EDITORIAL COMMENT

Heterogeneity of Acute Heart Transplant Rejection Can Be Visualized by Cellular and Functional Cardiac Magnetic Resonance*

Frederick H. Epstein, PhD
Charlottesville, Virginia

In the paper by Wu et al. (1) in this issue of JACC, a novel, two-pronged cardiac magnetic resonance (CMR) approach to imaging acute heart transplant rejection was investigated. The two-pronged approach employed both cellular and functional imaging to examine an animal model of acute rejection. Cellular CMR was performed by labeling macrophages using an intravenous delivery of ultrasmall superparamagnetic iron oxide (USPIO) particles and performing imaging 1 day later to assess macrophage infiltration of the myocardium, where labeled macrophages were seen as regions of reduced signal intensity. The CMR tagging was used for simultaneous functional assessment to quantify regional myocardial strain. Images depicting USPIO-labeled macrophages showed heterogeneous signal loss within the myocardium 1 day after administration in allografts but not in isograft controls. Similarly, myocardial tagging revealed heterogeneous changes in myocardial strain in allografts but showed normal contraction throughout the heart in isograft controls. As the grade of rejection, determined by pathology, increased, the sizes of the regions containing labeled macrophages and the regions of decreased strain increased.

The primary contribution of the article by Wu et al. (1) is the noninvasive in vivo demonstration of the heterogeneity of acute allograft rejection, directly visualized by imaging both macrophage infiltration (Fig. 4 of Wu et al. [1]) as well as myocardial strain (Fig. 5 of Wu et al. [1]). Even when large regions of myocardium did not have evidence of macrophage infiltration or contractile dysfunction, other regions showed marked signal loss on T$_2$*-weighted images, indicating the presence of labeled macrophages, and/or significant contractile dysfunction revealed by myocardial tagging. The heterogeneity of rejection was identified as a likely explanation for why endomyocardial biopsy, the standard clinical method for diagnosing acute rejection, can sometimes be inaccurate. Depending on the particular locations that are sampled, biopsy may or may not indicate rejection, even in the case of severe rejection. Because imaging can cover the entire heart without gaps, limited sampling is not a problem for CMR-based assessment of transplant rejection.

A second important finding of the paper by Wu et al. (1) is that, even though metrics describing global cardiac function, such as stroke volume and ejection fraction, do not discriminate between various grades of acute rejection, the number of regions with compromised strain increased as the grade of rejection increased (Fig. 6 of Wu et al. [1]). In this context, the investigators point out that because rejection does not occur in the spatial regions defined by the coronary territories, the interpretation of these images should not be based on the conventional 17-segment model, but rather using methods that are independent of the coronary architecture. Interestingly, regions with reduced strain correlated with, but did not exactly match, regions of macrophage infiltration. Further work is required to more thoroughly elucidate the relationship between macrophage infiltration and abnormal myocardial strain. Perhaps the 2 measurements reflect different aspects of rejection or perhaps

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

From the University of Virginia Health System, Charlottesville, Virginia. Dr. Epstein receives research support from Siemens Medical Solutions.
there are temporal dependencies to macrophage infiltration and contractile dysfunction that are yet to be explored.

Whether macrophages are the ideal target for cellular imaging of transplant rejection is an interesting question. As Wu et al. (1) discuss, B and T lymphocytes might be thought of as better targets due to their direct role in the rejection and inflammation processes. However, macrophages are quite easy to label in vivo using an intravenous injection of USPIO particles, and they also play their own important role in inflammation, so they certainly are an attractive target. In addition, although it is common to claim that intravenous injection of USPIOs labels macrophages, it is possible that some other cell types may also take up USPIOs and also become labeled. In the future, it would be interesting to learn in more detail about the spectrum of cell labeling and detection in USPIO-enhanced CMR of heart transplantation. Another target for molecular imaging of heart transplant rejection is phosphatidylserine, which is a marker of apoptosis. Indeed, single-photon emission tomography imaging with technetium-99m-labeled annexin-V, a protein that binds to phosphatidylserine with high affinity, has already shown promise for detecting acute rejection in patients who have undergone heart transplantation (2). Similar to the present study by Wu et al. (1), single-photon emission computed tomography imaging in hearts undergoing rejection also demonstrated spatial heterogeneous signal intensity. Due to its higher spatial resolution, CMR may have an advantage compared with single-photon emission computed tomography for detecting heterogeneous transplant rejection, as partial volume effects inherent with lower spatial resolution could obscure focal regions of rejection.

Limitations of the present study include: 1) the high dose of USPIO; 2) use of T2*-weighted imaging instead of quantitative measurement of T2* maps; 3) that gadolinium-enhanced imaging of transplantation (3) was not evaluated; and 4) that the investigators did not use the tagged images to investigate myocardial strain during diastole (4). The USPIO dose appeared to be almost 10-fold greater than a clinical dose of USPIO, although the exact weights of the rats used in this study were not provided, making it difficult to accurately calculate the dose. Thus, the question of whether clinical doses will be similarly successful remains unanswered. The acquisition of quantitative T2* maps, though more time-consuming than T2*-weighted images, might be useful for making studies such as this more reproducible by other labs. Also, as speculated previously in a clinical study (3), gadolinium-enhanced CMR may be sensitive to necrosis found in transplant rejection. The evaluation of gadolinium-enhanced CMR in this rat model might provide greater insight into the potential of this method for detecting fibrosis in transplant rejection. In addition, myocardial strain imaging, which was used to assess systolic function, might detect reduced diastolic function, which may be important in transplant rejection (4).

The methods used in the present study may be applied to human subjects after heart transplantation, perhaps in the near future. Indeed, the initial evaluation of USPIO-enhanced CMR for the assessment of kidney transplantation in humans has recently been published with encouraging preliminary results (5). It is a distinct possibility that the detection of acute heart transplant rejection will emerge as one of the first important clinical applications of cell-labeled CMR.

Reprint requests and correspondence: Dr. Frederick H. Epstein, Associate Professor of Radiology and Biomedical Engineering, University of Virginia Health System, Radiology Research, Room 155, Snyder Building, 480 Ray C. Hunt Drive, Charlottesville, Virginia 22908. E-mail: fredepstein@virginia.edu.

Key Words: cardiac magnetic resonance • noninvasive detection of acute cardiac rejection • cardiac transplantation • biopsy.