On the road from gene to therapy in Inherited Cardiomyopathies

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Summary: Almost 30 years after the discovery of the first genetic mutation for HCM, the development of new pharmacological approaches targeting cardiomyopathies and other orphan/rare cardiac disease is becoming closer to reality. Development of targeted therapies is enabled by new insights into the clinical and molecular aspects, and pathogenesis of cardiomyopathies, along with the establishment of large-scale international collaboration and the increasing engagement of the pharmaceutical industry. The road toward “cardiovascular precision medicine” is just beginning, with inherited and rare diseases leading the way in this exciting new era.

Key Points (3–5)
• Cardiomyopathies are a heterogeneous group of myocardial disorders
• Most are related to genetic abnormalities of the structural and functional proteins of the myocyte
• The clinical course recognize 3 phases: preclinical, overt (concealed), and end stage disease
• New insight on pathogenesis and mechanisms underlying inherited cardiomyopathies is opening the hope of present and future therapies

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The century that closed the second millennium was marked by enormous progress in all the life sciences, including medicine. In the 21st Century, we have an unparalleled ability to observe, describe,
and define clinical phenomena thanks to the discovery and progressive refinement of new tools able to determine the etiology and pathophysiology of different diseases. With better recognition, many diseases previously thought to be rare have become more commonplace.

The familial nature of cardiomyopathies was first recognized in the mid-20th century (1-5). One of the first families to be reported by Pare et al (5) was the key to the discovery of the genetic substrate of hypertrophic cardiomyopathy when Christine and John Seidman applied–for the first time in cardiology–linkage techniques to discover a mutation (Arg403Glu) in MYH7 on chromosome 14 (6). This landmark paper opened the door to the era of cardiovascular genetics with a cascade of new discoveries about the etiology and pathogenesis of cardiomyopathies. Today, genetic testing is an essential part of diagnosis and management of patients with cardiomyopathies, offering an invaluable tool for risk prediction, cascade genetic testing of at-risk relatives and reproductive testing options (7). Specialized multidisciplinary clinics including cardiologists and genetic counselors are now standard of care (7) and advances in genetic testing technologies have increased the yield and accuracy of genetic testing at ever reducing cost (7,8).

Cardiomyopathies as a group are a heterogeneous group of myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of any condition that can explain the observed phenotype (9). The estimated combined population prevalence of all cardiomyopathies is at least 3%(10). Most cardiomyopathies are genetic disorders affecting the structural and functional proteins of the cardiomyocyte (9,10,11,12,13,14,15). They can be primary genetic disorders of the myocardium, or be part of multisystem disorders (phenocopies) such as malformation syndromes, neuromuscular disorders, mitochondrial disease, and infiltrative/storage disease (13,14,15). Cardiomyopathies can be acquired—for example following exposure to a toxin or infective agent—but even in this scenario, genetic predisposition plays an important role. The complexity of the different pathways that lead to disease mean that a common classification of cardiomyopathies is still lacking, due to our inability to translate their heterogeneity and complexity in a single nosology. Nevertheless, a common language that encompasses some of the new insights on genotype and phenotype of cardiomyopathies is emerging and impacting on clinical practice.

For patients, the burden of cardiomyopathies lies in the development of heart failure and sudden cardiac death. The latter is particularly relevant in children and young adults (7, 16) where physical exercise can be a trigger. However, the physical and psychological benefit of sport activity in daily life should be balanced case-by-case with the potential risk of cardiac arrest (17,18). In the last 20 years, the use of implantable cardioverter defibrillators (ICD) have transformed primary and secondary prevention, although risk stratification for primary prevention and complications related to ICD implantation still represent challenges. Much work on risk prediction focuses on the search for new biomarkers such as high resolution imaging with tissue characterization. Efforts to improve the
risk/benefit of ICD implantation focus on new technologies such as subcutaneous ICD leads (S-ICD). The role of genotype in risk stratification for sudden cardiac death is still unclear, but molecular autopsy (proband genetic testing performed on postmortem DNA) can be a valuable tool for clarification of the cause of death and for allowing appropriate screening and risk stratification of family members (7,16).

Recent practice guidelines have highlighted the important contribution of inherited cardiomyopathies to the burden of heart failure (19). Dilated cardiomyopathy and advanced stage-HCM and arrhythmogenic cardiomyopathy (AC) represent important causes of heart failure with reduced ejection fraction (HFREF), while RCM and restrictive HCM represent extremes of heart failure with preserved ejection fraction (HFPEF) (20,21,22). Moreover, increased recognition of infiltrative disease (i.e. amyloidosis) is revealing common and potentially treatable causes of HFPEF in specific subgroups and ethnic populations (23,24). The future development of heart failure services will lie in closer collaboration between HF and cardiomyopathy specialists and multidisciplinary teams. Progress will also come from large scale collaborations, registries and national electronic health records which hopefully will provide the power to appreciate cumulative disease burden, define accurate risk estimates for adverse events, and determine how genotype impacts disease (9).

The mechanisms by which gene mutations lead to protein and cell dysfunction and clinical disease is an area of active investigation. Phenotypic characterization of preclinical sarcomere gene mutation carriers has yielded insights into the earliest biomechanical defects that link pathogenic variants to cardiac remodeling and dysfunction (25,26). For example, hyperdynamic ventricular contraction and diastolic dysfunction are the earliest identified biomechanical defect in human HCM, while systolic dysfunction is the first sign of pathophysiology in DCM (25,26). Sarcomeric protein gene mutations can result in either phenotype, but functional studies have shown that disease may relate directly to their impact on different functional domains and protein-protein interactions (25,26). Another recent discovery is that titin truncating variants (TTNtv), yielding titin haploinsufficiency, represent the most common cause of familial DCM (25-28). Experimental data seem to support the hypothesis that titin is critical for sarcomere assembly and content and that mutations lead to an abnormal and inadequate stress response (for example during increased haemodynamic load in pregnancy) (25-28). Considerable progress has also been made in understanding AC caused by genes encoding proteins of the cardiac desmosomes, which lead to disruption of inter-myocyte connections and alteration of intracellular signal transduction. Wnt/beta catenin and Hippo signaling pathways have been implicated in disease pathogenesis, as well known regulators of adipogenesis, fibrogenesis and apoptosis, the main cellular mechanisms underpinning the disease phenotype.

Therapies in cardiomyopathies vary according to the disease stage. Some treatments are essentially palliative but in DCM, ACE inhibitors and beta blockers delay progression and improve prognosis.
Disease modifiying treatments have not been identified for HCM or AC but there has been a recent surge of clinical trials testing new therapies for cardiomyopathies. One such therapy being tested for HCM is mavacamten (MYK-461, Myokardia, San Francisco, CA, USA), a small-molecule allostERIC myosin inhibitor that restores contractile balance in HCM hearts by decreasing adenosine triphosphatase activity of the cardiac myosin heavy chain (29,30). A phase 2a study has recently been completed to evaluate the efficacy, safety and tolerability of mavacamten in subjects with symptomatic HCM and LVOT obstruction (NCT02842242); a large Phase 2/3 study is due to start in 2018. This trial is supported by data from preclinical studies showing that in an HCM mouse model, mavacamten administered in an early stage prevented disease development (LVH, myocyte disarray and fibrosis) and down regulated both hypertrophic and pro-fibrotic gene expression (29,30).

Phenotype prevention or reverse remodeling is the ultimate goal of pharmacologic therapy. Different therapies have been, or are being tested in HCM. Diltiazem has shown some promise in sarcomere gene mutations carriers in a small clinical trial (31) while no benefit was apparent with N-acetylcysteine, atorvastatin, or ranolazine analogs (30, 32-35). Valsartan is currently under investigation in the VANISH trial (36). This trial was based on encouraging findings from a preclinical trial in which inhibiting TGFbeta by neutralizing antibodies or with losartan prevented phenotypic development in mice carrying a MYH7 mutation (37). Gene-targeted therapies are also on the horizon, enabled by recent advances in gene-editing technology. In a recent study, genetic engineering using CRISPR–Cas9 technique corrected a heterozygous MYBPC3 mutation in human preimplantation embryos (38, 39). However, the applicability of this technique to clinical practice is uncertain, in light of concerns about off-target effects and the current availability of pre-implantation genetic diagnosis which allows for implantation of genetically unaffected embryos.

Other innovative breakthroughs have emerged in the field of rare multisystem diseases, such as chaperone therapy (migalastat) for Fabry disease and antisense oligonucleotides (eteplirsen) for Duchenne muscular dystrophy, both recently approved in clinical practice (30). New developments are underway in Rasopathies, where short-term therapy with mTOR inhibitors (everolimus) has recently been used to prevent disease complications in patients with a severe form of HCM (40) and in Lamin A/C disease, where a p38α inhibitor. is under investigation in a small phase 2 study trial of Lamin A/C DCM (NTC02351856) (41).

In conclusion, almost 30 years after the discovery of the first genetic mutation for HCM the development of new pharmacological approaches targeting cardiomyopathies and other orphan/rare cardiac disease is closer to reality. Development of targeted therapies is enabled by new insights into
clinical phenotypes and molecular pathogenesis, along with the establishment of large-scale international collaboration and engagement of the pharmaceutical industry. The road toward cardiovascular precision medicine is just beginning, with inherited and rare diseases leading the way.

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