Familial Hypertrophic Cardiomyopathy
Is the Frank–Starling Law Kaput?

Sabine Huke, Björn C. Knollmann

Building on work by Otto Frank in the late 19th century, Ernest Starling described in the early 20th century the ability of the heart to change its force of contraction and therefore stroke volume in response to changes in venous return, which has been called the Frank–Starling law of the heart in honor of these 2 physiologists. The Frank–Starling effect enables the heart to match cardiac output to venous return on a beat-to-beat basis.1 A major mechanism responsible for the Frank–Starling effect and hence the beat-to-beat autoregulation of cardiac output is the sarcomere length-dependent activation of force development.2

Reduced Maximal Ca-Activated Force and Increased Ca Sensitivity Are Central Findings in Human HCM

HCM is a familial disorder commonly associated with mutations in genes encoding sarcomeric proteins.3 Consistent with previous animal and human studies,3 myofilament Ca sensitivity was increased in all 38 HCM patient samples compared with 12 nonfailing donor hearts. Notable, the authors observed that length-dependent activation was impaired, which, unlike the Ca sensitivity increase, seemed to be a primary effect of the mutant sarcomeric proteins because (1) it could not be rescued by increasing protein kinase A (PKA) phosphorylation and (2) was normalized when mutant troponin (Tn) proteins were replaced with wild-type protein. These new results suggest that impaired length-dependent activation and hence a defective Frank–Starling effect importantly contribute to the pathogenesis of HCM (Figure).

Impaired Length-Dependent Activation: A Trigger of HCM Pathogenesis?

The authors discovered a new common finding in human HCM muscle—impaired length-dependent activation, which, in contrast to increased Ca sensitivity, was not rescued by PKA treatment for all sarcomeric missense mutations studied. Furthermore, replacement of mutant with wild-type Tn corrected the impaired length dependence in the 2 mutations that could be studied. Hence, impaired length-dependent activation...
HCM mutations directly alter myofilament Ca sensitivity. (a) Impaired length-dependent activation can also be caused by protein kinase A (PKA) hypophosphorylation (ie, of troponin I [TnI]). (b) HCM mutations may directly interfere with phosphorylation of myofilament PKA targets. (c) Only a subset of mutations directly alter myofilament Ca sensitivity.

Figure. Pathophysiological framework of hypertrophic cardiomyopathy (HCM). Solid arrows indicate experimental findings reported by Sequeira et al.3 Open arrows indicate the consequences based on experimental evidence from other studies. (a) Impaired length-dependent activation can also be caused by protein kinase A (PKA) hypophosphorylation (ie, of troponin I [TnI]). (b) HCM mutations may directly interfere with phosphorylation of myofilament PKA targets. (c) Only a subset of HCM mutations directly alter myofilament Ca sensitivity.

may be a direct effect of many mutations that cause HCM in humans (Figure). What is the significance of this finding for the pathogenesis of HCM? Because a functional length-dependent activation is responsible for the Frank–Starling effect, it is intriguing to speculate that HCM mutations generate an intermittent inability to match cardiac ejection to dynamic changes in ventricular filling volume (ie, during the respiratory cycle or during exercise). The resulting increase in wall stress as a result of intermittent impaired ventricular emptying could trigger neuroendocrine activation and a hypertrophic gene program analogous to acquired heart disease with increased wall stress and an impaired Frank–Starling effect, such as postmyocardial infarction cardiomyopathy. Although not tested directly in the report by Sequeira, activation of neuroendocrine signaling could be the main culprit for the decrease in PKA phosphorylation of myofilament target proteins found universally in patients with HCM (Figure). In addition, some of missense HCM mutation (ie, in TnT or TnI) may directly interfere with the ability of PKA to phosphorylate TnI (Figure, dashed arrow b). PKA phosphorylation of TnI not only regulates myofilament Ca sensitivity but also is important for physiological length-dependent activation of cardiac muscle.11 Hence, PKA hypophosphorylation can independently contribute to impaired length-dependent activation, as was demonstrated by the authors for 2 groups of patients with HCM (ie, truncation mutations of myosin-binding protein C and genotype-negative HCM). In those patients, this can generate a vicious cycle that could be central to the pathogenesis in HCM, as shown in the Figure.

In addition to the impaired length-dependent activation, which is measured experimentally by the increase in Ca sensitivity (ΔpCa50) induced by increased sarcomere length (Sequeira et al., Figure 2), all sarcomeric missense mutations (but not myosin-binding protein C truncation mutants and genotype-negative HCM) also impaired the length-dependent increase in maximum force (Sequeira et al., Table 2). The latter is measured at fully activating [Ca] and reflects the intrinsic force-generating ability of the muscle. Although there can be many reasons for the reduced length dependence of maximum force (eg, loss of myofibrils), the net result is an even further compromised length–tension relationship and hence impaired Frank–Starling effect.

Open Questions
Several questions remain. Given that genetic background might affect the functional effect of the mutations and many of the individuals studied by Sequeira et al. were family members, the results of the study may not be quite generalizable to the general HCM population. By necessity, all human myocardial samples came from patients with significant cardiac hypertrophy and heart failure. Hence, it is still possible that altered length-dependent activation is the consequence of pathological remodeling of the sarcomeric apparatus in the diseased myocardium. Nevertheless, the rescue with wild-type Tn protein replacement provides compelling evidence that this is not the case, at least for 2 specific mutations. Furthermore, passive viscoelastic properties of human HCM cardiomyocytes are similar to those of cardiomyocytes from healthy donor hearts, further supporting the hypothesis that altered Ca and length-dependent regulation of muscle activation are central to the pathophysiology of human HCM (Figure). Not directly investigated in the current study, but likely also important for HCM pathophysiology is the inefficient ATP utilization (increased tension cost) caused by many HCM mutations.12 It remains to be seen which of these myofilament properties is the most significant driver of the disease.

Altered myofilament properties affect every myocyte in the heart starting at birth, and although some heterogeneity is expected, there are significant questions remaining. For example, what is the reason for the incomplete penetrance of the disease (age dependent, but possibly as low as 41%)?13 What is responsible for the focal nature of hypertrophy and fibrosis in HCM hearts? This clearly shows that the presence of an HCM mutation does not inevitably lead to disease, and even in an affected patient some regions of the heart remain normal. Such a phenotype may imply a second hit that is necessary to initiate the disease and remains to be identified. A potential culprit is the focal energy deprivation that occurs in HCM mouse models during stress, which can directly contribute to reentry arrhythmias15 but also has the potential to drive heterogeneous hypertrophy and remodeling.16 The next frontier will be to test whether therapeutic interventions aimed at normalizing Ca sensitivity, length-dependent activation, or inefficient ATP utilization are beneficial in HCM.

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References


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