Radiographic, ultrasound, nuclear, and magnetic resonance methods have become indispensable in the management of heart failure (HF). Imaging is widely used in decision making in HF, not only in relation to left ventricular (LV) systolic and diastolic function but also in the selection of medical, device, and surgical therapy in HF and valvular heart disease. Future developments in the care of advanced heart disease, including stem cell therapy, device therapy to control remodeling, and percutaneous valve interventions, as well as the need to identify subclinical heart disease, are likely to expand this use. Moreover, the epidemic of diabesity (diabetes and obesity) will augment the existing epidemic of HF just when it appeared to have peaked. Large numbers of patients will need information from imaging to guide clinical decision making (Table 1). The sources of this information will need to be expeditious, inexpensive, and preferably objective and quantitative.

**Functional Measurements: The Cornerstone of HF Management**

Although some of the measurements in HF patients are structural (LV mass and geometry), the main components of an imaging assessment in HF will continue to be primarily functional (LV ejection fraction, size, filling pressures, filling characteristics, and right ventricular [RV] function). A number of new technologies will enhance the future accuracy and reliability of these measures.

**LV Volumes and Ejection Fraction**

Routine techniques (contrast ventriculography, 2D echocardiography) provide real-time imaging in standard imaging planes. The only traditional method that has escaped this limitation has been radionuclide ventriculography, in which the ejection fraction is calculated from scintigraphic counts, but this introduces the separate potential problems of attenuation and overlying chambers.

**Limitations of 2D Imaging**

Two-dimensional imaging approaches require expert acquisition and observers and have limited reliability in obtaining appropriate cut planes in sequential studies. The limitation of requiring imaging planes in the correct axis is particularly an issue for 2D echocardiography, which may be constrained by limited imaging windows; in the pursuit of optimization of the resolution of structures, images are often obtained off-axis (Figure 1). Portrayal of a 3D object in 2 dimensions has adverse consequences with regard to the reproducibility of LV measurements. The increasing sophistication of medical treatments for LV dysfunction has created the need for accurate and reproducible measurements of chamber dimensions. Variations of imaging planes especially may pose a problem for long-term follow-up of LV volume, mass, and ejection fraction, and the evolution of these measurements may have important treatment implications.

**Future Role of 3D Imaging**

Because of these limitations of 2D imaging, 3D imaging (obtainable with 3D echocardiography [3DE], cardiac magnetic resonance [CMR], single photon emission CT [SPECT], and cardiac CT) is likely to become increasingly important in the provision of accurate measurement of global LV size and function in the assessment of HF. Multiple 2D images are used to reconstruct a 3D image with CMR and cardiac CT, but the imaging planes are not constrained by imaging windows. It appears to be predominantly the 3D display that drives the increased reliability of this method, rather than the nature of the imaging technique (Figure 2).

The establishment of 3D imaging as the standard imaging approach of the future will require further evolution in image acquisition, processing, and display. Although CMR images offer a clear distinction between blood and myocardium, this process may be difficult with 3DE. Nonetheless, in the 60% to 70% of patients with adequate images, a number of trials, including a recent multicenter study, have confirmed the accuracy of 3DE relative to CMR. When image quality poses a problem for echocardiography, echocardiographic contrast agents improve endocardial detection. The accuracy of 2D echocardiography is increased with contrast, and it appears likely that 3DE with contrast (perhaps using a highly stable microbubble) will be the optimal approach. A secondary goal of the move to 3D imaging will be to provide rapid acquisi-
tion of 3D data sets, even obtained remotely, with most of the processing being performed offline.

LV Filling Profiles
The LV filling profile has an established role as a prognostic component of the imaging report of the HF patient. LV filling can be measured by most imaging modalities, but 2 attributes are important: frame rate of the acquisition (which allows accurate assessment of isovolumic and deceleration time) and the ability to distinguish normal from pseudonormal filling patterns. Echocardiography is the best established technique for this evaluation, and its role has been strengthened by the echocardiographic estimation of filling pressure. This is derived from the ratio of passive filling and myocardial velocities (E/E' Figure 3) and is likely to assume increasing importance in relation to new diagnostic criteria and application to patient care management.

LV Morphology
The morphology of the LV, including its mass and shape, is an important component of the imaging evaluation of the failing heart, especially in the context of hypertension and hypertrophic cardiomyopathy. Mass is most accurately measured by CMR and 3DE, which should supersede M-mode echocardiography.

LV shape is a marker of the severity of HF and predicts outcome. This is most simply measured as the sphericity index (ratio of the maximum long- and short-axis dimensions), although this may be limited by regional problems, and a more global (perhaps 3D) measurement may be more useful. Both 3DE and CMR have been used in planning LV reconstruction; more sophisticated measurements of curvature may become important for this purpose.

The shape of the heart in LV hypertrophy may also be important. Small hearts have low transmural stress. Current techniques assume wall stress is uniform for the entire LV; it is hoped that the availability of 3D measurements of curvature will enable regional assessment of wall stress in the future.

Mitral Regurgitation
Mitral regurgitation (MR) is associated with outcome in HF. Functional MR is common, especially in ischemic cardiomyopathy, accounting for 50% of postinfarction patients with HF, and ischemic MR increases mortality even when MR is mild. New surgical and percutaneous devices, as well as an extension of the indications for cardiac resynchronization to the control of LV remodeling and functional MR, are likely to increase the importance of MR evaluation in the future.

The evaluation of MR in the failing heart should include an assessment of severity and characterization of the mechanism. Functional MR severity may be difficult to assess because it may change during systole and because of the variability and complexity of jet morphology. Typically, the severity of MR is greatest in early systole and is reduced as the LV volume decreases and the mitral leaflets are pushed back into the annular plane. The largest jet size, or even the vena contracta dimension, may be misleading as a marker of MR severity, and volumetric methods may have some attraction for the calculation of regurgitant volume to avoid errors due to inhomogeneity of MR.

Table 1. Established HF: What the Clinician Needs

<table>
<thead>
<tr>
<th>Category</th>
<th>Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection and diagnosis</td>
<td>Etiology</td>
</tr>
<tr>
<td>Cause of HF, mechanism</td>
<td>Systolic vs diastolic</td>
</tr>
<tr>
<td></td>
<td>Ischemic vs nonischemic</td>
</tr>
<tr>
<td></td>
<td>Exclude valvular contribution</td>
</tr>
<tr>
<td></td>
<td>Exclude ischemic contribution</td>
</tr>
<tr>
<td>Severity, risk stratification</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>therapeutic guidance</td>
<td>Filling pressure</td>
</tr>
<tr>
<td>Complications</td>
<td>Detection/evaluation of functional MR</td>
</tr>
<tr>
<td></td>
<td>LV hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
</tbody>
</table>

Figure 1. Limitations of 2D imaging for measurements of LV size. Top row illustrates 4-chamber views; the green line marks the plane of this view on the matching short-axis view on the bottom row. The view with optimal rotation (B) differs from off-axis cuts A and C by rotations of 10° to 20°; all would be considered acceptable acquisitions, but the difference between them could pose problems for sequential measurements.
Understanding the mechanism of MR involves a consideration of both LV and mitral morphology. The major categories relate to disturbances in the inferoposterior wall (usually from infarction), LV enlargement, and dyssynchrony. The former results in displacement of the posterior papillary muscle, with tethering of the posterior leaflet, and posteriorly directed MR, whereas the second involves displacement of both papillary muscles due to LV remodeling, which leads to failure of coaptation of the mitral leaflets and a central MR jet (Figure 4). Mitral valve procedures may not be a good solution to what is a ventricular problem, and advances in this area are likely to address specific mechanisms of the process.

**RV Function**

RV function is an important correlate of survival in HF. The nongeometric nature of the RV has made the size and function of this chamber difficult to characterize by conventional methods. Nongeometric techniques, such as tissue Doppler, are the simplest approach. CMR avoids the dependence of standard echocardiography on standard imaging windows; RV evaluation with this technique has been shown to correlate with outcomes. Methods that allow the chamber to be portrayed in 3D (3DE, CMR) may circumvent the lack of a geometric shape and appear likely to be the future techniques of choice (Figure 5).

**Figure 2.** Techniques for 3D imaging of LV size and function. A, 3D echocardiography will be gathered in a simultaneous (some manufacturers provide a near-simultaneous) data set. Tracing the ventricular border is required in multiple (8 to 12) image planes (more with a nongeometric LV shape). B, MRI images may be combined into a 3D data set; measurements are usually made in sequential short-axis slices, but attention must be paid to the location of the mitral annulus in systole and diastole.

**Figure 3.** Assessment of LV filling pressure. Measurements are made from pulsed-wave Doppler of transmural flow (peak diastolic E velocity) and annular tissue Doppler (peak E’ or Ea velocity). The resulting E/E’ has been shown to correspond to pre-A pressure. Decel indicates deceleration; E vel, E-wave velocity; Em vel, early diastolic myocardial velocity; and LVEDP, LV end-diastolic pressure.

Echocardiographic assessment of pulmonary artery systolic pressure is dependent on the estimation of right atrial pressure and the detection of a tricuspid regurgitant jet; the use of contrast often facilitates the detection of this signal even when it is difficult to identify on color Doppler. Pulmonary vascular resistance should be estimated, especially if RV stroke volume is reduced (Figure 6).

Which Test?
The foregoing discussion would suggest that no single imaging test is clearly superior to all others for the basic evaluation of the failing LV. Current guidelines propose echocardiography as the initial test, and it is difficult to see how this is likely to change given the attractions of an inexpensive and widely available technique for a very common condition. The incorporation of echocardiographic contrast agents is important if images are suboptimal, and 3D techniques are likely to become routine for volume measurements. CMR and cardiac CT provide well-validated 3D information on cardiac morphology and function and may combine functional data with tissue characterization and eventually noninvasive coronary angiography. Future clinical research must address the cost-benefit ratio of truly tomographic functional imaging compared with standard 2D echocardiography.

**Figure 4.** Characterization of MR mechanism. The first patient (4A) has predominantly posterior wall-motion abnormalities, restriction of the posterior mitral leaflet, and an anterior jet. The second patient (4B) has LV enlargement with diffuse wall-motion abnormalities (the posterior is best preserved), with restriction of both mitral leaflets and a central jet. Future LV interventions for these problems are likely to be quite different.

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**Novel Structural Measurements in the Diagnosis and Management of HF**
Although major changes in the management of HF have occurred over the last 2 decades, it remains a malignant disease. Patients often present with extensive ventricular damage, and the solution may be to recognize and treat LV dysfunction at an earlier stage (Table 2). The use of accurate imaging techniques will be essential for the identification of subclinical disease.

**Myocardial Properties**
Imaging already plays a central role in the distinction of systolic and diastolic HF. Although much work has focused on the myocardial responses to HF, myocytes account for only one third of myocardial cells. Less attention has been paid to interstitial disease, but both myocyte and collagen compartments participate in the process of ischemic cardiomyopathy and very likely other cardiomyopathies. In the future, myocardial characterization will enable a more sophisticated distinction of these entities, play a role in HF diagnosis (and possibly its classification), and perhaps guide therapy.

Changes in the interstitium relate mainly to fibrosis. There is a major increment of interstitial and perivascular fibrous tissue in pathological hypertrophy. Fibrosis may be either reparative (a regional process that reflects healing and/or replacement by scar) or reactive (a diffuse process). In addition to an increment of the amount of this tissue, its nature is also abnormal, as evidenced by an increase in type 1 collagen. The consequences of this fibrosis include abnormal coronary flow reserve, probably related to perivascular fibrosis, as well as HF and arrhythmias. Myocardial fibrosis is believed to play a significant role in the abnormal diastolic function present in hypertension, diabetes, and the elderly and will likely become a specific target for medical therapy.
CMR Methods
After myocardial infarction, gadolinium late-enhancement CMR images identify regional fibrosis and infarct size and predict functional recovery. The detection of localized fibrosis is ideal for recognition by gadolinium enhancement, based on the relative comparison between the region and a reference normal segment, but the test is ineffective for identifying diffuse fibrosis. However, there is twice as much diffuse as there is regional fibrosis in ischemic cardiomyopathy, and this is difficult to appreciate from relative gadolinium uptake. This phenomenon may be more marked in dilated cardiomyopathy, in which midwall fibrosis is detected in 30% of patients, despite the fact that probably 75% have evidence of fibrosis.

Other CMR methods may be useful in the detection of fibrosis. The T1 time is shortened by fibrosis, and T1 mapping is a potentially quantifiable marker of the extent and severity of fibrosis when validated against biopsy samples and applied in clinical settings associated with nonischemic fibrosis. Differences in transverse relaxation times of hydrogen protons (T2*) reveal differences in tissue water content, which may be attributable to fibrosis.

Ultrasonic Integrated Backscatter
Ultrasound techniques have traditionally been the test of choice for myocardial tissue characterization. In addition to reflection of ultrasound to the transducer by acoustic interfaces, some reflection derives from the tissue. The acoustic density of this tissue determines the degree of reflection, which may be measured by calibrated integrated backscatter.

Table 2. Stages in the Development of HF

<table>
<thead>
<tr>
<th>Stage</th>
<th>History of HF</th>
<th>Clinical CHF</th>
<th>Structural/Functional Heart Disease</th>
<th>Risk Factors for HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>No</td>
<td>...</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stage A</td>
<td>No</td>
<td>...</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stage B</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>...</td>
</tr>
<tr>
<td>Stage C1</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>...</td>
</tr>
<tr>
<td>Stage C2</td>
<td>Yes</td>
<td>...</td>
<td>Yes</td>
<td>...</td>
</tr>
<tr>
<td>Stage D</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>...</td>
</tr>
</tbody>
</table>
describing myocardial acoustic density, which is increased by fibrosis (Figure 7). Integrated backscatter is abnormal in a variety of hypertrophic and endocrine conditions. However, the technique is subject to signal noise and may never become part of the standard imaging repertoire.

**Nuclear Cardiology Techniques**

Scintigraphic methods have limited potential for characterizing myocardial fibrosis. The perfusable tissue index is obtainable with positron emission tomography (PET) imaging of H$_2$O and C$^{15}$O, which allows measurement of the perfusable tissue fraction. The perfusable tissue index is reduced in patients with dilated cardiomyopathy. Unfortunately, in addition to the cost and limited availability of PET, these techniques are technically challenging and are unlikely to be adopted for routine clinical use.

**Myocardial Performance**

Ejection fraction is load dependent and insensitive to subtle disturbances of myocardial performance. Radial thickening can be measured by techniques with good spatial and contrast resolution, such as CMR; however, because of the fiber architecture of the heart and the preferential involvement of different components of the heart (eg, endocardium) in some pathologies, reduction in thickening may be nonuniform. Techniques that examine deformation in multiple axes (especially the long axis) might be expected to be more sensitive than simply wall thickening.

Tagged CMR or echocardiography may be used to measure motion as velocity (which may be influenced by translation and tethering and is therefore not site-specific), strain (an index of deformation), or strain rate. Tissue Doppler-based measurements derive strain rate from color Doppler velocity, with high temporal resolution but potential limitations caused by signal noise. 2D strain (2DS) is based on speckle tracking at frame rates of 40 to 80 frames per second (Figure 8). The optimal technique varies according to the circumstances; high frame rates (eg, tissue-velocity imaging) are more important for measuring timing (eg, postsystolic thickening) and strain rate and at high heart rates. Lower frame rates (eg, 2DS, MR tagging) may be better at rest and in remodeled hearts, in which the orientation of the wall and imaging axis may be altered along the length of the wall (Figure 9).
Table 3 summarizes the reliability of these myocardial parameters in our laboratory. Systolic and diastolic tissue Doppler measurements are the most robust.

Table 3. Reliability of Echocardiographic Measures for Tissue Characterization

<table>
<thead>
<tr>
<th></th>
<th>Intraobserver Variation</th>
<th>Coefficient of Variation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sm</td>
<td>0.4±0.4 cm/s</td>
<td>8</td>
</tr>
<tr>
<td>Em</td>
<td>0.6±0.5 cm/s</td>
<td>5</td>
</tr>
<tr>
<td>Peak systolic SR (TVI)</td>
<td>0.06±0.24</td>
<td>11</td>
</tr>
<tr>
<td>Peak systolic e (TVI)</td>
<td>0.5±4.75</td>
<td>15</td>
</tr>
<tr>
<td>Peak systolic SR (2D)</td>
<td>0.00±0.27</td>
<td>11</td>
</tr>
<tr>
<td>Peak systolic e (2D)</td>
<td>1.06±0.61</td>
<td>10</td>
</tr>
<tr>
<td>Calibrated IB</td>
<td>2.7±2.0 dB</td>
<td>9</td>
</tr>
<tr>
<td>Cyclic variation of IB</td>
<td>1.5±1.2 dB</td>
<td>15</td>
</tr>
</tbody>
</table>

Sm indicates systolic myocardial velocity; Em, early diastolic myocardial velocity; SR, strain rate; TVI, tissue-velocity imaging; 2D, 2D imaging; and IB, integrated backscatter.

Contractile Reserve

In preclinical disease, systolic dysfunction is more likely to become apparent under stress than at rest. 3D delineation of functional data may make CMR and 3DE the optimal tests to quantify contractile reserve. The evaluation of regional function at rest and during stress can be used to identify ischemic and nonischemic cardiomyopathy.

In established HF, contractile reserve, measured invasively (eg, dP/dt) or noninvasively (eg, ejection fraction or cardiac output response) is related to outcome.30 Contractile reserve also mirrors sympathetic dysfunction,31 which makes this an inexpensive surrogate for tests of sympathetic status. In the future, this information may be used in tailoring HF therapy to the status of individual patients.

The response of E/E’ to stress may also be useful in the attribution of exertional dyspnea to diastolic HF.32 Conversely, the absence of raised filling pressure with exercise makes it difficult to attribute exertional dyspnea to diastolic HF. In the future, this observation may help the movement...
away from the diagnosis of exclusion ("HF with normal ejection fraction") to a positive diagnosis of diastolic HF.

**Coronary Perfusion and Vascular Imaging**

Systolic dysfunction caused by ischemic heart disease is the commonest cause of HF in the developed world.\(^{33}\) Rest and stress myocardial perfusion imaging can identify a subgroup of patients with HF who have potentially reversible dysfunction and are likely to benefit from revascularization.\(^{34}\) In LV dysfunction, a normal stress perfusion scan has high negative predictive value, but fixed and reversible perfusion defects are not specific for coronary artery disease, with fibrosis and reduced coronary reserve in nonischemic HF causing a limited specificity (40% to 80%) for SPECT and PET in HF.\(^{35}\)

The future diagnostic workup of HF patients will most likely include vascular imaging with cardiac CT or CMR to directly assess the anatomy of epicardial coronary vessels (Figure 10). The high negative predictive value of CTA may obviate the need for invasive coronary angiography.\(^{36}\)

**Metabolism (PET/MR Spectroscopy)**

HF is associated with abnormal myocardial metabolism, including energy depletion and reduced mechanical efficiency.\(^{37}\) These changes may play a role in the progression of HF and may potentially serve as therapeutic targets.

Fatty acid represents the major source of cardiac substrate metabolism, but its complex metabolism allows only semiquantitative measurements of substrate utilization with PET imaging of carbon 11-labeled palmitate.\(^{38}\) More recently, iodinated fatty acids such as β-methyl-iodophenylpentadecanoic acid (BMIPP) have provided a sensitive SPECT marker of altered fatty acid transport into the myocyte. Metabolic imaging may gain clinical acceptance if clinical trials confirm that a metabolic switch from fatty acids to glucose utilization in the failing myocardium improves outcomes of patients with HF.

PET imaging of \(^1\)C-labeled acetate allows assessment of cardiac oxidative metabolism without the complexity of substrate interaction between glucose and fatty acids.\(^{39}\) The early rapid clearance of acetate correlates closely with myocardial oxygen consumption, and the relationship of myocardial \(^1\)C-labeled acetate kinetics to cardiac work offers a noninvasive parameter for cardiac efficiency that can be used to demonstrate the effect of pharmacological and pacing interventions on cardiac energetics.\(^{40,41}\)

Fluorine 18-labeled fluorodeoxyglucose (\(^{18}\)F-FDG) traces cellular glucose uptake and phosphorylation and can be used to quantify regional glucose metabolism.\(^{42}\) \(^{18}\)F-FDG uptake defines tissue viability within malperfused segments in patients with advanced coronary artery disease and impaired LV function.\(^{43}\) Hybrid imaging such as MR/PET and PET/CT combines almost simultaneous anatomic, functional, and metabolic imaging for the improved visualization of cardiac and vascular function and may provide new quantitative tools to study the pathophysiology of HF in vivo (Figure 11).
Altered energetics play an important role in congestive HF.44 MR spectroscopy is able to measure energy metabolism through analysis of myocardial ATP and phosphocreatine.45 However, 31P-MR spectra may be difficult to quantify, and although the technique has been performed with standard 1.5-T systems, the signal-to-noise ratio is more favorable at high magnetic field strength. Although spectroscopy is likely to shed light on important mechanisms in congestive HF, its clinical adoption seems unlikely at present. Hyperpolarization and chemical shift imaging with 13C-labeled substances such as [13C]pyruvate may enhance the sensitivity of MR measures of cardiac substrate metabolism and may become a useful tool for experimental and clinical research.46

Cardiac Innervation
Disturbances of cardiac innervation have been associated with progression of HF, arrhythmias, and sudden cardiac death.47 Neuronal imaging may provide diagnostic and prognostic markers for the identification of high-risk patients and predict response to pharmacological and electrophysiological interventions. Parasympathetic LV innervation is sparse, which makes visualization of the parasympathetic presynaptic system difficult, whereas imaging of the sympathetic system is feasible and has provided promising results in HF.

Extraneuronal sympathetic neurotransmitter concentrations are regulated by an efficient amine uptake mechanism, the noradrenaline transporter (NAT), which can be used to visualize the sympathetic nerve terminal by radiolabeled norepinephrine analogues. The most commonly used SPECT tracer, metaiodobenzylguanidine (MIBG), undergoes avid uptake and storage in the cardiac nerve terminals but is not metabolized by monoamine oxidase. Uptake of this tracer is specific for the integrity of sympathetic nerve terminals. Cardiac MIBG uptake is measured by defining the heart-to-mediastinum uptake ratio, assessing washout kinetics, or quantifying the apex-base gradient of denervation in the failing heart.48 Iodine 123-labeled MIBG appears to have prognostic value in patients with LV dysfunction,49 and MIBG may be adopted clinically if prospective multicenter studies confirm its incremental prognostic value. Individual risk profiles for HF patients may permit more selective use of costly interventions such cardiac defibrillator implantation.50

The positron tracers [11C]hydroxyephedrine and [11C]epinephrine permit quantification of the density of sympathetic nerve terminals51,52 (Figure 12). [11C]hydroxyephedrine myocardial uptake correlates with norepinephrine tissue concentration and density of NAT. Postsynaptic β-receptor density can be assessed with [11C]CGP12177. The use of radiopharmaceuticals in imaging various aspects of neuronal function (transmitter uptake, release, metabolism, and storage) may permit guidance of pharmacological interventions and their effects on cardiac autonomic innervation.

Molecular Imaging
The understanding of signaling pathways has led to increasing interest in monitoring in vivo cell/cell and protein/protein interactions. Several new imaging strategies visualize molecular targets that represent angiogenetic, apoptotic, cell migration, and inflammatory processes. The laboratory use of molecular imaging has expanded rapidly, but the derived optical signals only penetrate a few centimeters of tissue; contrast agents are required to permit imaging, which introduces toxicity and pharmacological issues. Although the use of genetically altered material in targeted radiolabeled substances faces many regulatory hurdles, there is increasing
interest in new imaging probes to improve the diagnosis of disease and to evaluate targeted therapies.

The assessment of apoptosis and the assessment of angiogenesis are the initial molecular imaging tools that may help to characterize patients with HF. Apoptosis is an important mechanism of cardiomyocyte death in human myocardial infarction and HF, which can be imaged with labeled annexin A5. This shows selective and high-affinity binding to phospholipid exposed on the surface of apoptotic cells that triggers uptake of remnants by neighboring cells. Technetium Tc 99m-labeled annexin A5 demonstrates increased uptake in ischemically injured, reperfused myocardium, in nonischemic HF, and in transplant rejection. However, this tracer is not available for clinical use, and the development and validation of specific markers for apoptosis is needed.

Angiogenesis may be beneficial in end-stage coronary artery disease, but it is a complex and highly regulated process, which makes it challenging to develop a single imaging probe. Although both myocardial perfusion and functional recovery are final end points in the clinical evaluation of angiogenic therapy, specific imaging markers may monitor the effect of new drugs or interventions more directly. Potential imaging approaches involve reporter gene imaging of vascular endothelial growth factor expression or tracers that target vascular endothelial growth factor receptors. The current myocardial imaging of angiogenesis has been based mainly on tracers or nanoparticles that target αvβ3, a cell membrane glycoprotein receptor that is an important mediator of angiogenesis and is highly expressed on activated endothelial cells. The cyclic peptide RGD has been used as ligand for αvβ3-integrins in combination with fluorescence in SPECT/PET imaging, with nanoparticles for CMR, and with microbubbles for contrast-enhanced ultrasound. Initial results in ischemic myocardium show regionally increased RGD signals, which suggests upregulated integrin expression. However, the expression of integrins by cardiomyocytes, fibroblasts, and vascular cells and the potential involvement of integrins in a range of biological processes (hypertrophy, inflammation, wound healing, and scar formation) may limit the specificity of the observed RGD signal for angiogenesis. Further experimental and clinical research will focus on the specificity of the new imaging probes for angiogenesis and the prognostic and therapeutic relevance of molecular imaging signals.

**Cell Monitoring**

Cell transplantation is a promising future therapeutic option for patients with impaired regional or global function due to cell death. Methods to monitor cell migration, homing, survival, and engraftment may facilitate the understanding of heterogeneous results from early clinical investigations of intracoronary injection of bone marrow–derived cells. The tasks and strategies for imaging can be divided into 3 categories: short-term cell labeling, cell survival assays, and monitoring of cell differentiation.

Short-term visualization after transplantation may be obtained by direct labeling of stem cells with indium 111-labeled oxine, Tc-99m exametazime (HMPAO), or 18F-FDG, a process achievable without detectable changes in viability, functionality, migration, and proliferative capacity. Only a small fraction of radioactivity (<5%) is observed in the myocardium, which suggests regional retention by only a few injured cells. The duration of cell tracking ranges from a few hours with FDG-PET in human infarctions to 7 days after injection with 111In with SPECT/CT in dogs.

Paramagnetic nanoparticles can be used to facilitate nontoxic labeling of stem cells before transplantation, which would enable repeated imaging by MR. The high spatial resolution and direct correlation of cell signals to regional function and late contrast enhancement make this approach very attractive for experimental and clinical research. However, the signal is not directly related to cell viability, so it may lose specificity for transplanted cells after cell death and macrophage phagocytosis.

Monitoring of cell survival and differentiation requires imaging techniques linked to the integrity of cells and tissue-specific protein expression (Figure 13). Reporter gene imaging with optical imaging approaches is successful in small animal research, whereas scintigraphic techniques may be applicable to large animals and patients. Most studies label an enzyme or transporter (herpes simplex virus type I thymidine kinase) or the human iodide/symporter. The application of these approaches to clinical research will require further documentation of suitability and safety to pass regulatory hurdles.

**Conclusions**

The rapid advancement of cardiac imaging techniques has provided an increasing range of information that can now be obtained without affecting the imaged function or process. The successful application of these techniques will be determined not only by methodological progress but also by the integration of this information into clinical care. The latter requires not only rigorous clinical validation in prospective trials that adhere to evidence-based medicine criteria but also appropriate training of cardiovascular specialists in the cost-efficient use of imaging technologies. Although the basic characterization of cardiac function in HF patients will be supported primarily by echocardiography, these results will guide the use of other imaging procedures to address specific
questions such as etiology, severity, reversibility of LV function, and prognosis. The development of targeted therapy will require a combination of imaging and therapy, which will permit individualized management decisions and hopefully facilitate better clinical outcomes for HF patients.

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References


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