We See Only What We Look For
Imaging Cardiac Inflammation

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Myocarditis is responsible for a substantial minority of cases of sudden death and nonischemic dilated cardiomyopathy. In clinical case series of sudden death, myocarditis is often the third leading cause after hypertrophic cardiomyopathy and congenital and atherosclerotic coronary artery disease. In autopsy studies of young adults, myocarditis is responsible for 5% to 20% of sudden deaths. Nine percent to 40% of acute nonischemic cardiomyopathy cases are a result of myocarditis, a rate that varies depending on the histological or clinical diagnostic criteria used. A recent analysis based on hospital discharge International Classification of Diseases, Ninth Revision, codes estimated that between 0.5% and 4% of prevalent heart failure is caused by myocarditis. This value is likely an underestimate because the diagnostic test, endomyocardial biopsy, is not widely performed outside of tertiary care medical centers.

Timely diagnosis of myocarditis can refine estimates of cardiac risk and permit tailored treatment for heart failure. Several studies suggest that more severe myocardial inflammation predicts progression to dilated cardiomyopathy, increased risk of arrhythmias, and chronic heart failure. However, the cost, risks, and lack of availability of endomyocardial biopsy limit its widespread clinical use. For epidemiological studies, diagnostic criteria that rely on clinical syndromes, biomarkers, and imaging abnormalities have been proposed, but these criteria sacrifice diagnostic certainty. There are no clinically available and highly specific biomarkers or imaging tests that identify the histological type or quantify the severity of myocardial inflammation.

Past efforts to diagnose myocarditis noninvasively used various features of myocardial damage related to the inflammatory response. In the late 1980s, antimyosin scintigraphy to detect myocyte necrosis had a high sensitivity but low specificity for myocarditis. Echocardiography established the prognostic significance of left and right ventricular failure but never challenged the histological gold standard. Imaging has been limited in part because most cases of clinical myocarditis have a short duration or minor degree of myocyte damage. Cardiac magnetic resonance imaging using a combination of T2, early T1, and late T1 sequences achieved a sensitivity and specificity of ≈80%, but only in recent-onset cases. Although epicardial and midmyocardial patterns of signal abnormality suggest a postviral myocarditis or nonischemic scar, specific causes and cellular types such as giant-cell or eosinophilic myocarditis cannot be identified by magnetic resonance imaging or even fluoro-D-glucose (18F)–positron emission tomography.

In this issue of Circulation: Cardiovascular Imaging, the study by van Heeswijk et al overcomes previous challenges by demonstrating that intravenous injection of fluorodeoxyglucose (FDG) is taken up by inflammatory cells in the heart and can be detected with 18F PET cardiac magnetic resonance imaging in a male mouse model of autoimmune myocarditis. If this method can be applied successfully to clinical disease, it could allow widespread and earlier detection and a better understanding of the role of inflammation in the development of chronic dilated cardiomyopathy. Interestingly, PFCs were detected only in macrophages, granulocytes, and dendritic cells, not in lymphocytes. Yet, the signal from the PFCs correlated with the severity of myocardial inflammation. Although studies of myocarditis have focused on the role of lymphocytes in disease pathogenesis, and specifically on T-helper responses, the majority of cells present during acute myocarditis in autoimmune and viral animal models of myocarditis are monocyte/macrophages and granulocytes. For this reason, the technique presented by van Heeswijk et al holds particular promise for clinical diagnosis.

Quite a few issues remain to be addressed before 18F imaging will prove clinically useful. In an experimental setting, can PFCs detect inflammation in female mice, which have more lymphocytes, as well as it does in males, which have far more severe inflammation composed primarily of macrophages and granulocytes? Will this method work as well in other strains of mice or differ between patients susceptible or resistant to chronic dilated cardiomyopathy? The BALB/c mice used in these studies are susceptible to develop dilated cardiomyopathy but may accurately model only one type of myocarditis patient. Timing for the injection of PFCs may also be important. Some mouse models of myocarditis are biphasic, with inflammation disappearing quickly after peak inflammation. If this also occurs in patients with myocarditis, the timing of PFC injection may be critical. Ligands that can be detected with cardiac magnetic resonance imaging or positron emission tomography imaging will need to detect inflammation in >1 phase of the disease to be most useful as a diagnostic tool.

Questions that will arise early in the clinical arena include the impact of coexisting conditions such as pericarditis and prior ischemic myocardial damage that may lower the
specificity of 19F imaging for myocarditis. Common clinical 1.5-T or 3-T magnets may have lower spatial resolution for 19F than the 9.4-T research magnet used by van Heeswijk et al. The risks of 19F-PFC exposure in humans are not fully known. Recognizing these hurdles, the promise of a widely applicable and sensitive noninvasive test for myocardial inflammation is exciting and worth the attention of the entire myocarditis research community. We hope that the foundation provided by Heeswijk et al will open the door to an enduring stream of translational and clinical investigations.

Disclosures

None.

References

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