Imaging in patients with advanced therapies for heart failure

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“We are all hungry and thirsty for concrete images.” -Salvador Dali

Although the number of heart transplants performed in North America has been relatively stable over the last decade, median survival has steadily improved, according to the ISHLT Transplant Registry.¹ Likewise, the number of continuous flow left ventricular assist devices (LVADs) implanted each year in the United States has more than quintupled in 5 years, reaching a total of 2,420 implanted in 2013, according to the Sixth INTERMACS annual report.² The number of heart failure patients therefore is growing considerably, and so is the prevalence of the advanced therapies which require close and continuous monitoring and management.

In this issue of the Journal, Gupta et al³ have provided a broad and comprehensive yet succinct survey of the most recent literature describing multiple imaging modalities as they relate to the transplant and LVAD populations. Although imaging choice tends to lean heavily on what techniques are available or on institutional expertise, it is important to stay informed of the status and developments in other imaging modalities as research and patient care progresses at an unparalleled rate.

Transplant recipients face certain challenges related to the therapeutic window wherein the degree of immunosuppression to suppress rejection must be balanced with the short-term risk for infection and long-term risk for malignancy, each of which are represented in the leading causes of death in this population.¹ Monitoring the function of the transplanted heart is most easily done with standard echocardiography techniques. Gupta et al³ also touch on cardiac magnetic resonance (CMR), which can provide additional information that echo cannot accurately determine, such as presence of myocardial scar and right ventricular end diastolic volume index, which appear to be independent predictors of cardiovascular outcomes.⁴

Cardiac allograft vasculopathy is another significant cause of morbidity and mortality in post-transplant patients that has led to needed, and often impressive, investigation into the accurate and early detection of this potentially reversible condition. The current gold standard, invasive coronary angiography, has limitations related to the nature of the disease. Allograft vasculopathy and coronary atherosclerosis are distinct entities, the former thought to be driven by, among other things, non-self major histocompatibility complexes, e.g. HLA-DR, and the failure of outward remodeling as compensation for neointimal hyperplasia due to expansion of vascular smooth muscle cells.⁵ Allograft vasculopathy is diffuse, involving large epicardial and smaller intramyocardial arteries, and its course is unpredictable, and often clinically silent due to denervation.⁶ Approximately 10% of patients die in the 12 months following a diagnosis of cardiac allograft vasculopathy.¹ Yet, there are available therapies such as pharmacologic inhibition/modulation of cellular proliferative signaling, which have been associated with reduced incidence and slower progression⁶; thus the need for early and accurate detection is paramount. Invasive catheter-based conventional coronary angiography has long been the

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standard modality for assessment of allograft vasculopathy, but the addition of newer methods may hold promise for its early diagnosis. Adding intravascular ultrasound (IVUS) to invasive coronary angiography improves its detection rate considerably by providing additional information about maximal intimal wall thickness, of which an increase of at least 0.5 mm within the first year post-transplant has been associated with poor cardiovascular outcomes.^{6,7} Optical coherence tomography (OCT), a newer invasive catheter-based imaging modality, not only appears to correlate well with IVUS with regard to intimal wall thickness measurements, but can also provide better plaque characterization due to its higher image resolution.⁸ Beyond these catheter-based techniques, new noninvasive modalities offer the potential to accomplish this diagnosis in the earliest phases. In a meta-analysis covered in Gupta et al's article,³ coronary CT angiography offered excellent specificity and negative predictive value for the detection of vasculopathy compared to invasive coronary angiography as the gold standard.⁶ In addition to a robust appraisal of coronary CT angiography, Gupta et al's article provides a thorough and broad review of myocardial perfusion imaging with established perfusion techniques of SPECT and contrast-enhanced dobutamine stress echocardiography.³

An area not as extensively covered by Gupta et al³ includes the use of PET imaging, which offers another means of quantifying absolute myocardial perfusion to assess post-transplant patients for allograft

vasculopathy. In particular, in an interesting study by McArdle et al, relative perfusion defects, mean myocardial flow reserve, and mean stress myocardial blood flow on dipyridamole rubidium-82 PET imaging were all significant predictors of adverse outcomes, though no comparison was made to invasive coronary angiography or IVUS.⁹

CMR has intrinsic advantages for cardiovascular imaging and functional measurements, since it offers a means of quantifying absolute myocardial perfusion and vascular flow, in addition to being the most accurate and comprehensive tool for assessment of cardiac volumes and anatomy. Despite these attractive features, the application of CMR to the study of post-transplant patients has been rather limited. In Gupta et al's article,³ they report on a recent study on CMR myocardial perfusion reserve which outperformed coronary angiography in the detection of moderate and severe cardiac allograft vasculopathy.¹⁰ Furthermore, in the investigational setting, CMR offers the ability to determine myocardial energetics through MR spectroscopy, although in vivo CMR studies employing Phosphorus-31 NMR spectroscopy to assess myocardial high-energy phosphate energetics have not shown consistent ability to predict rejection.¹¹ Despite all this promise, the noninvasive assessment of acute allograft rejection can be summed up, to date, as inconsistent and in need of further study before endomyocardial biopsy is supplanted as the gold standard.

Table 1. Echocardiography in patients with heart transplant or LVAD

Useful in diagnosis or assessment of
Dysfunction of the native or transplanted heart (i.e. valvular or right ventricular pathology)
Intracardiac shunting
Malposition of inflow or outflow cannula
Intracardiac thrombus
Septal position and left ventricular loading abnormalities
Hematoma
Pericardial effusion and tamponade
Inflow cannulae velocity abnormalities
Outflow graft distortion
Native aortic valve disease and opening
Myocardial recovery
Noninvasive pulmonary pressure assessment
Cardiac output generated by device and left ventricle
Disadvantages
Reverberation signals
Linear artifacts, blind spots
Body habitus and device-limiting acoustic windows
ICU equipment can interfere with image acquisition in early post-op period
Difficulty assessing degree of aortic regurgitation
Difficulty visualizing left ventricular apex, and right ventricular function in early post-op period

Table 2. Cardiac CT in patients with heart transplant or LVAD

Useful in diagnosis or assessment of
Driveline position
Pericardial effusion
Hematoma
Abscess
Neointimal hyperplasia/stenosis of the outflow cannula
Cardiac output (with dynamic CT angiography)
Vasculopathy and intimal thickness (coronary CT angiography)
Left and right ventricular function
Septal position and left ventricular loading abnormalities with ECG-gating
Aortic valve opening with ECG-gating
Thrombus within the cannula
Aortic root thrombus
Air bubbles within the cannula (suggestive of infection or suboptimal flushing during implantation)
Disadvantages
Risk of contrast nephropathy
Radiation exposure
Imaging artifacts
Difficulty transporting critically ill patients to CT
Inability to provide specific hemodynamic data

Gupta et al's³ article also covers imaging in patients with LVAD implantation. As more patients are receiving LVADs as destination therapy every year, more patients are experiencing complications such as neurologic events, infection, device malfunction, bleeding, and right heart failure.² Imaging plays a role in the diagnosis of such complications, and guides management. Additionally, it is critical for the optimization of device hemodynamics and in some cases, the evaluation of myocardial recovery. Tables 1 and 2 summarize the particular uses of both echocardiography and CT, as well as the disadvantages that limit their utility in the clinical setting.^{12–14} Gupta et al³ also include a concise section on predicting myocardial recovery of function by ¹²³I-mIBG scintigraphy to evaluate myocardial sympathetic innervation and downregulation of sympathetic receptors, and PET imaging related to myocardial blood flow and related measures. In these areas, it is clear that more studies are needed.

Overall, in their review, Gupta et al³ draw attention to a rapidly growing population of patients living with advanced therapies for heart failure, and the available imaging modalities used to evaluate and help treat them. As their clinicians, we will increasingly rely on a diverse array of imaging modalities for screening, early diagnosis, and monitoring response to different treatment regimens. In the absence of detailed outcome-proven algorithms for the ongoing management of these populations, we have great latitude to tailor the diagnostic test for the individual patient and the question at

hand. While measurements of absolute myocardial blood flow by PET and MRI hold great promise in the early detection and monitoring of cardiac allograft vasculopathy, newer methods in intracoronary imaging including IVUS and OCT and CT angiography offer an increasingly recognized complement to the core gold standard assessments by echocardiography and conventional catheter coronary angiography. Likewise, standard echocardiography and cardiac CT continue to be valuable tools in the ongoing management of patients with LVADs, especially with regard to both device optimization and complications, as well as monitoring native heart function and recovery. CMR, SPECT, and PET methods also have an important role. Invasive and noninvasive imaging could become (and indeed may already be) a factor in improving survival and quality of life in this notoriously ill-fated group.

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