Image-guided therapies for myocardial repair: concepts and practical implementation

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Cell- and molecule-based therapeutic strategies to support wound healing and regeneration after myocardial infarction (MI) are under development. These emerging therapies aim at sustained preservation of ventricular function by enhancing tissue repair after myocardial ischaemia and reperfusion. Such therapies will benefit from guidance with regard to timing, regional targeting, suitable candidate selection, and effectiveness monitoring. Such guidance is effectively obtained by non-invasive tomographic imaging. Infarct size, tissue characteristics, muscle mass, and chamber geometry can be determined by magnetic resonance imaging and computed tomography. Radionuclide imaging can be used for the tracking of therapeutic agents and for the interrogation of molecular mechanisms such as inflammation, angiogenesis, and extracellular matrix activation. This review article portrays the hypothesis that an integrated approach with an early implementation of structural and molecular tomographic imaging in the development of novel therapies will provide a framework for achieving the goal of improved tissue repair after MI.

Keywords

- Acute myocardial infarction
- Wound healing
- Myocardial regeneration
- Molecular imaging
- Computed tomography
- Magnetic resonance

Introduction

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide. Advances in therapy have led to a decline in mortality during the acute phase, but this decrease is paralleled by an increase in chronic heart failure in survivors with significant myocardial damage. The development of heart failure after AMI is determined by the infarct extent, the wound healing response that occurs in the days and weeks after the event, and chronic remodelling of the damaged heart. Modern reperfusion therapy is highly efficacious in limiting infarct size in patients presenting early after symptom onset. Current drug and device therapies attenuate ventricular remodelling in the chronic phase after AMI. The wound healing response, however, provides a largely unexploited window of opportunity to further improve clinical outcomes in AMI.

As more and more specific therapies emerge for the support of wound healing and myocardial regeneration, the need for equally specific diagnostic tests is growing. Serum biomarkers reflect the systemic response of the organism to cardiac disease. But only direct imaging of the heart provides insights into alterations of organ morphology and tissue biology. Echocardiography is routinely used to obtain information on cardiac morphology and contractile function. And invasive imaging during the interventional procedure may provide information about morphology, haemodynamics, and electrophysiology. This review, however, will focus on the value of advanced non-invasive tomographic imaging techniques after AMI.

Cardiac magnetic resonance and computed tomography (CT) have emerged as accurate tests to define infarct scar, muscle mass, chamber geometry, and function, which are used as surrogate endpoints in clinical trials. Additionally, a new generation of molecular probes for positron emission tomographic (PET) or single-photon emission computed tomographic (SPECT) radioisotope imaging has emerged. These probes enable the interrogation of biological mechanisms involved in healing. Integration of these diagnostic procedures and novel therapies has great potential to support the goal of improved tissue repair after myocardial infarction (MI) to prevent the progression to heart failure.
Wound healing after MI

Timely reperfusion of the infarct-related coronary territory is the most effective strategy for limiting tissue necrosis. Some patients, however, present late after symptom onset when most of the ischemic area has become necrotic and can no longer be salvaged by reperfusion. Although cardiomyocyte turnover has been documented in the human heart, and although the capacity for cardiomyocyte regeneration may increase after AMI, these endogenous regenerative mechanisms are usually overwhelmed by the massive tissue damage. Tissue necrosis elicits an inflammatory response that leads to the replacement of the necrotic area with a collagen-rich scar. Inflammatory cells accumulate quickly after AMI to eliminate dead cells and interstitial matrix debris. Neutrophils accumulate first, followed by monocytes and macrophages. The monocyte response is biphasic. First, pro-inflammatory monocytes dominate the cellular infiltrate, and then reparative, pro-angiogenic monocytes take over. As the inflammatory infiltrate is replaced by granulation tissue, extensive angiogenesis occurs to provide oxygen and nutrients to the highly dynamic and metabolically active wound tissue. At this stage, myofibroblasts accumulate in the infarct region and produce interstitial collagens, thereby initiating scar formation. Myofibroblasts possess contractile properties, which help prevent infarct expansion. As a mature scar is formed, the infarct vasculature undergoes a maturation process. Some newly formed vessels acquire a coat comprised of smooth muscle cells and pericytes, whereas most uncoated endothelial cells undergo apoptosis.1–3

Infarct expansion describes the thinning and lengthening of the infarct zone before extensive deposition of collagen has led to its stabilization. Infarct expansion depends on the extent and quality of wound healing. It is a main contributor to early left ventricular dilatation, and patients developing infarct expansion are at increased risk of developing heart failure. Infarct rupture is a fatal complication of infarct expansion that is commonly observed in mice but less frequently in patients. Inflammation, angiogenesis, and myofibroblast activity need to be tightly controlled after AMI to permit the formation of a small and durable scar. As shown in animal models, subtle perturbations in these processes may result in infarct expansion and rupture.1–4

Emerging therapies to support wound healing and regeneration

Therapeutic interventions that carefully adjust the balance between the beneficial and detrimental facets of inflammatory wound healing could have a major impact on cardiac function and prognosis after AMI. The intention of such therapies would be to attenuate infarct expansion and reduce final scar size, thereby preventing early left ventricular dilatation and functional compromise. Formation of a mature scar takes about 2–3 months in patients with AMI,5 and therapies aimed at improving wound repair need to be applied within this time window (Figure 1).

Therapies that enhance myocardial regeneration may provide another means to improve outcomes after AMI. One approach would be to stimulate the expansion of endogenous cardiac progenitor cells with a drug or paracrine factor, in the same way that erythropoietin is given to stimulate bone marrow progenitor cells to produce erythrocytes.6 A second approach involves the propagation of cardiac cells ex vivo followed by the implantation of these cells directly into the injured area. Considering the complex 3D tissue architecture of the myocardium, full restoration of cardiac function would require not just regeneration of cardiomyocytes,6 but the recreation of the distinct anatomical elements required for tissue contractility and electrical conduction.7–12

Figure 1. Emerging therapeutic targets in AMI (see text for details).
of the heart, which is a very challenging and complex task\textsuperscript{7} that is unresolved after AMI.

But several strategies to support wound healing and regeneration after AMI are under development. These emerging therapies aim at sustained preservation of ventricular function by enhancing tissue repair after myocardial ischaemia and reperfusion.

**Cell therapy**

Several cell types are currently under intense investigation.\textsuperscript{6} Clinical translation is most advanced with (mono)nucleated bone marrow cells (BMCs).\textsuperscript{9} More than 20 randomized, controlled, phase II trials have been performed, in which autologous BMCs were applied via the culprit coronary artery within the first week after reperfusion therapy. A meta-analysis of these trials concluded that BMCs reduce infarct size, attenuate left ventricular dilatation, and improve left ventricular systolic function.\textsuperscript{9} Notably, the meta-analysis also provided a strong signal that BMCs improve survival and reduce major adverse coronary events.\textsuperscript{9} A phase III trial exploring whether BMCs can reduce all-cause mortality after large AMI will start recruiting patients in 2013 (ClinicalTrials.gov identifier: NCT01569178).

More recently, heart-derived cells have entered clinical trials. In the CADUCEUS study, endomyocardial biopsies were obtained \~4 weeks after AMI.\textsuperscript{10} Biopsies were placed into culture to expand ‘cardiosphere-derived cells’ (CDCs), which are clonogenic and have multilineage potential. These cells were then infused into the infarct-related artery 1.5 to 3 months after AMI. As shown by magnetic resonance imaging (MRI), CDC-treated patients had smaller scar sizes and improved regional contractility at 6 months.\textsuperscript{10} Since CADUCEUS had only 17 patients in the treatment arm and no placebo group, larger studies will have to establish the safety and efficacy of this approach.

Initially, transplantation of BMCs was conceptualized as a means to deliver pluripotent stem and progenitor cells from the bone marrow into the infarcted area, which would then transdifferentiate into cardiac cell types, including cardiomyocytes. In the meantime, it has become clear that the beneficial effects of BMCs are not the result of engraftment but the release of paracrine factors. Paracrine factors produced by BMCs may support wound healing by acting on multiple target cells in the infarct wound, including inflammatory cells, vascular cells, and (myo)fibroblasts.\textsuperscript{11,12} Paracrine factors may also activate endogenous cardiomyocyte progenitors to promote cardiac regeneration.\textsuperscript{13} Although the cardiomyogenic potential of CDCs is still debated, it is becoming clear that these cells also exert potent paracrine activities.\textsuperscript{14} Reprogramming of skin fibroblasts (or other somatic cell types) into induced pluripotent stem cells (iPSCs) offers a reliable source of patient-specific pluripotent stem cells that can be differentiated in \textit{vitro} into virtually all cell types, including cardiomyocytes.\textsuperscript{15} Human iPSCs can be expanded in mass culture to yield the cell numbers required for potential clinical applications.\textsuperscript{16} Experimental data show that transplantation of human embryonic stem cell-derived cardiomyocytes can result in stable grafts that couple electrically with resident cardiomyocytes in the infarct border zone and improve systolic function after AMI.\textsuperscript{17} Protocols that would allow a safe and efficacious delivery of iPSC-derived cardiac cells in patients still need to be developed. Conceptually, direct reprogramming of scar fibroblasts into cardiomyocytes may represent yet another approach to regenerate the infarcted heart.\textsuperscript{18,19}

**Protein-based therapeutics**

Inflammatory wound healing after AMI involves multiple cell types that are interacting with each other in a highly orchestrated manner. This inter-cellular communication occurs primarily through secreted proteins. The mounting recognition of the importance of paracrine signalling in the infarcted heart has revived interest to develop secreted proteins as therapeutics.\textsuperscript{20} Therapeutic application of recombinant proteins (e.g. growth factors, cytokines, and matricellular proteins) promises to provide a non-invasive treatment option to support tissue repair after AMI. Advantages of protein-based therapeutics include the relative ease of standardization and large-scale production; the potential for off-the-shelf, systemic, and repetitive administration; and the potential to design protein cocktails tailored to specific disease settings.

Previous clinical trials exploring the therapeutic potential of granulocyte colony-stimulating factor or erythropoietin in AMI have been disappointing for various reasons.\textsuperscript{21,22} However, there is a growing list of candidate factors that have been found to improve tissue repair in animal models. For example, therapeutic application of follistatin-like 1 or thymosin β4 has been found to reduce infarct sizes in pigs with reperfused AMI by attenuating reperfusion injury and inflammation.\textsuperscript{23,24} Fibroblast growth factor 9 promotes angiogenesis in the infarct border zone, thereby stimulating adaptive cardiomyocyte hypertrophy.\textsuperscript{25} Intravenous administration of the matrix-interacting protein TSG-6 has been shown to reduce infarction and infarct size in mice.\textsuperscript{26} Therapeutic application of stem cell factor enhances the recruitment of putative cardiac progenitor cells to the infarct area and stimulates cardiomyocyte cycle activity, thereby reducing infarct sizes and left ventricular remodelling after AMI.\textsuperscript{27} Finally, administration of secreted frizzled related protein 2 reduces left ventricular fibrosis and prevents functional deterioration after AMI.\textsuperscript{28}

The most obvious challenge for protein-based therapies is the necessity to maintain therapeutic concentrations of the protein in the infarct wound or border zone for the necessary length of time. New strategies to address this issue and to allow sustained and targeted therapeutic delivery of recombinant proteins are emerging. One approach is to fuse the cytokine or the growth factor of interest with a peptide or protein that will be attracted to the infarct wound after systemic delivery. Fusion partners may be designed to preferentially bind to vascular structures, or extra-cellular matrix proteins in healing wounds.\textsuperscript{29,30} Another approach is to fuse cytokines or growth factors that are otherwise rapidly cleared from the circulation, with polyethylene glycol polymer chains (PEGylation) or with large non-functional polypeptides (XTENylation) to extend their plasma half-lives while maintaining their biological activities.\textsuperscript{31} Another approach is to engineer growth factor mutants that are protease-resistant and, therefore, more stable in plasma and ischaemic tissues.\textsuperscript{32}

**MicroRNA-based therapies**

MicroRNAs (miRNAs) are emerging as important and versatile modulators in cardiovascular disease. miRNAs are \~22-nucleotide
single-stranded, non-coding RNAs that inhibit the expression of specific mRNA targets. miRNAs typically exert modest inhibitory effects on several mRNA species which often encode proteins that govern the same biological pathway. Expression levels of multiple miRNAs change in a time-dependent and spatially controlled manner after AMI. The dynamic expression or down-regulation of miRNAs provides an extra layer of regulation controlling important aspects of wound healing after AMI, including cardiomyocyte survival, inflammation, angiogenesis, and scar formation. Therapeutic miRNA manipulation, therefore, provides an opportunity to target these complex biological processes. Indeed, therapies based on anti-miRs or miRNA mimetics are being developed to suppress pathological miRNAs or over-express protective miRNAs. Anti-miRs are chemically modified antisense oligonucleotides that are taken up by a variety of tissues and block the function of their cognate miRNAs. A bit further behind are efforts to design and deliver pharmacologically active synthetic miRNAs, or miR mimetics. Unlike most other drugs that are designed to affect only one target, miRNA-based therapies affect families of genes under the control of the target miRNA. A number of miRNA-based therapies have been explored in rodent models of AMI. But several steps are required to move miR-based therapies into the clinic. Lead sequences and anti-miR chemistries must be carefully designed to optimize tissue distribution and uptake and reduce toxic and unwanted off-target effects in other tissues.

**How will therapies supporting infarct repair benefit from imaging?**

Imaging is expected to play an essential role when these therapies are developed from small and large animal models towards clinical application. On the one hand, robust surrogate endpoints for clinical trials are needed. Echocardiography and established advanced tomographic techniques such as cardiovascular magnetic resonance (CMR) imaging and cardiac CT, but also radionuclide imaging of myocardial perfusion, function, and viability will serve for this purpose initially. On the other hand, imaging may be used to directly guide therapy to the appropriate target region. Invasive electromechanical mapping may be used for this purpose and may be integrated with non-invasive tomographic imaging. Intramyocardial injection of the therapeutic agent may then occur in the same session, guided by multimodality imaging. Then, imaging may be used to directly track the therapeutic agent such as cell, protein, or miRNA. And finally, a series of novel molecular markers for non-invasive assessment of mechanisms involved in infarct healing (e.g. inflammation, angiogenesis, or scar formation) or myocardial regeneration have been developed. These will provide insights into the mechanistic underpinnings of emerging therapies. When integrated into the development of the novel therapies, molecular imaging holds the potential to be jointly developed towards a future clinical practice where specific molecular therapy is guided by diagnostic test results. The advent of hybrid imaging systems, which allow for fusion of standard clinical CMR and CT techniques with highly specific molecular radionuclide probe signals, is expected to further strengthen image-guided therapies to support infarct repair.

**Role of CMR and cardiac CT to characterize myocardial damage**

Although CMR has been initially introduced as a technique for accurate imaging of contractile function, detection of myocardial damage has emerged as a powerful technique soon thereafter. Cardiac CT, on the other hand, has its strength in high-resolution non-invasive coronary angiography, but more recently its ability to provide information about myocardial damage in a manner similar to CMR has also been established. CMR does not employ ionizing radiation, but its applicability in patients with implanted devices is limited.

Although CMR and CT differ in acquisition technique, they have several strengths in common. Both offer unsurpassed spatial resolution and the ability to quantify acute myocardial necrosis, microvascular obstruction, and chronic collagenous scar. In addition, high-resolution imaging provides accurate quantification of left ventricular volumes and function.

**Gadolinium and iodine-based contrast agents**

Contrast agents for CMR and CT are similar in that they are small molecules capable of diffusing into the extracellular space, but are excluded by intact cellular membranes. This characteristic enables these agents to diffuse into areas of acutely infarcted myocardium with cell membrane disruption and chronic myocardial scar with a relatively large extracellular space compared with normal myocardium. This results in hyperenhancement of damaged myocardium that can be detected differentially by CMR and CT. In the case of CMR, hyperenhancement results from gadolinium-induced alterations in water proton relaxivity and the indirect measurement of gadolinium concentration. In the case of CT, hyperenhancement due to iodine-containing contrast agents is directly related to the concentration of the agent and its attenuation of X-rays. In addition to hyperenhancement, a variety of further imaging parameters can be determined (Table 1). Of note, both techniques also enable the detection of a peri-infarct

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CMR, cardiovascular magnetic resonance imaging; CT, cardiac computed tomography.
zone with mild enhancement, which represents a mix of viable and damaged tissue that may undergo dynamic changes over time44,45 (Figure 2).

**Imaging of AMI**

Delayed imaging of a hyperenhanced myocardium can distinguish between a viable and a non-viable myocardium. Quantification of infarct size has been extensively validated in pre-clinical studies of MI, where infarct size by T1 imaging has been compared against gross pathology and post-mortem histochemical staining.46,47 Of clinical importance, the transmural extent of hyperenhancement in the setting of AMI has been shown to predict functional recovery following revascularization.48 In addition to hyperenhancement, hypoenhancement within the infarct has been shown to signify microvascular obstruction. This has been validated against histochemical stains49 and is an independent predictor of cardiovascular complications, fibrous scar formation, and adverse ventricular remodelling.50 CMR has been used as a primary endpoint in several myocardial cell therapy trials in AMI patients.51,52 In these studies, the beneficial effects of cell therapy on changes in left ventricular function and infarct size were measured.

Like CMR, CT has been validated for the evaluation of AMI. Using an animal model of AMI, excellent agreement between the area of CT hyperenhancement and histochemical staining was demonstrated, and areas of hypoenhancement within the infarct indicated microvascular obstruction.53 A second study, performed in a porcine model of acute MI, compared infarct size by delayed CT to histopathology and CMR, and showed excellent correlation.54 Similarly, the peri-infarct zone, as assessed by CT, is well correlated to CMR and histopathology45 (Figure 3). Clinical validation of CT imaging of AMI has also been obtained. Early CT hypoenhancement underestimated infarct size, but delayed hyperenhancement showed excellent agreement with CMR.55

**Imaging of chronic myocardial scar**

Similar to AMI, chronic myocardial scar will hyperenhance with gadolinium-based contrast agents and CMR imaging. However, differentiating acute from chronic MI cannot be done by hyperenhancement alone. The presence of myocardial thinning can assist in this differentiation, but another robust method is to use T2-weighted MR images of oedema. Chronic scar will not appear hyperintense on T2 images, but acute MI will.56 One of the advantages of high-resolution CMR myocardial imaging is its ability to detect subendocardial infarcts that are often missed by lower resolution radionuclide imaging.57 Similar to AMI, the transmural extent of delayed enhancement on CMR is also related to functional recovery following revascularization in chronic infarction.58 The ability to image chronic MI by CMR is currently exploited in several cell therapy studies in animals and patients with ischaemic cardiomyopathies, where multiple markers of chamber geometry, ventricular function, and infarct size will be used to determine therapeutic efficacy.59,60

Delayed-enhanced CT, similar to CMR, has been validated for the detection of chronic myocardial scars.53 Delayed-enhanced CT does present some challenges for the quantification of infarct size due to limitations in the contrast-to-noise ratio between infarcted and remote territories and difficulties differentiating the LV blood pool from the scarred myocardium. However, CT has been shown to be capable of detecting infarct heterogeneity, and it can detect changes in infarct size similar to CMR when evaluating the effectiveness of myocardial stem cell therapies.55,61 CT is being used as a substitute to CMR in cell therapy trials when patients have contraindications to CMR.60,62
Molecular probes for the imaging of infarct healing

Radionuclide imaging traditionally provides well-established clinical information about myocardial perfusion, contractile function, and myocardial viability, which are used for the identification of infarct size and ischaemic compromise, and as surrogate markers of therapy success after MI (Table 2). SPECT is the traditional clinical standard technique, whereas PET is a high-end technique with superior resolution and absolute quantification that increasingly penetrates the clinics.

Recently, a series of specific molecular imaging markers, which enable insights into various biological processes that are activated after AMI, have been introduced (Figure 4). Together with the advent of dedicated small animal radionuclide imaging systems, these novel probes promise to improve the pathobiological

![Figure 3](image)

**Figure 3.** Characterization of tissue heterogeneity in the peri-infarct zone using delayed enhancement CT (A and B) and CMR (D and E) in a pig model. (C and F) Masson trichrome stain depicts a viable myocardium in red from non-viable tissue in blue. Scanning electron microscope images of the densely packed collagen fibres 6 months after MI (G) and viable myocytes (H) characterize the ultra-structure of the chronic infarct. (I) Transmission electron microscopy shows the clear delineating of the collagenous scar (white arrows) and viable tissue (asterisk). Reprinted with permission from Schuleri et al.45

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<td>Transgene expression, cell migration</td>
<td>PET &gt; SPECT</td>
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SPECT, single-photon emission computed tomography; PET, positron emission tomography.
understanding of infarct healing and the assessment of biological effects of novel therapies.

**Imaging of myocardial inflammation**

Although the glucose analogue F-18 deoxyglucose (FDG) is typically used for the detection of myocardial viability under conditions of insulin stimulation and/or glucose loading, interest on its use for detecting myocardial inflammation is increasing. Activated monocytes/macrophages typically show high glucose utilization, but their detection requires algorithms for efficient suppression of myocyte glucose uptake. Long-term fasting and heparin administration have been suggested for this purpose.63 Recent animal studies in rodents and pigs have validated that FDG can, indeed, be used to determine inflammation in the infarct region early after MI.64,65 Other, more specific inflammation imaging markers, which do not have the limitation of potential physiological binding to viable myocardial tissue, are under exploration,66 including those discussed in subsequent sections. A logical next step would be to employ inflammation imaging early after infarction in order to identify subjects at high risk for subsequent ventricular remodelling, or in order to determine the effect of therapies aiming at the modulation of inflammation during the wound healing phase.

**Imaging of cell death and apoptosis**

Various tracers for the imaging of myocardial cell death have been introduced. Molecular targets include intracellular myosin or histones, sarcolemmal phosphatidylserine, or more recently intracellular caspases.67 There is a specific interest in enabling the early detection of programmed cell death (apoptosis) at a stage when it may still be reversible. Various, mostly experimental, studies have used molecular imaging to identify the effect of novel therapies on the magnitude of cell death after MI.68

**Imaging of extracellular matrix activation**

The interaction between myocardial tissue and extracellular matrix is an important component of the early inflammatory response to MI, subsequent scar formation, and potential development of ventricular remodelling.

Matrix metalloproteinases (MMPs) have emerged as a target for radionuclide imaging, and initial experimental work has shown that activation of MMPs occurs within the infarct area in the first few weeks after the event.69,70 Notably, patients with ineffective infarct healing resulting in lethal cardiac rupture have more inflammatory cells and higher MMP activities in the infarct area compared with patients who do not develop this complication.71 The imaging signal can be linked to the development of contractile dysfunction and may, thus, predict chamber remodelling.69

The intrinsic renin–angiotensin system of the heart is another imaging target that plays a role in the modulation of myocardial fibrosis. Myocardial angiotensin-converting enzyme can be detected by radionuclide imaging.72 The angiotensin II type 1 receptor is another robust imaging target that has been shown to be up-regulated in the early phase after MI in experimental models.73,74

**Imaging of angiogenesis**

Angiogenesis is considered an important step during wound healing after ischaemic myocardial damage. It has been an early target of molecular therapies directed at myocardial repair.75 Accordingly, several molecular probes for target structures involved in the angiogenic process have been developed. Alpha(3)beta(3) integrin is an adhesion molecule which plays an important role in angiogenesis. Various SPECT and PET markers have been developed for the imaging of its expression in damaged myocardium, showing up-regulation within the first few weeks after infarction (Figure 5).76,77 Those markers hold the potential to predict the risk for subsequent remodelling, as suggested in a recent experimental study where a strong early integrin imaging signal from the infarct region in rats was associated with less ventricular remodelling in subsequent weeks, suggesting that integrin expression is a potential biomarker of repair.78 In another experimental project, integrin imaging was used to monitor the effect of pharmacological intervention in myocardial remodelling in mice. Interestingly, various drugs which prevented remodelling attenuated the integrin signal in this study.79 Clearly, further work needs to be done to clarify the complex relationship between the timing of
imaging, signal strength, and functional outcome. Of note, some of these probes have already been applied clinically.80

Direct imaging of the therapeutic agent

Finally, it should be recognized that the therapeutic agent itself can be radiolabelled in order to track its fate after delivery for improved myocardial repair. Stem cells can be labelled using various radionuclides, magnetic particles, or reporter genes. The reporter gene approach can also be used for the imaging of exogenously delivered genes or for the interrogation of endogenous processes such as protein–protein interactions or gene programme activation. The details of these approaches are reviewed elsewhere.42,81,82 Importantly, such imaging techniques of the therapeutic agent may be combined with the molecular imaging of the target tissue for detailed insights into the interaction between therapeutic interventions and tissue biology.

Putting the pieces together: from ‘hybrid imaging’ towards ‘hybridization of imaging and therapy’

The specificity of novel molecular imaging probes results in an image signal that is weaker than the perfusion or metabolism signal obtained for routine clinical imaging. In order to facilitate detection and localization of the molecular signal, fusion with a morphological imaging technique is desirable.83 Hybrid imaging systems such as SPECT–CT, PET–CT, and more recently PET–MRI are, thus, the important innovations required for practical implementation of molecular myocardial imaging. They enable correction of the molecular signal for attenuation and scatter, as well as gross localization of the molecular signal within the heart. The new hybrid device generation also enables integration of molecular radionuclide tests with contrast-enhanced CT or MR imaging of the infarct scar within a single imaging session (Figure 6).64,83,84 The full clinical potential of these specific molecular hybrid imaging techniques has not yet been exploited. Mechanical revascularization therapy and standard medical therapies are increasingly well linked to, and guided by, imaging of perfusion/flow and coronary anatomy.85 Currently established therapies may only gain little from novel molecular imaging techniques. New molecular and cellular therapies, however, which aim at the improvement of myocardial repair, may benefit from molecular imaging in multiple ways: a strong, radionuclide-determined inflammation signal from the CMR- or CT-determined infarct area may, e.g., identify the optimal time point for targeted therapy to recruit endogenous progenitor cells for healing. Or, increased expression of integrins as adhesion molecules in the infarct region may identify optimal conditions for targeted delivery and subsequent engraftment of stem cells. The delivery of the cells could not only be guided to the biologically active region, but the cells, once delivered, could be tracked by imaging in order to determine the success of delivery.

However, before their clinical implementation, such new molecular imaging strategies will have to demonstrate that they can support clinical decision making, e.g. by enabling the selection of patients after an AMI.81,86 Likewise, novel therapies will need powerful and specific imaging tests for guidance towards an effective use. Hence, the fate of molecular imaging and molecular therapy is inherently interconnected.
The next step beyond the development of hybrid imaging is, thus, a ‘hybridization’ of molecular imaging and therapy. When combined at early pre-clinical developmental stages, it is expected that both imaging and therapy will benefit from each other in order to successfully cross the bridge towards clinical application.

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