It’s Never Too Early to Look
Subclinical Disease in Sarcomeric Dilated Cardiomyopathy

Jil C. Tardiff, MD, PhD

The observation that ≈30% of nonischemic dilated cardiomyopathy (DCM) is genetic in origin represents one of the most important advances in modern cardiology and has transformed our view of this common disorder.1 Equally surprising is the more recent finding that sarcomeric genes previously linked to the development of hypertrophic cardiomyopathy (HCM) were also causative in the pathogenesis of DCM.2 Mutations in most of the protein components of the cardiac sarcomere have now been linked to DCM, many of them arising in close proximity to known HCM mutations, and provide a unique challenge: how can such divergent patterns of ventricular remodeling arise from such closely related structural changes? Although it may appear to be straightforward that discrete alterations in sarcomeric function caused by gene mutations could eventually lead to either left ventricular (LV) dilation or hypertrophy, our lack of understanding regarding the earliest clinical stages of DCM before the effects of secondary changes are manifest have precluded mechanistic insight. In this issue of Circulation Genetics, Lakdawala et al used a unique and well-characterized sarcomeric DCM cohort to directly determine whether abnormal systolic function can be detected in genotype-positive patients with normal LV ejection fraction and size. Their robust approach, including determination of echo strain and systolic myocardial tissue velocity and comparisons among subclinical DCM, overt DCM, and control (genotype-negative) family members across 4 independent mutation groups, revealed a significant decrease in systolic function in the subclinical group. These results complement their previous findings that gene mutations linked to HCM cause diastolic dysfunction in subclinical cohorts and fully establish that the primary mechanisms driving diverse ventricular remodeling in sarcomeric cardiomyopathies are tightly coupled to the underlying changes in sarcomere dynamics.3

Since the publication of the first linkage studies in 1990, >1000 mutations in genes encoding the protein components of the cardiac sarcomere have been associated with the development of cardiomyopathic remodeling.3 Although the disorder is unique in that the overall structure and function of the affected proteins are well established, this extensive biophysical understanding has not yet translated to patient care, and the lack of genotype–phenotype correlation has hindered the use of genotype to predict prognosis and direct clinical management. Indeed, due in part to the characteristic phenotypic heterogeneity in patients with sarcomeric cardiomyopathies, it has been suggested that the goal of genotype-driven patient management may not be attained.4 Two major observations have refocused efforts to establish robust genotype–phenotype relationships in HCM and DCM. First, the biophysical basis of the clinical disorder was established by the overall concordance among the in vitro studies in identifying precise alterations in sarcomeric function coupled to the persistent finding in animal models that contractile dysfunction preceded histopathology. Second, longitudinal studies of genotyped cohorts have begun to establish the progressive nature of the ventricular remodeling caused by sarcomeric mutations.5,6 These findings mirrored those in animal models, where initial abnormalities in sarcomeric function led to activation of multiple downstream myocardial signaling pathways that drove cardiac remodeling. The latter observation is similar to the difficulties in determining the cause in patients with congestive heart failure; in that end-stage, remodeled tissue is temporally removed from the initial pathogenic process. Thus, to mechanistically couple a primary biophysical abnormality to a specific pattern of ventricular remodeling, it is imperative to identify and study the earliest stages of cardiomyopathy, exactly the approach taken in the current study.

To directly address this central question, the authors have assembled a unique clinical cohort drawn from 5 independent families carrying mutations in 3 sarcomeric proteins previously linked to DCM (MYH7, TMP1, and TNNT2). Although the statistical power was insufficient to elucidate mutation-specific information and the reliance on families for recruitment may limit the ability to address some questions raised by the data (eg, the intriguing sex differences), the multigenerational cohort yielded 3 well-defined groups for study. The main subgroup (subclinical DCM) was composed of 12 genotype-positive patients with baseline clinical and standard echo parameters largely indistinguishable from genotype-negative controls, including normal LV size and ejection fraction. Of note, many of these parameters exhibited clear differences compared with the genotype-positive subgroup with overt DCM. Application of more sensitive global systolic echo methodologies, including tissue Doppler and strain imaging, revealed striking differences in nearly all indices within the subclinical group compared with controls. As noted by the authors, the decreases in global peak systolic myocardial tissue velocity, longitudinal peak systolic strain, and strain rates all remained significant after controlling for LV geometry and ejection fraction. Although

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Departments of Medicine, Sarver Heart Center and Cellular and Molecular Medicine, University of Arizona, Tucson, AZ. Correspondence to Jil C. Tardiff, MD, PhD, University of Arizona, 1656, East Mabel St, MRB 312, MS 245217, Tucson, AZ 85724. E-mail jtardiff@email.arizona.edu


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Circ Cardiovasc Genet is available at http://circgenetics.ahajournals.org

DOI: 10.1161/CIRCGENETICS.112.964817
subsequent tests for the predictive power of these indices to differentiate genotype-positive from genotype-negative individuals again revealed significant differences, the aggregate data did not support the use of these metrics for driving clinical management. This limitation does not, however, diminish the potential use of these indices for longitudinal study of disease progression, a clear future step. Finally, application of these approaches to a previously published preclinical HCM cohort did not reveal systolic dysfunction in any measured parameter, whereas diastolic indices were preserved in the subclinical DCM group. Thus, in the context of largely preserved LV geometry, the earliest stages of sarcomeric DCM and HCM are distinguishable, and indeed can be defined by, the degree of impairment in high-resolution systolic and diastolic indices, respectively. This robust coupling between cardiac dysfunction in early disease states and the eventual clinical phenotype is not only clinically relevant, it again reinforces the importance of elucidating the primary biophysical mechanisms whereby individual mutations cause these precise pathophysiological responses in cardiac muscle.

Given the relatively small size of the subclinical DCM group, the authors were reasonably circumspect in the extrapolation of their results to the broader questions of genotype–phenotype correlation and eventual patient management in genetic cardiomyopathies. Nonetheless, the current study raises important questions that will spur both basic and clinical investigations. As noted in an extensive recent review by Moore et al., HCM-linked myosin mutations tend to enhance contractility, whereas the DCM-linked subset decrease contractile function. Although biophysical data are limited (especially for the myosin motor mutations, where the challenge of exogenously expressing myosin is a significant limitation), the mutations studied in the current report generally fit within the framework of elucidating the primary biophysical mechanisms whereby individual mutations cause these precise pathophysiological responses in cardiac muscle.

Analysis of molecular motor defects before overt histopathology, mirroring the clinical DCM phenotype, but also deficits in contractile function were both cases, homozygous animals not only recapitulated the phenotype correlation and eventual patient management in genetic cardiomyopathies. Nonetheless, the current study approaches to a previously published preclinical HCM cohort did not reveal systolic dysfunction in any measured parameter, whereas diastolic indices were preserved in the subclinical DCM group. Thus, in the context of largely preserved LV geometry, the earliest stages of sarcomeric DCM and HCM are distinguishable, and indeed can be defined by, the degree of impairment in high-resolution systolic and diastolic indices, respectively. This robust coupling between cardiac dysfunction in early disease states and the eventual clinical phenotype is not only clinically relevant, it again reinforces the importance of elucidating the primary biophysical mechanisms whereby individual mutations cause these precise pathophysiological responses in cardiac muscle.

From the standpoint of sarcomeric dynamics, structure, and function, the varied functional roles of the 4 independent protein mutations are intriguing. Why would 4 such disparate mutations cause such a similar clinical phenotype? All 4 mutations are located within highly conserved regions of the affected proteins (Figure). The MYH7 mutations S532P and A893V occur in the globular N-terminal domain of the myosin motor. Specifically, the S532P mutation is within the actin–myosin interface, whereas the A893V mutation is immediately distal to the regulatory light chain–binding domain in close proximity to the transition between the neck and hinge. Although no biophysical studies have been performed on the A893V mutation, this unique linker region of the motor is thought to, in part, modulate intermolecular interactions between the 2 myosin molecules. Either of these domains could thus alter motor efficiency. Comparing the effects of either mutation on predicted secondary structure using the PSIPRED algorithm reveals potentially significant effects on local structure (Figure). At residue 532 in the actin-binding domain, the substitution of the nonpolar Phe residue for Ser is predicted to decrease the overall helical character of the region and lengthen the linker domain. The relatively conservative Ala to Val substitution at residue 893 also significantly decreases the helical nature of the region, in this case, appearing to favor a structure more consistent with a β-sheet. Either of these structural changes would be predicted to alter both local and distant inter- and intramolecular protein interactions and contribute to a decrease in motor efficiency. Computational modeling of protein dynamics would provide additional mechanistic detail.

Like all benchmark translational studies, the current work raises the bar and generates a new framework for future studies on both the biophysical and clinical sides of the genetic cardiomyopathy divide. The early onset of systolic dysfunction in the preclinical DCM cohort both establishes the primary role of the biophysical changes in sarcomeric function that determines disease onset and lends further
support to the emerging consensus that deficits in contractile function drive the development of DCM. Although at present the high-resolution echo techniques used in the current study are not sufficiently predictive to be used to identify relatives at risk, it is likely to change as larger patient cohorts are obtained. This latter point is key, because this study illustrates the way forward for future work, with a focus on genotyped, multigenerational cohorts and careful longitudinal characterization of clinical phenotypes from the earliest stages of disease. The techniques described here will clearly be useful in following the progression of the cardiac dysfunction, a crucial next step in developing a more robust understanding of the natural history of HCM and DCM. The demonstration that diverse protein mutations can cause similar patterns of early ventricular remodeling will help focus efforts to develop more functionally driven molecular studies where the structural and dynamic effects on single proteins can be better integrated into multiprotein in silico and in vitro approaches and finally provide insight as to how mutations in proteins of the cardiac sarcomere cause distinct patterns of ventricular remodeling. The eventual results will be fully translational in that they will identify unique points of therapeutic intervention and move us closer to the goal of using genotype to inform clinical management in this not uncommon disorder.

**Sources of Funding**

This work is supported by grants from the National Institutes of Health (5R01HL107046-02, 5R01HL075619-8) and the Children’s Cardiomyopathy Foundation. Dr Tardiff is also supported by the Sarver Heart Center’s Gootter Chair for the Prevention of Sudden Cardiac Death.

**Disclosures**

None.
References


Key Words: Editorials • sarcomeric cardiomyopathies • computational modeling • contractile function • genetic dilated cardiomyopathy • sarcomeric structure
It's Never Too Early to Look: Subclinical Disease in Sarcomeric Dilated Cardiomyopathy
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*Circ Cardiovasc Genet.* 2012;5:483-486
doi: 10.1161/CIRCGENETICS.112.964817
*Circulation: Cardiovascular Genetics* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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