Editorial

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

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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 divergent ventricular remodeling in sarcomeric cardiomyopathies are tightly coupled to the underlying changes in sarcomere dynamics.3

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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 myocellular 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, TMAP1, 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
subsequent tests for the predictive power of these indices to
differentiate genotype-positive from genotype-negative in-
dividuals 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,
while 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 extrap-
olation 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.,6 HCM-linked myosin mutations tend to enhance
contractility, whereas the DCM-linked subset decrease con-
tractile function. Although biophysical data are limited (espe-
cially 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
this paradigm. Both the S532P myosin and del210K cardiac
Troponin T mutations have been modeled in mice, and, in
both cases, homozygous animals not only recapitulated the
DCM phenotype, but also deficits in contractile function were
detected before overt histopathology, mirroring the clinical
findings in the current study.6,9 Analysis of molecular motor
function for the S532P myosin isolated from homozygous ani-
mals revealed significant decreases in actin sliding velocity
and ATPase activity, in direct contrast to previous results from
the HCM-linked R403Q myosin mice.10 The combination of
the accumulating evidence from animal models and in vitro
studies provides strong support for the hypothesis that HCM
and DCM mutations cause differential disease states via pre-
cise (and opposite) modulation of sarcomeric efficiency. The
link between these changes, however, and the diverse ventric-
ular remodeling patterns remains unclear.

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.11 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.12 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)13 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.14 Although it is relatively straightforward to envision
the role of structural changes in myosin as a cause of altered
motor function, the molecular effects of the thin filament
mutations TMP1 D230N and TNNT2 del210K are less clear.
The regulatory thin filament directly determines the access
of actin and myosin, in part by allosterically modulating the
position of tropomyosin in response to calcium binding to
cardiac troponin C. Until recently, the complexity of the
protein–protein interactions within the complex and the
lack of high-resolution structure for the N-terminal domain
of cardiac troponin T have complicated disease insight for
thin filament mutations. Transgenic mouse models of HCM-
linked cardiac troponin T mutations have demonstrated both
significantly altered energetics and inefficient ATP use that
can be partially rescued by genetically switching the myosin
isoform in vivo.15,16 These results support a direct role for the
troponin complex in modulating cross-bridge dynamics
that may, in part, explain how thin filament mutations can
cause similar clinical phenotypes compared with thick
filament mutations. Interestingly, the local structural and
functional effects are likely to be different than the myosin
mutations, although both the TMP1 and TNNT2 mutations in
the current study also occur in highly helical domains. This
is illustrated in the secondary structure predictions (Figure),
where no change in helical character is observed for either
mutation. Depending on the position of the mutated residue
within the helical array (eg, D230N faces away from the
inner coiled-coil structure), the effects of the mutations are
likely to influence protein–protein interactions within the
complex via changes in electrostatics and flexibility. Again,
molecular dynamics will be a useful approach in determining
the molecular mechanisms.

Like all benchmark translational studies, the current work
both 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.

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None.
References


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