The Future of Cardiovascular Imaging in the Diagnosis and Management of Heart Failure, Part 2
Clinical Applications

Thomas H. Marwick, MD, PhD; Markus Schwaiger, MD, PhD

Part 1 of these articles focused on the targets of the imaging examination in heart failure (HF) and also reviewed the individual techniques that might be used to address these features. This article will concentrate on specific clinical situations.

Diagnosis of Early Stage Disease
Despite improvements in outcomes related to new treatments for HF, the prognosis of this condition remains poor. The guidelines of the American College of Cardiology and the American Heart Association have emphasized the importance of the detection of early disease in patients at risk (stage A) and those with asymptomatic evidence of left ventricular (LV) damage (stage B). The identification of these entities should lead to the initiation of prophylactic therapy. In those already on therapy (eg, antihypertensive drugs), the detection of target organ disease (eg, LV hypertrophy) may justify more intensive therapy.

Early Detection of HF
Despite interest in biomarkers, imaging seems to be the optimal strategy for HF screening. It is likely that this will be performed in the community and it is probable (because of cost and availability considerations) that the test of choice will remain echocardiography. The increasing workload provided by the HF epidemic may alter the workflow, with an increasing role for imaging in primary care. Although the wider use of echocardiography by noncardiologists will bring challenges with respect to training, this process will be facilitated by progressive miniaturization and automation, which will allow better quantification and reduced subjectivity. The subjective assessment of echocardiography is a well-recognized limitation that has been improved, but not avoided, by modern technical developments. The availability of a simple quantitative parameter to support the clinician’s interpretation of resting echocardiographic images may be provided by the assessment of 2D myocardial strain, based on speckle tracking, although it remains to be shown to what extent the variability of normal ranges will limit the ability to distinguish normal and abnormal. Automation is likely to facilitate the acquisition of ejection fraction (EF), regional wall motion, and left atrial (LA) and diastolic function assessments. The assessment of LV diastolic function, measurement of LV mass, and recognition of geometric patterns are important aspects of recognizing subclinical disease.

Diastolic Dysfunction
The first part of this review emphasized the technical aspects of the evaluation of diastolic function. Two aspects are particularly pertinent to the detection of early disease. First, although LV filling disturbances are associated with increased risk, they are common in older subjects and sometimes not considered pathological. Assessment of LA size is critical to the recognition of persistent LA pressure elevation and is readily performed. Second, the increasing availability of this information will influence criteria for the distinction of isolated diastolic dysfunction and HF (Figure 1).

Left Ventricular Hypertrophy
The first part of this review emphasized the assessment of LV geometry and the adverse consequences of the portrayal of a 3D object in 1 or 2 dimensions on the reproducibility of LV measurements. This is especially pertinent to the sequential assessment of LV mass for possible decision-making, and 3D techniques (3D echocardiography, cardiac magnetic resonance [CMR], single-photon emission computed tomography [CT], and cardiac CT) are most accurate and reproducible.

When increased wall thickness is identified, the entities that need to be distinguished are athletic from pathological LV hypertrophy, hypertrophic cardiomyopathy, and hypertensive heart disease. Physiological hypertrophy is characterized by preservation of tissue velocity, which is reduced in hypertensive heart disease and very reduced in hypertrophic cardiomyopathy and infiltration. The identification of in-
cardiac substrate selection and its response to therapy. PET may help to detect and monitor therapeutic agents such as Herceptin, and apoptosis markers may be useful.

Myocardial Characterization in Early Disease

The detection of subclinical dysfunction should prompt steps to understand the etiology of myocardial disease. As discussed in more detail below, this will be guided by the clinical setting and initial echocardiographic findings and may involve steps to detect coronary artery disease (CAD). In patients with diastolic dysfunction, steps will be taken to characterize the mechanism of the process, likely focusing on the contribution of fibrosis as a potential therapeutic target. Myocardial characterization may be performed with echocardiography (backscatter, tissue Doppler, and deformation approaches), magnetic resonance (contrast, T1, and T2* imaging), and nuclear techniques. The relative merits of these approaches, as indeed the nature and efficacy of potential therapies, will be investigated over the next decade.

Specific diagnoses in at-risk patients will require particular imaging strategies. For example, phenotypic evidence of disease may be recognized in at-risk relatives with familial hypertrophic cardiomyopathy. Sequential imaging may be of value in the identification of myocardial injury with therapeutic agents such as Herceptin, and apoptosis markers may be useful.

The assessment of substrate utilization with positron-emission tomography (PET) may help to detect and monitor cardiac substrate selection and its response to therapy. Newer therapeutic strategies aim at the energy metabolism of the failing heart; for example, experimental and initial clinical data suggest that metabolic modulations enhancing myocardial glucose oxidation may improve cardiac function in patients with chronic HF. There is increasing evidence that insulin resistance is a primary etiologic factor in the development of nonischemic HF. Potential options for treatment consist of the use of antidiabetic drugs or metabolic modulating agents. Future studies using various imaging approaches will need to address the relationship of hemodynamic performance and energetic efficiency in the failing human heart.

Patients with hemoglobinopathies requiring blood transfusions may develop an iron overload state, but there is a disassociation between cardiac and extra cardiac iron, related to a much lower rate of iron clearance from the heart. The importance of imaging specifically for cardiac rather than hepatic iron overload has been emphasized in recent trials.

Imaging in New Presentations With HF

Hemodynamics

The goals of the initial imaging evaluation include the confirmation of HF, an evaluation of severity, and recognition of its etiology. Foreseeable developments seem unlikely to displace the suitability of echocardiography for these initial steps, which include the provision of data about systolic (EF, volumes, if necessary with contrast) and diastolic function (LV filling characteristics and filling pressure, LA size, pulmonary vein flow), valve disease (primary or secondary), and morphology (LV mass, geometry). Clearly, other modalities are able to provide this information in whole or part but are more expensive and less available. If the patient’s echocardiographic windows are poor (eg, because of body habitus), CMR can provide the requisite information noninvasively.

The resting echocardiogram may identify a clear cause for symptoms of HF, including valvular, pericardial, and congenital heart lesions, infiltrative diseases such as amyloidosis or other storage diseases (which will be further elucidated by biochemical testing), or hypertrophic cardiomyopathy (which will lead to genetic and biochemical testing). Exclusion of CAD

The next step will involve specific investigation for the underlying etiology and depends on the clinical setting and imaging findings (Figure 2). The primary division of patients with dilated cardiomyopathy is between those likely to have ischemia and nonischemic cardiomyopathies, so the exclusion of CAD will be necessary in most middle-aged and elderly patients. Although this has traditionally been accomplished with coronary angiography, the high predictive value of negative CT angiography has put this in a favorable position for this purpose. Hybrid imaging provided by single-photon emission CT as well as PET-CT may combine the high positive predictive value of perfusion imaging with the high negative predictive value of CT angiography to enable a comprehensive cardiac examination to characterize hemodynamics, coronary morphology, and functional vascu-
Consideration of Myocardial Viability

If CAD is identified with severe LV impairment, observational data suggest that LV function, functional capacity, and outlook may be improved by coronary revascularization. Testing for myocardial viability will identify the tissue that is likely to recover. Because recovery of function is the result of a complex repair and remodeling mechanism, other end points such as perioperative complications and long-term clinical outcome may be of even greater importance. Because the risks of revascularization are increased in severe LV dysfunction (LVD), viability testing may shed further light on the risk-benefit evaluation of revascularization. The simplest initial test is gadolinium-enhanced CMR; the presence of extensive transmural scar makes recovery unlikely. However, the lack of transmural scar may not necessarily predict recovery, as CAD and myopathic processes may coexist (Figure 3). Moreover, as ischemic burden is also important in assessing the benefit of revascularization, CMR should be interpreted in conjunction with a stress-imaging test, stress CMR, nuclear, or echocardiography. Dysfunctional viable myocardium (stunned, hibernating) has been shown to be associated with poor clinical outcome in numerous studies. The upregulation of glucose utilization (evidenced by increased $^{18}$F fluorodeoxyglucose uptake; Figure 4) may identify a high-risk population for cardiac complications and serve as marker for clinical instability.

Nonischemic Cardiomyopathies

The identification of specific etiologies if CAD is disproven or considered unlikely depends on clinical, laboratory, and imaging cues. Sophisticated imaging may not be required; for example, noncompaction cardiomyopathy (which may be sporadic or familial) is a specific situation in which morphological identification of the underlying disease is possible on the echocardiogram.

The characterization of nonischemic cardiomyopathies with gadolinium late-enhanced CMR may permit selection of specific therapies when a specific distribution of myocardial scar corresponds to a particular disease. Bohl et al have recommended a systematic analysis whereby the presence of late enhancement is judged visually, assigned locations within the 17-segment model, and the number of positive segments counted. Segments are characterized as having a subendocardial, subepicardial, intramyocardial, or transmural pattern, and these are also quantified for transmural extent of scar. Lesions are visually assessed as focal or diffuse, and the mass of late enhancement is calculated by contouring the lesions and multiplying by slice thickness and tissue density, enabling late enhancement mass to be expressed as a percentage of LV mass. Although there is some association of these findings with prognosis, there is a poor correlation between the amount of late enhancement and ejection fraction, which contrasts with situation in ischemic heart disease.

The involvement of the papillary muscles, as well as patchy transmural scar (Figure 5), is associated with sarcoid heart disease. Midmyocardial scar may be detected after myocarditis in muscular dystrophies, glycogen storage disease, and Fabry disease. Subendocardial changes are identified in the presence of vasculitis and amyloidosis, but unlike the subendocardial changes of CAD, they are global, rather than regional. The barriers to the adoption of MRI for this purpose are that therapeutic and prognostic implications of these patterns remain to be defined and that the reliability of these findings is imperfect.

Myocarditis

If myocarditis is considered on clinical grounds (eg, prodromal viral illness, inflammatory markers, serology), nuclear imaging or CMR may be of value. The high spatial resolution of CMR combined with the ability of late enhancement to identify irreversible injury has made this technique useful for the evaluation of myocarditis. A CMR protocol for myocarditis might include standard functional imaging, a T2-weighted fast spin echo for edema detection, and a T1-weighted sequence before and after contrast to identify increases in the interstitial space, followed by late contrast-enhanced imaging to visualize necrosis. This approach has been used for monitoring steroid therapy and sarcoidosis, and T2 quantification has been used for monitoring myocardial involvement in systemic lupus erythematosus (SLE).

Advanced HF

Selection for ICD Therapy

The secondary prevention of sudden cardiac death with ICD therapy requires limited imaging evaluation other than consideration of possible concurrent disease, especially CAD. In primary prevention, a major component of risk is the severity of LV dysfunction, and the guidelines based on large trials propose an LVEF cutoff of 30% to 35%. Although routine methods were used for EF measurement in these
trials, the clinician may be concerned to minimize variability in EF assessment. As discussed in the first part of this work, EF can be most reliably be defined on the basis of 3D techniques, and the difference between 3D and 2D methods is sufficient to significantly influence implantation decisions. It seems likely that 3D methods will be increasingly used for this purpose.

Neuronal factors are known to be important modulators of hemodynamic adaptations in the failing heart. Although in vitro biomarkers have been proposed for staging and prognostication of HF, imaging of cardiac innervation permits the direct visualization of myocardial sympathetic nerve terminals. In several single-center studies, the reduction of myocardial neuronal tracer retention assessed by single-photon emission CT or PET has been associated with cardiac mortality, and these findings are additive to the association of conventional markers such as LVEF. However, no definite relationship has been established between the imaging results and the incidence of sudden cardiac death in HF populations.

Current multicenter studies are being conducted to compare natriuretic peptide measurements and metaiodobenzylguanidine (MIBG) imaging as prognostic markers in HF, as well as to correlate cardiac denervation (defined by MIBG) with the incidence of defibrillations after ICD placement in patients with HF. It is hoped that neuronal imaging will provide prognostic parameters that are adjunctive to LVEF to identify high-risk patients who will benefit from ICD placement. On the other hand, a high negative predictive value of maintained innervation will be of importance to

Figure 3. Balanced ischemic and nonischemic etiologies for HF. This middle-aged man with type 2 diabetes experienced an anterior ST segment elevation myocardial infarction (STEMI) with severe LV dysfunction. Dobutamine stress and contrast echocardiography were combined. There was scar in the left anterior descending (LAD) territory, but no augmentation in the posterior circulation (A, loops), despite normal refill on destruction replenishment images using contrast echo (B), signifying preserved perfusion. Contrast-enhanced CMR only showed LAD scar (C). Coronary revascularization was performed, but no functional improvement was detected, suggesting the posterior wall dysfunction was of nonischemic etiology.
allow ICD therapy in patients with moderate LV dysfunction (30% to 40% LVEF) based on individual risk profiles.

**Evaluation Before Cardiac Resynchronization Therapy**

The selection of patients for cardiac resynchronization therapy (CRT) is currently based on the presence of LV dysfunction, ongoing functional limitation despite optimal medical therapy, and electric evidence of dyssynchrony. Nonetheless, the evaluation of CRT candidates is likely to remain a potential growth area for imaging. The goals of imaging are listed in the Table. Although much recent controversy has focused on the assessment of mechanical synchrony, some of the other listed aspects seem more likely to be incorporated into the guidelines.

With the exception of the use of markers of interventricular dyssynchrony in CRT candidates with intermediate QRS duration, the Cardiac Resynchronization in Heart Failure Study and major trials (and therefore current guidelines) have not included mechanical indices of dyssynchrony in the selection criteria for CRT. The current evidence base does not favor the use of markers of mechanical dyssynchrony in most treatment decisions. First, although the frequency of nonresponse is cited as 30% to 40%, it remains controversial about how best to define this. Is the patient with symptomatic improvement but without reverse remodeling a “responder” (even if the effect is a placebo effect) or a “nonresponder”? The distinction of responder and nonresponder is unfamiliar in HF care, even though it may be implicit in high-cost management decisions for other conditions and will likely be required if device costs for the epidemic of HF are to be controlled. Second, the use of imaging criteria for synchrony assumes that either patients not already captured by...
current criteria will become eligible for CRT. Despite favorable single-center reports, trials of CRT in narrow QRS HF with mechanical dyssynchrony have been disappointing. Conversely, as CRT has been shown to provide a survival benefit, decisions to avoid CRT in wide-QRS HF would need techniques with a high sensitivity for the definition of mechanical dyssynchrony to minimize the number of patients inappropriately declined. As few imaging techniques have a sensitivity >90%,32 ≥10% of patients who could experience benefit would be denied potential prognostically beneficial therapy if imaging tests were used in patient selection. Finally, the recent Predictors of Response to CRT trial emphasized the predictive value of echocardiographic parameters for a 15% reduction of end-systolic volume or improvement in a clinical score to be modest, and large intra- and interobserver variations of tissue Doppler parameters were documented (10% to 15% and >30%, respectively). These results contrast strongly with the results of previous single-center studies and reflect the contributions of special expertise that is difficult to replicate at other sites, publication bias, and the technical problems of using parameters that have a relatively poor signal-to-noise ratio (Figure 6).

New markers of dyssynchrony allow this to be assessed in the short axis, and this may be more reliable than long-axis synchrony. Speckle-based strain allows the assessment of short-axis function and is also more robust than the Doppler markers. New CMR acquisitions may allow better temporal resolution than standard CMR and may incorporate considerations regarding not only timing but also LV function. Alternative imaging strategies (including gated blood-pool imaging, perfusion single-photon emission CT, and CT) may assess asynchrony, regional tissue viability, and ventricular geometry by a single test providing a combination of criteria for patient selection and lead placement. However, the ability

Table 1. Imaging Solutions to Clinical Questions Regarding Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Technique</th>
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<tbody>
<tr>
<td>Is the EF truly &lt;35%?</td>
<td>Limitations of 2D echocardiography close to cutoff Consider 3D echocardiography or CMR</td>
</tr>
<tr>
<td>Is there viability?</td>
<td>CRT response unlikely if site of lateral wall pacing is infarcted or there is extensive scar</td>
</tr>
<tr>
<td>Is there dyssynchrony?</td>
<td>Optimal technique remains undefined—insufficient evidence to use reported methods to withhold CRT in wide QRS heart failure without mechanical dyssynchrony or apply it in narrow QRS heart failure with dyssynchrony</td>
</tr>
<tr>
<td>Is there a suitable target vein? Does it correlate with the site of maximal delay?</td>
<td>Single-center studies have supported the observation of better outcomes when pacing site is concordant with site of maximal delay, although optimal technique is undefined</td>
</tr>
<tr>
<td>What follow-up?</td>
<td>Majority of efficacy studies have incorporated optimization of atrioventricular delay, although this is often neglected in practice</td>
</tr>
</tbody>
</table>

Figure 6. Limitations of tissue velocity imaging for the assessment of LV synchrony. Spatial variation in the velocity profile may cause confusion as to the optimal measurement location (A). Tracking of passive movement may lead to apparent dyssynchrony that is not confirmed using deformation imaging (B).
of the temporal resolution of these methods to identify the 50- to 60-ms delays that may constitute significant mechanical dyssynchrony may only allow identification of more marked delays.

The future role of mechanical evaluation of synchrony is unclear. Clearly, more reliable parameters are needed if it is to be used to select patients with a broad QRS (>150 ms), and trial evidence will be needed for it to be applied to QRS <120 ms. However, if a single, robust parameter is defined, it may have something to offer in patients with QRS duration 120 to 150 ms.

Assessment and Monitoring of Cell Therapy
Imaging seems uniquely suited to accompany the translation of cell therapy from preclinical models to clinical application. Despite some promising results in small clinical trials, many questions remain regarding optimal cell type, dosage of cells, and route of delivery after acute myocardial injury. Established imaging procedures have been used to assess changes of global and regional function, perfusion defect size, tissue viability, and contractile reserve as surrogate markers of therapy success. Because the observed changes in the treated subjects were relatively small (EF changes of 5% to 15%) and also occurred in the control groups, the results were often of questionable significance. Quantitative analysis of imaging data has to be further improved to apply these techniques as study end points. Currently, MRI and nuclear imaging seem most appropriate for the provision of robust and reproducible measurements.

Besides documenting the clinical effect of cell therapy, imaging may provide a mechanistic understanding of variations in the success rate. Prelabeling of cells with iron particles or long lineal isotopes allows migration and survival studies after cell injection. However, these depend on the sensitivity and resolution of the imaging approach because of the small number of cells retained in the target tissue. Survival and differentiation of cells can be studied in the animal laboratory, using reporter gene imaging using nuclear or optical probes, but these techniques cannot be translated into the clinical environment because of safety and regulatory restrictions. Again, multimodality approaches may be most attractive for clinical research combining high-resolution morphological data with cell-specific molecular signals defining the cell differentiation process. Cell therapy represents a treatment strategy that requires in vivo imaging as means to optimize technique and protocols as well as to understand the mechanism of observed effects. Imaging is likely to become an integral part of this therapy, starting from evidence for local delivery, monitoring of survival and differentiation, and understanding the hemodynamic consequences.

Evaluation Before Cardiac Surgery
If imaging before cardiac transplantation and circulatory support are considered a separate topic, the main indications for imaging before surgery in HF relate to LV reduction procedures and interventions for functional MR. These problems are linked by disturbances of LV shape. Accordingly, 3D methods are optimal for LV evaluation, and CMR has been used to plan LV reduction procedures. Likewise, LV geometry should be considered in the management of functional MR, the management of which remains controversial. Both quantitation of MR and a complete understanding of MR mechanism are required for valve interventions, and the evidence is strongest for the management of ischemic MR in combination with coronary revascularization.

The right ventricle is an important determinant of survival and treatment response in LV dysfunction, and right ventricular assessment is an important component of the evaluation in all of these situations. As discussed in the first part of this review, 3D strategies and quantitative methods for assessing right ventricular deformation will likely play a role.

Office Management and Sequential Imaging
Current Status
There is little justification for repeat imaging in stable patients with HF. However, if information from imaging were shown to alter management, echocardiography would be the logical technique to deliver this to the outpatient office, as this technique has benefited from the revolution in computing, which has brought increasing processing power and increasing miniaturization.

The problem is that the reliability of sequential imaging is poor. Some variation is due to physiological variations from day to day, but in addition, technical issues include obtaining images at different parts of the respiratory cycle, beat-to-beat variation, acquisition at inappropriate depth, and especially foreshortening and LV geometry. The coefficient of variation for 2D EF is 15%, such that the smallest change of EF that can be recognized with 2D echocardiography is 11%. The test-retest variability of volumes varies between 11% for end-diastolic and 15% for end-systolic volume. Similarly, the smallest change of LV mass that can be detected with 95% confidence is 59 g, rather larger than the 20- to 40-g change in a year on antihypertensive therapy. The use of 3D techniques is much more reliable for sequential measurement, but they are less amenable to sequential measurement in the physician’s office. Although miniaturized echocardiography machines do not yet support 3D imaging, they do offer newer measures such as tissue Doppler imaging and LA volumes. Unfortunately, these are subject to as much, if not more, variation as 2D imaging.

Future Applications
Volume Control
There is some evidence that functional parameters can be used to predict the outcome of patients under management for HF. For example, the persistence of a restrictive filling pattern despite medical therapy identifies a group at high risk of adverse outcome. Likewise, failure to control volume overload has been associated with early readmission. The missing link has been to show that this finding can be used to drive alterations in management that will alter the course of the patient. Some investigators have proposed that titration of medical therapy with type B natriuretic peptide can reduce admissions and complications, but there is considerable random variation of type B natriuretic peptide that may make this unsuitable.
LV Remodeling

Changes of LV volume, infarct surface area, infarct-subtended volume, and wall curvature and stress could provide valuable information to guide management. In a meta-analysis of 72 randomized controlled trials, involving >6000 patients in whom ejection fraction and volumes were assessed an average of 6 months after some kind of intervention for HF, therapies with a survival benefit (eg, angiotensin-converting enzyme inhibitors, β-blockers) showed short-term favorable effects on ejection fraction and volumes. In contrast, drugs with neutral or unfavorable effects on survival showed no such changes. 47 Similarly, in the Survival and Ventricular Enlargement trial, patients who had no cardiovascular events had a minor change of LV volume over 1 year, particularly if they were on treatment, whereas those who had events showed LV enlargement. It seems plausible that a favorable change of ejection fraction and volume early after treatment is a marker of subsequent survival. With the advent of drugs targeting molecular processes, new imaging probes will be necessary to visualize the targets and to monitor changes under therapy. Angiogenesis is one target, which has been addressed in ischemic HF, and imaging probes will become available through molecular imaging.

Conclusions

The great German philosopher Arthur Schopenhauer believed that the most common folly of humans was to lose track of their original intent. This tendency is writ large in the approach to cardiac imaging in HF. Although echocardiography is the appropriate initial test, subsequent investigations need to be tailored to specific clinical questions, which will vary from case to case. Given the increasing frequency of HF, inappropriate selections readily translate into significant inappropriate costs. Exciting new techniques, including CMR, CT angiography, and targeted nuclear and echocardiographic techniques come at a time of unprecedented growth in healthcare expenditure, with imaging being a major contributor. In selecting the sequence of imaging investigations, constant attention should focus on how the new techniques can be used to reduce disease burden, cost, or both. Indeed, the use of imaging in HF may control costs related to treatment and device selection, dose titration, and avoidance of decompensation, leading to individualized, risk-adapted patient management.

Besides these clinical benefits, new imaging technologies will change cardiovascular research by providing unique tools to quantitatively study the disease process in animal models and humans. This will not only improve our understanding of the disease process but will also accelerate the evaluation of new drugs and their availability to patients.

Disclosures

Dr Marwick’s research group has collaborative research projects with GE Medical Systems, Siemens, Philips, and Lantheus Medical Imaging.

Sources of Funding

This work was supported in part by a Centres of Clinical Research Excellence Award from the National Health and Medical Research Council of Australia (Canberra, Australia).

References


Key Words: diagnosis, heart failure, imaging
The Future of Cardiovascular Imaging in the Diagnosis and Management of Heart Failure, Part 2: Clinical Applications
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Circ Cardiovasc Imaging, 2008;1:162-170
doi: 10.1161/CIRCIMAGING.108.811109

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