visualization of the shaft and the tip, while the external coils are primarily used to define the catheter orientation (Figure 6). The catheter also had dimeters between 9-11F and its distal end incorporates a 27G needle that can be protruded
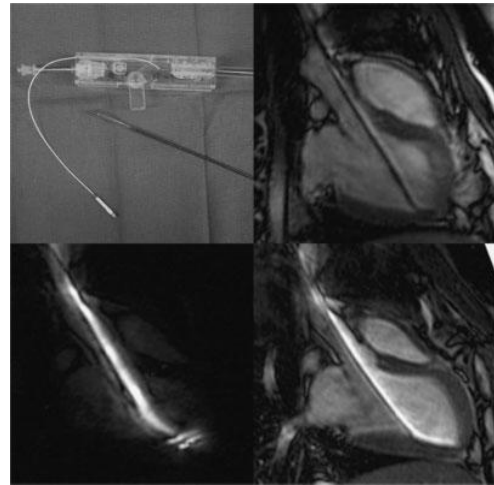

Figure 8: A catheter for MRI-guided intramyocardial injections (top left), which has been used for passive (top right) or active tracking (bottom). On the top-right image the catheter coil is switched off and the surface coil is on, showing the catheter as a dark object. On the bottom left image, the surface coil is off and the catheter coil is on, providing a bright signal around the shaft and tip of the catheter. On the bottom-right image both surface and catheter coils are on, providing a bright signal around the catheter and delineation of the aorta and entire LV.
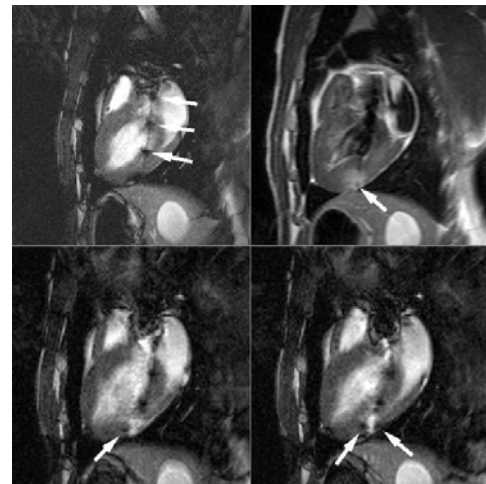

Figure 9: Electrocardiographically gated dual-inversion-recovery T1-weighted contrast-enhanced MR images (500/40). Top left: The gadolinium oxide markers (arrows) on the catheter are clearly visualized inside the LV chamber before the injection of the contrast materials. Top right: Diluted gadodiamide (0.05 mol/L) produced a bright zone (arrow) by shortening the myocardial T1. Two injections of undiluted gadodiamide (ie, 0.2 mL of 0.5 mol/L) had been administered to deliver the contrast agent to the borders of the enhanced area of interest—that is, to hit the target. Bottom left and right: Undiluted gadodiamide injected into the myocardium created a signal intensity loss owing to the T2* effect of the contrast material (arrows).

between 3-5mm, depending on the LV wall thickness.

The endovascular catheter was tested in beating hearts and used to deliver tissue markers (mixture of vital dye and MR contrast media) transendocardially. In this study, we found that the contrast media caused myocardial signal enhancement at the tip of the catheter and at postmortem provided evidence that the injection is truly in myocardium (Figure 7).
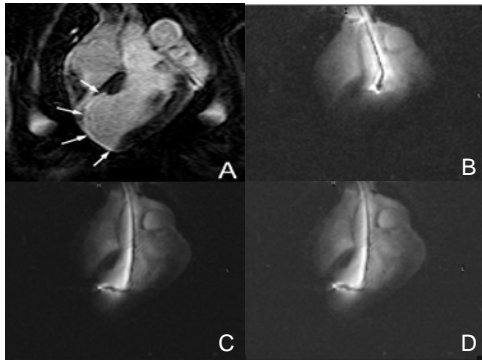
Figure 10: Contrast enhanced MR image shows the scar in the left ventricle (A, arrows). Real time snapshots of the advancement of the active catheter into the aorta (B), left ventricle (C) and injection of therapy into the target (D). This procedure was used to deliver angiogenic genes and labeled stem cells.

Figure 11: The X-ray/MR suite for interventional radiology at the University of California San Francisco. The main features of this combined system are a short-bore magnet, a sliding door between the two systems to shields RF and X-ray exposure, and a movable tabletop to connect the two systems.

Figure 12: Histology of scar infarct in control (left) and VEGF gene–treated animals (right) 8 weeks after infarction. Sections A-D were stained with Masson trichrome stain, while E and F were stained with biotinylated isolectin B4. I = infarction in both groups which is comprised of homogeneous replacement fibrosis with a distinct boundary at the interface between scar and viable Myocardium (M). Treated animal (right) contained numerous vessels (arrows), while control animal contained very few vessels. Biotinylated isolectin B4 localized vessels with brown reaction product, accentuating the neovascularity in VEGF gene–treated infarct animal compared with control animal. LV = left ventricle, calibration bars = 80 μm.

MRI offers interactive 3D steering of imaging plane, moderate soft tissue contrast and wash in/wish out of injected contrast media. Furthermore, fast MRI acquisition allows guiding and tracking of the catheters in the aorta and LV (Figures 8).

Figures 9 and 10 show two types of endovascular catheters; namely passive and active catheters, respectively, during the transendocardial injections of the tested materials, using XMRI hybrid scanner (Figure 11). The active catheter was used for delivering angiogenic genes at the peri-infarct zone in swine and canine hearts subjected to infarction [17,19-21,23-28,30,47-50]. In these studies, the positive effect of the injected genes on myocardial function, perfusion and viability was evident.

MR guided and tagging sequences demonstrated the intramyocardial administration of AAV-VEGF gene and the positive changes in circumferential strain, respectively [23]. Infarct size reduction and the formation of new blood vessels was confirmed on histology (Figure 12). These capabilities have positioned MR imaging as an important approach to pursue for assessing the benefits of delivered genes [18,51,52].

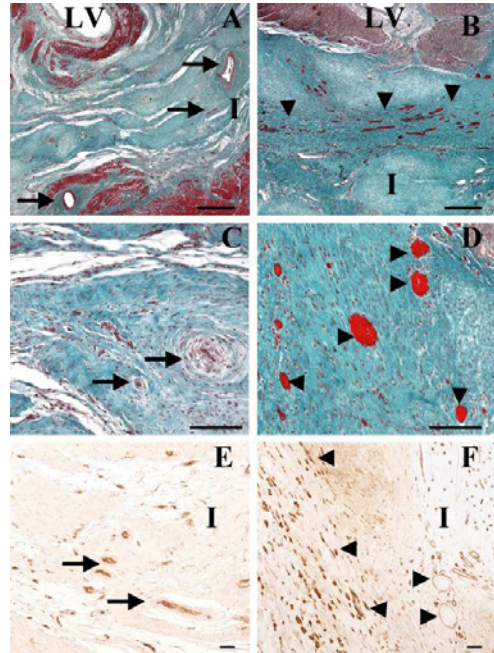Future direction: In the future, treatment of ischemic heart disease involves a collaborative effort of molecular/cellular biology, cardiology, pathology and radiology. In this mini-review we report novel approaches for delivering local therapeutic agent in infarcted myocardium and the value of non-invasive MRI in assessing the effectiveness of gene therapies. Future developments in MR-guided procedures include the design of flexible and durable active catheters, which can be tracked and navigated easily. The spatial and temporal resolution of images will also have to be improved to ensure a higher success rate and more accuracy in interventional procedures.

Limitations

The use of endoscopic and endovascular catheter is associated with 10% mortality rate based on our experience. The major complications of in using these devices are LV arrhythmia. In cases of endovascular MR-guided catheter the possibility of perforating the aortic valves and/or myocardium is high as well as the heating in the MRI environment [52]. The limitations of endoscopic approach are pneumothorax and limited access to the septal LV wall.

Conclusion

The endoscopic and endovascular catheter techniques are feasible and minimally invasive. Direct intramyocardial delivery of therapies is useful in occlusive infarct. It provides promising results. Intramyocardial injected genes caused improvement of LV function, regional perfusion and reduction in infarct size measured noninvasively on MRI. The findings confirmed at postmortem

histopathologic assessment. Thus, direct delivery of genes in myocardium may be promising in treating patients with ischemic heart disease. Controlled studies with a large population of patients are needed to evaluate the efficacy of direct therapy in promoting myogenesis and angiogenesis. The use of these devices could reduce the pain and speedup the recovery time caused by open-chest surgery. We propose that minimally invasive endoscopic and endovascular catheter techniques and local gene therapies have the potential to change the treatment paradigm in patients with high operative risks, elderly patients, or patients not willing to undergo surgery. Further development of MRI sequences is mandatory for direct intramyocardial drug delivery. It should be noted that at the present time technical challenges remain using both approaches.

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