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EDITORIAL COMMENT

Detecting and Targeting Inflammation in Genetic Cardiomyopathies

Are We There Yet?*

Sean P. Pinney, MD,[a] Douglas L. Mann, MD[b]

Cardiomyopathies are disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient by itself to cause the observed phenotype.[1] Within this classification reside dilated cardiomyopathies and arrhythmogenic cardiomyopathies (ACMs), genetically determined myocardial diseases encompassing arrhythmogenic right ventricular cardiomyopathy, left-dominant arrhythmogenic cardiomyopathy, and biventricular ACM. Within families sharing the same pathogenic variant, these inherited disorders can be phenotypically heterogenous. Environmental, infectious, and immune drivers intersect with genetically susceptible individuals to differentially express the phenotype and influence clinical outcomes. This presents a challenge to the clinician when trying to classify patients and, by extension, anticipate and respond to clinical outcomes. When genotype- vs phenotype-based classification schemes have been compared, genotype-based classification was better able than phenotypic ones to predict the risk of sudden cardiac death and major ventricular arrhythmic events.[2] This is especially true for lamin A/C (*LMNA*) populations, who have particularly worrisome outcomes for arrhythmic events, often at lesser degrees of myocardial dysfunction. Unfortunately, because a definitive genetic cause can be identified in fewer than half of the cases of dilated cardiomyopathy and ACM, detecting and classifying cardiomyopathies still relies on phenotypic nosologies.

Over the past decade, the mechanistic pathways describing how the presence of a pathogenic genetic variant can produce cardiac myocyte damage and lead to extensive replacement fibrosis are now better understood. Key to this understanding is the central role played by inflammatory cytokines and inflammatory infiltrates.[3] Whether through strenuous exercise, viral infection, or neurohormonally mediated tissue injury, damaged and necrotic cardiac myocytes release proteins referred to as damage-associated molecular patterns that provoke the release of inflammatory cytokines and chemokines from immune and nonimmune cells, which in turn recruit $CD45^+$ leukocytes, including $CCR2^+$ monocytes and $CD3^+$ T lymphocytes, to the site(s) of tissue damage. These inflammatory cells appear to be particularly abundant during hot phase bursts (HPBs), paroxysms of clinically significant chest pain with troponin release, electrocardiographic changes, and cardiac magnetic resonance (CMR) findings diagnostic for myocarditis. These inflammatory pathways, whether as a result of or putative cause of myocyte injury, represent a potential therapeutic target to abrogate myocyte damage and halt replacement fibrosis. However, currently, no clinical data exist to support the use of immunomodulatory therapy in this context.

In this issue of the *JACC: Basic to Translational Science*, Peretto et al[4] address 3 specific knowledge gaps in terms of our understanding of inherited cardiomyopathies: Can multimodal imaging reliably detect inflammation in patients with genetic cardiomyopathy? Can specific imaging patterns be used to

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From the [a]Zena and Michael A. Wiener Cardiovascular Institute/Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [b]Cardiovascular Division, Department of Medicine, Washington University, St. Louis, Missouri, USA.

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distinguish various underlying genotypes? Can immunomodulatory therapy favorably affect the clinical course of disease? Peretto et al[4] enrolled 25 probands with class 4 or 5 mutations in cardiomyopathic genes who were undergoing multidisciplinary assessment for myocardial inflammation. All patients had endomyocardial biopsy (EMB)-confirmed inflammatory infiltrates consisting of at least 14 leucocytes/mm^2 and 7 or more CD3-positive lymphocytes/mm^2, consistent with the European Society of Cardiology guidelines for diagnosing inflammatory cardiomyopathy in the absence of common cardiotropic viruses in the myocardium.[5] Most underwent CMR (24 of 25) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (15 of 25). Patients were followed every 3 to 6 months and assessed for clinical events consisting of cardiac death, transplantation, HPB, severe left ventricular systolic dysfunction, and major ventricular arrhythmic events including sudden cardiac death, ventricular tachycardia, or an appropriate implantable cardioverter-defibrillator shock. After excluding the presence of intramyocardial viral genomes, 18 patients were treated with immunosuppressant medications, including various combinations of prednisone, mycophenolate mofetil, azathioprine, and anakinra.

The patients were clustered based on the identified pathogenic or likely pathogenic gene variants: 12 (48%) desmosomal, 10 (40%) cytoskeletal, and 3 (12%) others including *LMNA*, sodium voltage-gated channel alpha subunit (*SCN5A*), and potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*). Clinically, they presented with chest pain (n = 9), acute heart failure (n = 4), or ventricular arrhythmias (n = 12). All had lymphocytic inflammatory infiltrates seen on EMB with a low prevalence of necrosis but widespread replacement fibrosis. Myocardial inflammation was detected in 92% of patients undergoing CMR and 53% undergoing FDG-PET. Patients with desmosomal gene variants uniformly presented with myocarditis-like chest pain and arrhythmias, whereas those with cytoskeletal gene variants were more likely to present with a dilated cardiomyopathy phenotype with both higher levels of natriuretic peptides and worse NYHA functional class. A ring-like pattern on CMR with gadolinium contrast was frequently seen with desmoplakin (*DSP*) or filamin C (*FLNC*) sequence variations and was not present in others. The combination of a dilated cardiomyopathy and absence of a ring-like pattern helped to identify those with titin (*TTN*) sequence variations.

None of the 25 patients died over a median follow-up of 71 months. Major ventricular arrhythmias were twice as common in patients with desmosomal variants vs all others (50% vs 23%). In addition to receiving guideline-directed medical therapy, 18 patients received immunomodulatory treatment. This appeared to be associated with less frequent HPBs, nonsustained ventricular tachycardia, and more favorable ventricular remodeling. At last follow-up, myocardial inflammation was less commonly seen in treated vs untreated patients (33% vs 57%). Incidentally, this study was the first to show CMR-, FDG-PET- and EMB-proven inflammation in *LMNA* cardiomyopathy, albeit in only 1 proband. These findings add to the growing body of evidence implicating *LMNA* sequence variations as being associated with inflammation and adverse arrhythmic events.

This study is unique in many ways. It is the first to study a uniform cohort of patients with genetic cardiomyopathies and EMB-proven inflammation. It demonstrates the ability of multimodal imaging to detect inflammation in the vast majority of cases, and it uses specific late gadolinium enhancement patterns to discriminate between gene variants. Finally, it suggests that targeted immunomodulatory treatment may favorably alter myocardial and electrical remodeling, leading to better clinical outcomes—or at least forestalling adverse outcomes. Taken together, Peretto et al[4] present important evidence that multimodal imaging can be used to detect, classify, and guide treatment for inherited cardiomyopathies.

However, the study has several notable limitations that warrant discussion. This was a small patient population (n = 25) enrolled over a reasonably long period of time (13 years) that accounted for a limited number of genetic variations. There was no clear guidance as to the choice or timing of the administration of immunosuppressive therapy. Most importantly, there was no control group to allow comparisons regarding the true impact of targeting and treating inflammation, which has been a major problem that has plagued the interpretation of studies that have used immunosuppression to treat nonviral inflammatory cardiomyopathies. One-third of patients on immunosuppressive therapy had residual inflammation at last follow-up. Without an appropriate control group, it is difficult to know what the expected prevalence of residual inflammation was in the absence of immunosuppressive therapy. Furthermore, because all patients were symptomatic at the time of their initial evaluation, one might reasonably assume that the sensitivity of EMB and multimodal imaging to detect inflammation would be

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higher than during the interceding periods of quiescence.

Although Peretto et al[4] should be congratulated for shedding light on the potential pathogenetic role of inflammation in genetic cardiomyopathies as well as the ability to detect inflammation noninvasively, their work raises many questions. Does the absence of inflammation on multimodal imaging exclude the presence of a clinically significant inflammatory infiltrate? Can imaging be used to detect subclinical inflammation, or should it be symptom limited? Should first-degree relatives of affected probands be screened and, in the absence of symptoms, at what frequency? How well does treatment with immunosuppressive treatment track with resolution of inflammation? Importantly, does treatment favorably affect survival and other clinical outcomes? Should the immunosuppressive treatment target be expanded to include specific cytokines (eg, interleukin 1 antagonism with anakinra or canakinumab) or signaling pathways (eg, prednisone and nuclear factor κ B)?[6] Further studies are warranted to address these important questions.

Placed into the context of the current paradigm for treating genetic cardiomyopathies, the findings by Peretto et al[4] in this issue of the *JACC: Basic to Translational Science* provide important insights into the pathogenesis of inherited cardiomyopathies by highlighting the role of inflammation as a mediator of disease progression. Additionally, these studies also offer the promise of using multimodal imaging to detect, classify, and perhaps even guide treatment for these lethal cardiomyopathies. Nonetheless, given the small numbers of patients and the heterogeneity of the inherited cardiomyopathies that were studied, as well as the absence of a control group of comparable patients who were not treated with immunosuppressive therapies, these results are best thought of as provisional and exploratory. That said, this study does raise the intriguing possibility that inflammation may represent a novel adjunctive target for treating a unique group of cardiomyopathies that we do not have good treatment options for today.

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ADDRESS FOR CORRESPONDENCE: Dr Sean P. Pinney, Division of Cardiology, Mount Sinai Morningside, 440 West 114th Street, New York, New York 10025, USA. E-mail: sean.pinney@mountsinai.org.

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