

Experimental Therapies in Hypertrophic Cardiomyopathy

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Abstract The quintessential clinical diagnostic phenotype of human hypertrophic cardiomyopathy (HCM) is primary cardiac hypertrophy. Cardiac hypertrophy is also a major determinant of mortality and morbidity including the risk of sudden cardiac death (SCD) in patients with HCM. Reversal and attenuation of cardiac hypertrophy and its accompanying fibrosis is expected to improve morbidity as well as decrease the risk of SCD in patients with HCM. The conventionally used pharmacological agents in treatment of patients with HCM have not been shown to reverse or attenuate established cardiac hypertrophy and fibrosis. An effective treatment of HCM has to target the molecular mechanisms that are involved in the pathogenesis of the phenotype. Mechanistic studies suggest that cardiac hypertrophy in HCM is secondary to activation of various hypertrophic signaling molecules and, hence, is potentially reversible. The hypothesis is supported by the results of genetic and pharmacological interventions in animal models. The results have shown potential beneficial effects of angiotensin II receptor blocker losartan, mineralocorticoid receptor blocker spironolactone, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors simvastatin and atorvastatin, and most recently, N-acetylcysteine (NAC) on reversal or prevention of hypertrophy and fibrosis in HCM. The most promising results have been obtained with NAC, which through multiple thiol-responsive mechanisms completely reversed established cardiac hypertrophy and fibrosis in three

independent studies. Pilot studies with losartan and statins in humans have established the feasibility of such studies. The results in animal models have firmly established the reversibility of established cardiac hypertrophy and fibrosis in HCM and have set the stage for advancing the findings in the animal models to human patients with HCM through conducting large-scale efficacy studies.

Keywords Hypertrophic Cardiomyopathy · Sudden Cardiac Death · Genetics · Statins · N-acetylcysteine · Losartan

Introduction

Despite the modern recognition of hypertrophic cardiomyopathy (HCM) for over five decades and in spite of considerable advances in its phenotyping and molecular genetics, current pharmacological treatment of patients with HCM has remained largely unchanged and empiric. The primary emphasis in the management of patients with HCM has been on the risk of sudden cardiac death (SCD), as HCM is a common cause of SCD in the young [54]. Prudent use of automatic internal defibrillator/cardioverters (AICDs) has provided the physicians with an effective option for prevention of SCD in the high-risk patients [55, 56]. However, implantation of an AICD does not influence the underlying cardiac pathology, namely, myocyte hypertrophy, disarray, and interstitial fibrosis. Likewise, catheter-based septal ablation and surgical myectomy, while are highly effective in reducing the left ventricular outflow tract (LVOT) obstruction, alleviating symptoms (functional improvement), do not substantially alleviate the underlying arrhythmogenic substrate [53, 60, 78, 88, 95, 104, 115]. In contrast, the tissue scar at the site of percutaneous septal

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ablation has the potential to increase the risk of ventricular arrhythmias [7, 26, 59, 89, 95].

The effective treatment of HCM, whether pharmacological or otherwise, has to target the underlying mechanism(s) responsible for the clinical phenotype. The current phenotypic emphasis is on cardiac hypertrophy, as it, in the absence of a discernible cause, epitomizes the clinical diagnosis of HCM. The prominence of hypertrophy as the main target of therapy stems from the fact that adult cardiac myocytes are terminally differentiated cells and their primary response to pro-growth stimulants is increased size, i.e., hypertrophy [105]. Partial understanding of the molecular pathways involved in the pathogenesis of cardiac hypertrophy has further enhanced the interest in targeting hypertrophy for the effective treatment of HCM. The clinical significance of cardiac hypertrophy also legitimizes it as the primary therapeutic target. Underscoring the point is that pathological cardiac hypertrophy, regardless of the cause or the ethnic background, is an important determinant of mortality, morbidity, and the risk of SCD [4, 14, 20, 33, 34, 77, 96]. Likewise, cardiac hypertrophy is also an important determinant of diastolic dysfunction and failure as well as susceptibility to arrhythmias [18, 25, 58, 61, 68, 70, 71, 83, 120, 121].

Reversibility of Cardiac Phenotype in HCM An important clinical question in HCM has been whether cardiac hypertrophy and fibrosis, once established, could be reversed or attenuated and whether evolving phenotype could be prevented. Conventionally used pharmacological agents have not proven to prevent or reverse established cardiac hypertrophy. The current evidence for potential regression of hypertrophy stems from observational studies following percutaneous septal ablation and surgical myectomy suggesting left ventricular remodeling and regression of cardiac hypertrophy upon relief of the LVOT obstruction [16, 30].

The most direct and robust evidence for the regression of established cardiac hypertrophy and fibrosis is derived from experimental studies in genetically modified animal models of HCM. We have advocated that cardiac hypertrophy in HCM is a secondary phenotype due to activation of pro-growth signaling molecules instigated by the functional defects imparted by the mutations and, hence, it is potentially reversible and preventable [46]. In proof-of-principle studies, we generated switch-on/switch-off bigenic mice, wherein expression of the transgene could be turned off and on, as desired [45]. We showed that turning off expression of the mutant transgene was associated with reversal and normalization of the induced phenotype [45]. Subsequently, we extended our studies by targeting signaling pathways involved in cardiac hypertrophic response [42, 51, 82, 91, 111]. Collectively, the findings, which are discussed in the present review, have established the potential to prevent the evolving and reverse the

established cardiac hypertrophy and fibrosis in patients with HCM.

Ineffectiveness of Current Pharmacological Therapies in Reversing Cardiac Hypertrophy in HCM Current pharmacological treatment of human HCM, while is effective for symptomatic improvement, has not been established to prevent, attenuate, or reverse cardiac hypertrophy in humans with HCM or even impact the prognosis [49, 50]. The most commonly used pharmacological agents are the β -blockers, which are the mainstay of therapy and the first choice in the absence of a contraindication. The proposed mechanisms of effects include improved ventricular relaxation and increased diastolic filling time and, hence, improved left ventricular end diastolic pressure as well as perfusion. In addition, treatment with β -blockers is expected to reduce ventricular and supra-ventricular arrhythmias. An observational retrospective study in a mixed pediatrics HCM population suggests potential beneficial effects of high-doses β -blockers on total survival [81]. Otherwise, the benefits of β -blockers on mortality and the risk of SCD in patients with HCM and their impact on prevention or reversal of cardiac hypertrophy in HCM remains to be established.

Verapamil and diltiazem exert their beneficial effects in part through their negative inotropic and chronotropic effects and in part through improving myocardial diastolic properties. These agents have been used for over two decades but not been proven to impart significant effects on cardiac hypertrophy or prognosis in patients with HCM. In a small study comprised of six mutation carriers without cardiac hypertrophy, treatment with diltiazem was found to improve myocardial tissue Doppler velocities [62]. Diltiazem also has been shown to improve cardiac systolic function and reduce interstitial fibrosis in the α -MyHC-Q403 mice, which exhibited reduced left ventricular systolic function [90]. However, the finding of improved systolic function with diltiazem in the mouse model may not have direct implications for human HCM, as global systolic function in HCM patients is enhanced or at least preserved.

Dihydropyridine calcium channel blockers, such as nifedipine are avoided in patients with HCM, because of the concern about the vasodilatory effects inducing hypotension, syncope, and possibly death. Overall, the clinical utility of Ca^{+2} channel blockers in treatment of patients with HCM is hindered by the risk of hypotension and syncope, at rest or particularly during exercise. This is not a trivial concern in patients with resting or provoked LVOT obstruction, who could comprise up to 70% of the patients with HCM [57, 79].

Disopyramide, a class I anti-arrhythmic drug, is used in conjunction with β -blockers to attenuate LVOT obstruction and improve symptoms [92]. The beneficial effects of disopyramide are largely due to its negative inotropic effects. Hence, it is most effective in patients with LVOT

obstruction. Disopyramide does not reverse or attenuate cardiac hypertrophy in patients with HCM [92].

Mechanistic Approach to Effective Treatment of HCM The seminal report of the R403Q mutation in *MYH7* in a family with HCM by Dr. Seidman's group in 1990 unraveled the genetic enigma of HCM [106]. The discovery led to subsequent identification of over a dozen causal genes for HCM [49, 66]. The known causal genes encode sarcomeric including the Z disk proteins. Accordingly, *MYH7* and *MYBPC3* have emerged as the two most common causal genes for HCM, together accounting for approximately 50% of the HCM cases. Mutations in *TNNT2*, *TNNI3*, *TPMI*, and *ACTC1* collectively account for about 10% of the HCM cases and other causal genes, such as the Z disk proteins *MYOZ2* and *TCAP*, encoding myozenin 2 and telethonin, respectively, are less common [31, 80]. Overall, the causal mutations in approximately two thirds of the patients with HCM have been identified.

Mechanistic studies have elucidated a diverse array of functional defects imparted by the causal mutations in HCM. The diversity perhaps is best illustrated for the Ca^{2+} sensitivity of myofibrillar ATPase activity and force generation, which vary according to the causal genes and are context dependent [17, 19, 22, 64, 65, 69, 72, 73, 85, 86, 93, 98, 107, 108]. For example, mutations in the β -MyHC when engineered in the background of β -MyHC isoform, as in the human heart, decrease Ca^{2+} sensitivity of the myofilament force generation and ATPase activity [43, 69]. In contrast, the same mutation when engineered into α -MyHC isoform in the background of α -MyHC is associated with reduced Ca^{2+} sensitivity of the myofilament force generation [6]. It merits noting that in the human heart, the β -MyHC isoform encoded by the *MYH7* comprises over 90% of the total myosin heavy chains. Likewise, in the rabbit heart, the β -MyHC isoform is the predominant isoform, comprising more than 85% of the total myosin heavy chain. This is in contrast to the mouse heart, which predominantly (>95%) contains the α -MyHC isoform, encoded by the *MYH6*. The α and β isoforms differ considerably in their ATPase activities and rate of actin displacement. The differences may influence delineating the responsible mechanisms for HCM caused by mutations in *MYH7*. In addition, *TNNT2* mutations that cause HCM are associated with enhanced Ca^{2+} sensitivity of myofibrillar protein ATPase activity and force generation and so are mutations in *TPMI* and *TNNI3* that cause HCM [21, 23, 24, 41, 63, 84, 94, 98, 99, 110, 118]. Moreover, the pathogenesis of HCM caused by *MYOZ2* mutations is likely to involve activation of the calcineurin protein phosphatase pathway [80].

The diversity of the mechanisms involved in the pathogenesis of HCM restricts the utility of targeting a specific pathway for the therapeutic benefits in HCM. The

diversity could necessitate target-specific interventions, mandated by the functional phenotype of the causal mutations. An alternative approach is targeting mechanisms/pathways that are common to cardiac hypertrophic growth, such as oxidative stress pathways, which are common to various forms of cardiac hypertrophy including HCM [42, 51, 91, 103, 109]. We have shown that myocardial levels of lipid peroxides, markers of oxidative stress, as well as levels of oxidized mtDNA are increased in transgenic mouse and rabbit models of HCM [51, 91]. Thus, interventions aimed at mechanisms that regulate oxidative stress in the heart could emerge as desirable for reversal of cardiac hypertrophy and fibrosis in HCM as well as other hypertrophic conditions [42, 103]. The concept is further supported by the shared anti-oxidant properties of various pharmacological agents that have previously shown to effectively regress cardiac hypertrophy in animal models of HCM, namely losartan [37], spironolactone [111], statins [82, 91], and N-acetylcysteine (NAC) [42, 51]. Hence, therapies targeted at oxidative stress pathway have emerged as potentially effective agents in reversal of established cardiac hypertrophy and fibrosis in HCM.

Distinction between (sarcomeric) HCM and Phenocopy Conditions Genetic discoveries have also elucidated the fallacies inherent to the clinical diagnosis of HCM, as many patients with the clinical diagnosis of HCM might have phenocopy conditions. The current clinical diagnosis of HCM, based on detection of cardiac hypertrophy, is neither sufficiently specific, because of the presence of phenocopy conditions [1, 9], nor sufficiently sensitive, because of low penetrance of certain causal mutations [74, 75]. Phenocopy conditions, such as storage diseases, are typically indistinguishable from true HCM [9]. Nevertheless, the distinction between HCM caused sarcomeric protein mutations, and phenocopy conditions are crucial for an effective treatment of HCM. The clinical significance of such distinction is highlighted by the differences in the treatments of the two conditions. For example, enzyme replacement therapy with human α -Gal A (agalsidase α) or recombinant human α -Gal A (agalsidase β) suppresses progression of Fabry disease [87, 114]. In contrast, conventional treatment for HCM in patients with phenocopy conditions is not expected to impart significant benefits [50]. The true incidence of phenocopy condition in patients with the clinical diagnosis of HCM is likely to be approximately 10% [47].

Specific Experimental Pharmacological Agents in HCM

Inhibitors of Renin-Angiotensin-Aldosterone System (RAAS) Given the well-established anti-hypertrophic and anti-fibrotic effects of the inhibitors of the rennin-

angiotensin-aldosterone system (RAAS), we have tested the potential beneficial effects of treatment with losartan, an angiotensin II receptor blocker in the cTnT-Q92 mouse model [37]. Likewise, we have investigated the potential beneficial effects of spironolactone, a mineralocorticoid receptor inhibitor, in reversal of cardiac interstitial fibrosis in two independent (test and replication) randomized studies [111]. In these studies, treatment with losartan or spironolactone normalized myocardial collagen content, in part through their anti-oxidant effects and partly through inhibition of pro-fibrotic effects of transforming growth factor- β and protein kinase D (Table 1) [37, 111].

The studies in animal models were followed by pilot clinical studies in humans with HCM [2, 117]. The results in human studies, although preliminary, have been to a large extent unsatisfactory. Yamazaki et al. treated ten patients with HCM who did not have LVOT obstruction with 50 mg of losartan per day for 1 year and reported only a 7% change in LV mass, which was not significant [117]. Likewise, Araujo et al. treated 20 patients with non-obstructive HCM with 100 mg of losartan per day for 6 months and reported no significant changes in the echocardiographic indices of cardiac hypertrophy but modest improvement in selected indices of diastolic function [2]. The null findings of these two studies regarding regression of cardiac hypertrophy and given the potential risk of hypotension and syncope, particularly in those with resting or latent LVOT obstruction, have reduced the enthusiasm for the potential utility of the angiotensin II receptor blockers in treatment of human patients with HCM.

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) Reductase Inhibitors HMG-Co A reductase inhibitors or statins are pleiotropic agents with various effects including anti-oxidant effects [8, 11, 36, 67, 76, 102]. We tested the potential effects of simvastatin in reversal of established cardiac hypertrophy and fibrosis in a randomized placebo-control study the β -MyHC-Q403 transgenic rabbits [82, 91]. We showed that treatment with simvastatin reduced left ventricular mass, wall thickness, myocyte size, and normalized interstitial fibrosis [82]. In addition, indices of cardiac diastolic function and filling pressure were improved [82].

In a subsequent study, we tested the effects of atorvastatin on prevention of cardiac hypertrophy and fibrosis in the β -MyHC-Q403 transgenic rabbits [91]. We showed administration of atorvastatin early and prior to the development of cardiac hypertrophy prevented cardiac hypertrophy [91]. However, interstitial fibrosis was not significantly affected, suggesting dissociation of mechanisms involved in the pathogenesis of hypertrophy and fibrosis in HCM. At mechanistic levels, treatment with statins reduced myocardial levels of lipid peroxides and oxidized mitochon-

drial DNA. In addition, treatment with statins restored expression levels of anti-oxidant genes and levels of activated membrane-bound Ras and pERK44/42. Studies in other animal models of cardiac hypertrophy and heart failure overall have corroborated the potential beneficial effects of statins in prevention and attenuation of hypertrophy and fibrosis [8, 28, 44, 102].

In contrast to animal studies, performed in a uniform population of HCM caused by a specific mutation, preliminary clinical studies in humans with HCM have not confirmed beneficial effects of statins in regression of established phenotype [3]. Bauersachs et al. reported no significant change in LV mass in 11 patients treated with 80 mg of atorvastatin for 9 months [3]. Likewise, we have performed a pilot feasibility study and have treated 21 HCM patients with established cardiac hypertrophy with escalating dose of atorvastatin, maximized at 80 mg per day for a total of 2 years. Fifteen and 11 patients completed 6 and 24 months of therapy. We detected no significant effects of treatment with atorvastatin on LV mass or ventricular wall thickness or other indices of cardiac hypertrophy and function.

N-acetylcysteine (NAC) Oxidative stress has emerged as a common and important mediator of cardiac hypertrophic and fibrotic responses [103, 109]. Likewise, we have implicated increased oxidative stress and thiol-sensitive mechanisms in the pathogenesis of HCM and have shown that levels of lipid peroxides, oxidized mtDNA, and oxidized glutathione, markers of oxidative stress, are increased in the hearts of transgenic animal models of HCM [42, 51, 91]. It is also noteworthy that a common mechanism among losartan, aldosterone, simvastatin, and atorvastatin in inducing regression of cardiac hypertrophy and fibrosis is their actions against oxidative stress. In pursuit of testing the potential beneficial effects of NAC, we have performed placebo-control randomized studies in the β -MyHC-Q403 transgenic rabbits and cTnT-Q92 transgenic mice. NAC is a precursor to glutathione, which is the most abundant intracellular non-protein thiol pool against oxidative stress [119]. We have treated the genetically modified mice and rabbits with either a placebo or NAC for 3 to 14 months. We showed that treatment with NAC normalized myocardial and blood levels of oxidized glutathione (glutathione/glutathione disulfide ratio), which was increased in the transgenic rabbits treated with placebo. Treatment with NAC reversed cardiac and myocyte hypertrophy and interstitial fibrosis, prevented left ventricular systolic dysfunction, and improved arrhythmogenic propensity in our animal models (Fig. 1) [42, 51]. At mechanistic levels, we showed involvement of multiple mechanisms including effects on thiol-sensitive active protein kinase G, calcineurin target NFATc1 and phospho-p38, as well as glutathiolated sarcomeric protein cardiac α -actin. The finding

Table 1 Experimental pharmacological agents in treatment of human hypertrophic cardiomyopathy

Pharmacological agent	Mechanism of anti-hypertrophic effects	Favorable effects	Unfavorable effects
Losartan	Blockade angiotensin II mediated pro-hypertrophic and pro-fibrotic signaling Reduces oxidative stress	Regression of fibrosis	No effects on cardiac hypertrophy in two small studies Potential for hypotension and syncope
Statins	Inhibition of Rho-A and Rac1 small GTPases Reduces oxidative stress	Regression of hypertrophy and fibrosis	No effect on cardiac hypertrophy in two small pilot studies Liver toxicity Skeletal myopathy
Spirolactone	Blockade of PKD Blockade of TGF-β Reduces oxidative stress	Regression of fibrosis	Hyperkalemia Possible hypotension
Calcineurin inhibitors	Inhibition of Calcineurin-NFATc hypertrophic pathway	Established anti-hypertrophic effect	Deterioration of cardiac structure and function in a mouse model of HCM
N-acetylcysteine	Reduces oxidative stress Thio-modifications of proteins and signaling molecules	No major side effects Reverses established hypertrophy and fibrosis	Unpleasant taste for some unless mixed with juice/soda

of an anti-hypertrophic effect of NAC in our models is in accord with the results of a recent study in streptozotocin-induced diabetic cardiac hypertrophy [116]. Likewise, the observed anti-fibrotic effect of NAC is in accord with the findings in other models and organs [12, 27, 32, 39, 40]. The collective data indicating the anti-hypertrophic and anti-fibrotic effects of NAC in animal models of HCM and other forms of cardiac hypertrophy have set the stage for clinical trials to test potential salutary effects of this safe prodrug in reversal of cardiac hypertrophy and fibrosis in humans with HCM.

Calcineurin Protein Phosphatase 2B Inhibitors Inhibition of calcineurin-NFATc pathway has been established to reverse and prevent cardiac hypertrophy in various pathological states [10, 13, 38, 97, 100, 101]. However, Dr. Seidman’s group reported that treatment of the α-MyHC-Q403 mice with FK506 or cyclosporin A, inhibitors of calcineurin, worsened cardiac and myocyte hypertrophy, myocyte disarray, and interstitial fibrosis and increased mortality [15]. The observed deleterious effects of inhibition of calcineurin in the α-MyHC-Q403 mouse model of HCM have subdued the overall enthusiasm for the potential utility of calcineurin inhibitors in HCM. Nevertheless, given the diversity of the mechanisms involved in the pathogenesis of HCM and potential involvement of the calcineurin pathways in HCM due to MYOZ2 mutations, calcineurin inhibitors may impart beneficial effects only in a subset of HCM patients.

Challenges in Translating the Results of Experimental Therapies in Animal Models to Human Patients with HCM Despite the remarkable results in the animal models of HCM documenting prevention, attenuation, and reversal

of cardiac phenotype, the results of the preliminary studies with statins and losartan in humans have been less remarkable, if not completely null, as discussed earlier. We note that the human studies thus far have been conducted in a small number of patients and are considered feasibility studies that provide the preliminary data for designing the efficacy studies. Nevertheless, the discrepancy in the results of pharmacological interventions in humans and animal models of HCM is likely to reflect the genetic and phenotypic heterogeneity of HCM in humans as opposed to the genetically modified animals, wherein HCM is caused by a specific mutation in a more homogenous background. Accordingly, in a pharmacological intervention study, the animals share the same causal gene/mutation. In contrast, a group of human patients who are treated with the same

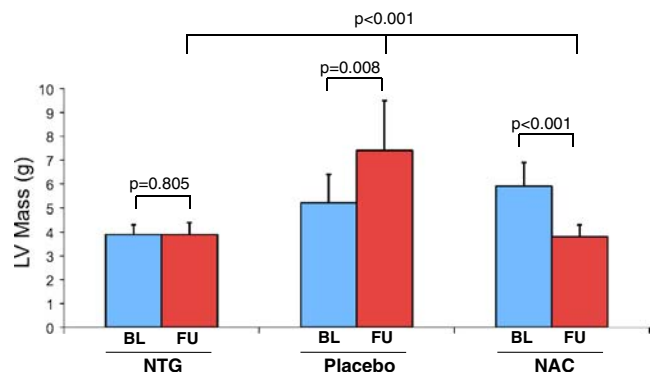


Fig. 1 Effect of N-acetylcysteine (NAC) on left ventricular mass (LVM). LVM was increased in the β-myosin heavy chain-Q403 transgenic rabbits as compared to nontransgenic rabbits and continued to increase during the follow-up time (FU) in the placebo group. In contrast, LVM was reduced to normal in the NAC group at FU (N=10 per group; dose, 500 mg/Kg/day; duration of treatment, 12 months)

pharmacological agent typically have a diverse array of causal genes and mutations. As noted earlier, the pathogenesis of HCM caused by different mutations could vary significantly. Therefore, diverse mechanisms are likely to be involved in a group of unrelated human HCM patients as opposed to more uniform mechanisms in the animal models. A pharmacological agent, such as statin or losartan, is unlikely to effectively block various mechanisms that may be involved in the pathogenesis of HCM in a group of unrelated human patients. The same agent, however, may effectively block the specific pathway involved in the pathogenesis of the phenotype in a specific animal model. For example, statin could inhibit geranyl-geranylation of Rho and Rac signaling, which may be involved in the pathogenesis of a subtype of HCM, represented by the β -MyHC-Q403 rabbits, but could not be activated in all cases of HCM caused by various mutations. It is also important to consider the potential confounding effects of the phenocopy conditions in humans that could render a specific pharmacological therapy ineffective or at least dilute its effect. In addition, the genetic background of animals is likely to be more homogenous, while human patients with HCM are expected to have heterogeneous genetic background. Moreover, the potential differences in the pharmacokinetic and pharmacodynamics of specific pharmacological agents in humans and animals merit considering when designing clinical trials in humans built on animal data.

Prospective

The current clinical diagnosis of HCM is based on detection of cardiac hypertrophy, typically on an echocardiogram [49, 52]. The clinical diagnosis, however, is neither sufficiently specific nor sufficiently sensitive [1, 9, 74, 75]. Phenocopy conditions, such as storage diseases, are typically indistinguishable from true (sarcomeric) HCM [9]. Likewise, individuals with the low penetrant mutations do not express cardiac hypertrophy despite carrying the causal mutations.

Given the limitation of the phenotype-based diagnosis, particularly for the early diagnosis, one would expect that DNA-based diagnosis would be used increasingly to complement the clinical diagnosis. The advent of deep sequencing technology, whether used in conjunction with target enrichment or whole genome sequencing, is expected to make DNA-based diagnosis practical, particularly in the early diagnosis and prior to and independent of the clinical phenotype. However, the DNA-based diagnosis is not without caveats, as no protein is perfect and each may carry a number of sequence variants that may not be responsible for the phenotype. The recent sequencing of individuals genomes clearly illustrates the presence of three to four million DNA sequence variants including several thousand insertions/deletions and copy number variants in

each individual's genome [5, 29, 35, 112, 113]. The challenge is to distinguish the DNA sequence variants that impart major phenotypic effects and/or are disease-causing variants and those that have modest if any biological effects [48].

In conjunction with the implementation of a DNA-based diagnosis, pharmacological treatment/prevention of HCM is also likely to evolve and become largely individualized. The notion is supported by the results of the mechanistic studies of causal mutations showing involvement of a diverse array of functional defects [17, 19, 22, 64, 65, 69, 72, 73, 85, 86, 93, 98, 107, 108]. The diversity of the responsible mechanisms perhaps is best illustrated for the Ca^{2+} sensitivity of myofibrillar ATPase activity, which varies according to the causal genes and is context dependent. The diversity of the responsible molecular pathways in HCM limits the potential utility of targeting a specific pathway. For example, Ca^{2+} channel blockers would be expected to be beneficial only in the subset of HCM that is caused by mutations that increase the Ca^{2+} sensitivity of myofibrillar force generation. In contrast, such agents could potentially be harmful in the subset that is caused by mutations that decrease the Ca^{2+} sensitivity of the myofibrils. Thus, one potential future approach would be to individualize the therapy based on the specific mechanisms involved in the pathogenesis of the phenotype.

The opposite end of the spectrum of approach to treatment of HCM is to broaden the application of a specific therapy to various subtypes of HCM by targeting mechanisms that are common to cardiac hypertrophic growth, the main clinical phenotype of HCM. An example of such common mechanism is increased oxidative stress, which is involved in the pathogenesis of cardiac hypertrophy in HCM as well as other pathological hypertrophy [42, 51, 91, 103, 109]. As discussed earlier, pharmacological interventions targeted to reduce oxidative stress have been used successfully to reverse cardiac hypertrophy and fibrosis in animal models of HCM as well as in other hypertrophic states [42, 103]. The findings in animal models of HCM beckon the need for clinical studies in humans to determine the potential beneficial effects of therapies targeted at oxidative stress pathway in prevention, attenuation, or reversal of cardiac phenotype in HCM.

Cardiac phenotype in human HCM evolves slowly and typically over a couple of decades and often even longer. The slow evolution of the phenotype may necessitate long-term pharmacological interventions in a relatively large number of patients in order to attain robust results with experimental therapies. Similarly, genetic-based diagnosis prior to expression of cardiac hypertrophy could afford the opportunity to intervene early to prevent the evolving phenotype. Whether prevention of the evolving phenotype or reversal of the established phenotype, the success will

mandate recruitment of a large number of individuals to the study. Given that HCM is a relatively uncommon disease, collaborations among multiple centers would be essential for the design of adequately powered efficacy studies to test the potential salutary effects of experimental therapies in human patients with HCM.

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