Advances in Heart Failure

Patterns of Disease Progression in Hypertrophic Cardiomyopathy
An Individualized Approach to Clinical Staging

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After the recent celebrations of the 50th anniversary of the modern description of hypertrophic cardiomyopathy (HCM) by Teare and Lord Brock, the time is ripe to reflect on what remains to be discovered.[1–3] With the full realization that a massive amount of information relating to the disease has already been uncovered, and paying tribute to all those involved in this process, it is essential to concentrate on the gaps in our knowledge that require concerted efforts to advance the field, particularly in relation to patient management, which continues to be perceived as less than optimal.[3] We believe that this is largely due to the partial disconnect between basic research, and an incomplete understanding of the fundamental mechanisms molding a continuously, often insidiously changing phenotype. A thorough comprehension of these processes requires a translational approach based on long-term clinical observation of large HCM cohorts, coupled with basic scientific research, and represents an essential step toward the development of innovative therapies which need to be both disease- and patient-specific.[2,3]

Traditionally, the focus of HCM literature has been polarized on 2 aspects of indisputable clinical relevance: the pathogenesis, clinical consequences, and management of dynamic left ventricular (LV) outflow obstruction,[1] and the issue of arrhythmic risk stratification and prevention of sudden cardiac death (SCD).[4,5] By comparison, limited attention has been devoted to the life-long process of LV remodeling and progressive dysfunction that occur in a substantial proportion of HCM patients and culminates in the rare but dramatic clinical evolution termed as *end-stage* or *burned-out* phase.[6–9] Consequently, the stages that precede this severe condition are still relatively unknown, representing an important target for research.[3] Indeed, because of the slowly evolving nature of HCM, timely identification of patients at risk of developing advanced LV dysfunction and heart failure (HF) may allow effective preventive strategies over a time span of several years before clinical demise.[7–9]

To aid the characterization of different phases of HCM in individual patients, we propose a simple framework for systematic clinical staging of the disease. To this purpose, 4 clinical stages are identified, with special emphasis on diagnosis, potential mechanisms, challenges for management, and targets for future investigation: these are defined as *nonhypertrophic HCM*, *classic* phenotype, *adverse remodeling*, and *overt dysfunction* (Figure 1 and Table).[3,6,7,10]

Stage I: Nonhypertrophic HCM

Definition and Diagnosis

Nonhypertrophic HCM is a state characterized by the absence of LV hypertrophy in individuals harboring HCM-causing mutations, investigated in the course of systematic family screenings. In most HCM patients, a hypertrophic phenotype is generally absent in newborn or very young children, and tends to manifest during the second decade of life.[7,10,11] Due to incomplete penetrance and age-related onset, however, genotype-positive individuals can develop LV hypertrophy as late as the 6th or 7th decade, and a significant minority seem to never develop the disease at all.[10–11] In a recent Dutch study, an age-dependent 41% penetrance of HCM was observed in mutation carriers.[12]

Importantly, *nonhypertrophic* is not equivalent to *phenotype-negative* HCM. Family studies have shown that ECG abnormalities may be evident even in the absence of LV hypertrophy on the echocardiogram.[7] Subtle echocardiographic abnormalities may be found at this stage, such as impaired LV relaxation, mitral valve or subvalvar abnormalities, and mild degrees of left atrial (LA) dilatation, all of which are not diagnostic per se but may be instrumental to suspecting HCM in a familial context[7,13] (Figure 2). Furthermore, elevated levels of type I collagen precursors have been described in genotype-positive individuals[14] and coronary microvascular function may be altered in HCM patients with very mild phenotype,[9] suggesting that a whole spectrum of abnormalities may be present in individuals with nonhypertrophic HCM.

As the capabilities offered by diagnostic techniques advance, the proportion of truly phenotype-negative individuals becomes progressively smaller. With cardiac magnetic resonance (CMR), as many as 16% genotype-positive with
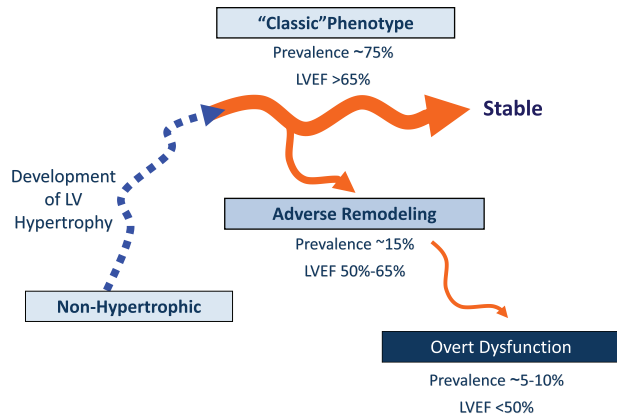
Figure 1. Stages of hypertrophic cardiomyopathy (HCM). Thickness of the **orange lines** reflects prevalence of each stage in HCM cohorts. Prevalence of nonhypertrophic HCM is unknown. LVEF indicates left ventricular ejection fraction.

negative echocardiography examination appear to have some degree of LV hypertrophy.[10] Thus, individuals in this stage should be considered for CMR at initial evaluation to rule out mild but significant expressions of disease.

Mechanisms of Disease

HCM is termed a disease of the sarcomere, because mutations in a number of genes encoding cardiac contractile and Z-disk proteins have been convincingly shown to cause the disease.[2,3] HCM-causing mutations generally cause single amino-acid substitutions in proteins that become incorporated into the sarcomere and exert their pathological effects as poison peptides that alter normal sarcomere function in a concentration-dependent manner.[2,3,15,16] An exception to this rule are most myosin binding protein C (MYBPC3) mutations, which result in insufficient protein production for normal sarcomere function (haploinsufficiency).[2,17] Haploinsufficiency can be attributed to cell surveillance mechanisms, including nonsense-mediated decay of mRNA transcripts that contain premature termination codons and/or ubiquitin-mediated proteasomal degradation of misfolded proteins.[17] Even before the development of LV hypertrophy, HCM-causing mutations may exert various adverse effects on cardiomyocyte intracellular calcium and energy handling, accounting for early diastolic abnormalities in nonhypertrophic HCM.[11,14] Over time, the effects of HCM-causing mutations are subject to the interplay of modifier genes and environmental factors, likely crucial in determining an "awakening" of the phenotype.[18,19]

Clinical Course and Outcome

Prognosis of genotype-positive individuals in the nonhypertrophic stage is unresolved, but presumed favorable, possibly comparable to that of the healthy population.[10,11] Although potentially malignant ventricular arrhythmias and SCD has been reported in nonhypertrophic HCM, such occurrence is considered exceptional.[7]

Targets for Management and Research: Preventing Disease Development

No evidence-based treatment is available for nonhypertrophic HCM. Avoiding emphasis on competitive activity may be considered in these individuals, although this issue remains highly controversial.[10,19] Pharmacological strategies aimed at

Table.   Stages of Hypertrophic Cardiomyopathy Based on Clinical and Instrumental Evidence of Disease Progression

	LVEF (by CMR)*†	LGE (% of Whole LV Mass)*†	Coronary Microvascular Dysfunction*†	Symptoms and Functional Limitation†	LV Filling Pattern and TDI†	LVOTO (Resting or Provokable)†
Stage I						
Nonhypertrophic	Normal or supernormal	Absent	Unknown; possibly present	None	Normal; TDI–E′ may be reduced	Absent
Stage II						
"Classic" phenotype	>65%	Absent or <5%	Variable from mild to severe	Variable; may be severe with LVOTO/MR or massive LVH	Normal or delayed relaxation TDI–E′ usually reduced	Common (70%)
Stage III						
Adverse remodeling	50% to 65%	10% to 15%	Moderate to severe	Variable; generally mild to moderate	Pseudonormal or restrictive TDI–E′ reduced	Less common; loss of prior obstruction may be observed
Stage IV						
Overt dysfunction	<50%	Extensive (25% to 50%)	Severe	Generally moderate to severe	Pseudonormal or restrictive TDI–E′ severely reduced	Absent; loss of prior obstruction may be observed

LVEF indicates left ventricular ejection fraction; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; TDI, tissue Doppler imaging; LVOTO, left ventricular outflow tract obstruction; NSVT, nonsustained ventricular tachycardia; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LA, left atrial; LVH, left ventricular hypertrophy; MR, mitral regurgitation; SCD, sudden cardiac death; TDI-E′, TDI–septal E′ velocity; Tx, heart transplant; and VAD, ventricular assist device.

*Associated with evidence of progressive LV remodeling and dysfunction.

†Associated with increased risk of heart-failure related complications and adverse outcome.

preventing development of LV hypertrophy have been proposed, based on encouraging preclinical data with agents such as statins, losartan, and diltiazem.[20,21] A randomized trial with diltiazem is currently underway to test this hypothesis in humans.[22] It is hoped that new genetic technologies, allowing cost-effective screening in HCM families, will contribute to our understanding of the prevalence and outcome of individuals with nonhypertrophic HCM and allow pharmacological trials on a larger scale.[20]

Stage II: The "Classic" HCM Phenotype

Definition and Diagnosis

"Classic" *HCM phenotype* is defined as the phase in which the hypertrophic phenotype is fully expressed and the LV is hyperdynamic (as defined by an ejection fraction [EF] >65%), in the absence of extensive fibrotic changes suggesting unfavorable progression. More than three-quarters of HCM patients in cross-sectional studies belong to this stage (Figure 1).[23–25] The distribution of LV hypertrophy is typically regional and asymmetrical, generally involving the basal septum and anterior wall, but can develop in all imaginable patterns within the LV and involve the right ventricle and papillary muscles[3,7,10] (Figure 3 and Table). Besides cardiac hypertrophy, the HCM phenotype includes a constellation of mitral valve and subvalvar abnormalities, subaortic, midventricular and right ventricular outflow obstruction, atrial remodeling, coronary myocardial bridging, crypts, and autonomic nervous system abnormalities.[1,2,7,13] At the microscopic level, HCM is characterized by classic features such as myocardial disarray, microvascular remodeling, and interstitial fibrosis.[3,10]

The LV in "classic" HCM is characterized by small or normal-sized cavity and enhanced contractility. In a recent CMR study, resting LV ejection fraction (EF) in more than 300 unselected HCM patients averaged 71%.[23] In the presence of altered LV geometry and marked mitral valve abnormalities, enhanced contractility represents a determinant of dynamic LV outflow obstruction, occurring in resting conditions or under provocation in about 70% of patients.[1,7] Although regional diastolic abnormalities are almost always present, the transmitral filling pattern may be normal or only mildly abnormal (delayed relaxation); more severe degrees of diastolic impairment are less common and generally occur in patients with severe outflow obstruction or massive LV hypertrophy and restrictive pathophysiology.[7,9,23] Late gadolinium enhancement (LGE) at CMR is present in less than half of HCM patients with "classic" phenotype and occupies a small percentage of the LV, with a median value of 2%[23] (Figure 3D and Figure 4), suggesting that collagen deposition at this stage reflects an exaggerated activation of the matrix rather than a reparative process.[14]

Mechanisms of Disease

HCM-causing mutations are believed to trigger LV hypertrophy in response to compromised cardiomyocyte energetic balance,[2,21] due to the excess ATP utilization required to generate isometric tension within the sarcomere.[26] Additional disease mechanisms involve impairment of mechanisms that switch off contraction at low cytosolic [Ca^{2+}], leading to incomplete relaxation and diastolic dysfunction while increasing energetic compromise.[26–28] Chronic dysregulation of cardiomyocyte Ca^{2+} homeostasis may cause multiple downstream effects involving secondary activation of Ca^{2+}-regulated signaling pathways, cardiac remodeling and, possibly, apoptosis.[29]

Table.   Continued

| Atrial Remodeling†	Atrial Fibrillation†	NSVT	Complex Genotypes*†	Outcome	Priorities for Management and Research
Absent	No	No	Unknown; presumed rare	Favorable; SCD reported but exceptional	Prevention of disease development
Mild to moderate isolated LA dilation; severe only with LVOTO/MR	Rare; more common with long-standing LVOTO or in the elderly	Rare	3% to 5%	HF-related complications uncommon; SCD 0.5%/1%/y	Control of symptoms; relief of LVOT obstruction; risk stratification for SCD
Moderate to severe LA dilatation	Common	Common	Unknown; probably intermediate	Unknown; probably intermediate	Control of symptoms; management of AF and HF; prevention of progression; risk stratification for SCD
Severe bi-atrial dilatation	Very common	Very common	~15%	High HF-related mortality. SCD 10%/y	Amelioration of LV dysfunction and symptoms; management of AF and HF; consideration for ICD-CRT, VAD, and Tx
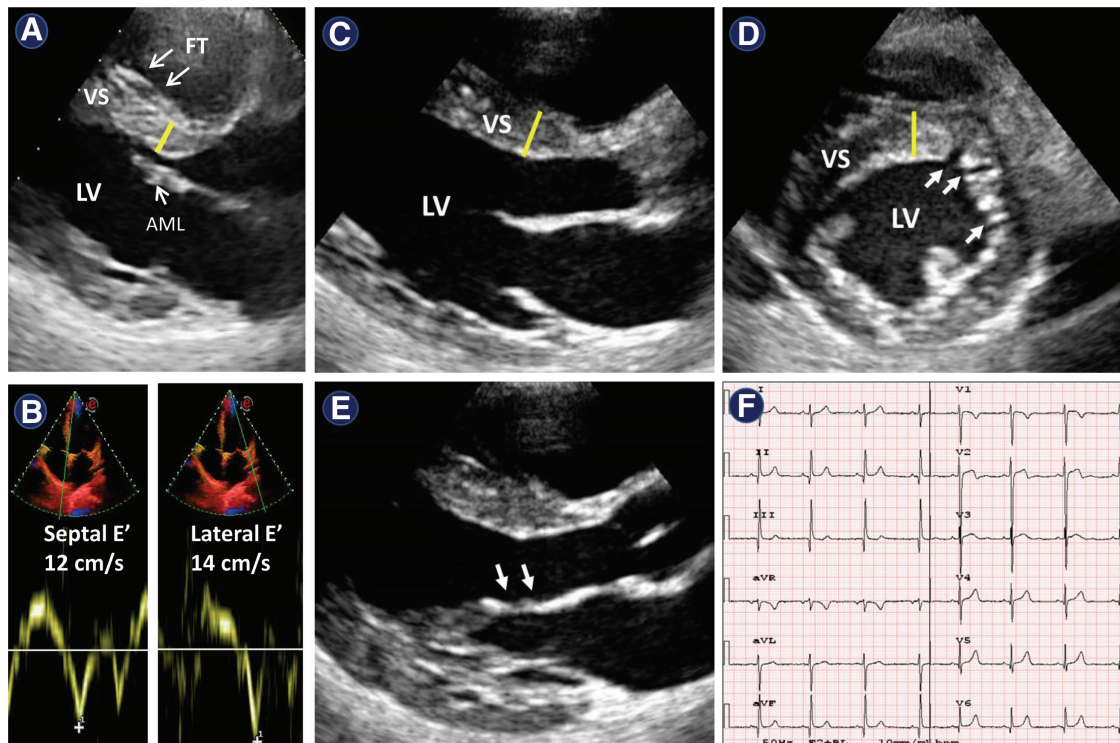
Figure 2. Nonhypertrophic stage and early phenotype. **A** and **B**, Twenty-six–year-old male patient with family history of hypertrophic cardiomyopathy, carrying the β-myosin heavy chain (MYH7) mutation Lys865Arg (NM_000257.2 c.2594A>G). Parasternal long-axis view shows normal LV thickness values, with redundant mitral leaflets (**A**). Tissue Doppler imaging velocities of the mitral annulus appear reduced (**B**). **C** and **D**, Ten-year-old boy carrying the myosin binding protein C (MYBPC3) mutation Glu258Lys (NM_000256.3 c.772G>A). Parasternal long- and short-axis views show mild increase in septal thickness (11 mm; **C** and **D**), with presence of crypts (**arrows**). **E**, Early systolic frame shows abnormal papillary insertion into the anterior mitral leaflet (**arrows**). Inferolateral Q waves are evident on the ECG (**F**). AML indicates anterior mitral leaflet; FT, false tendon, LV, left ventricle; and VS, ventricular septum.

Furthermore, sarcomeres and their Z-disk components are now recognized centers of mechano-sensation, mechano-transmission, and mechano-transduction.[30] In HCM, altered sarcomere mechanics due to faster force generation kinetics, hypercontractility, or incomplete relaxation may trigger hypertrophy and adverse remodeling by activating these sensors.[22] Of note, the abnormal sarcomere contractile status is held responsible for the persistent increase in sympathetic stimulation observed in HCM patients, itself a potential codeterminant of hypertrophy.[31] Finally, coronary microvascular dysfunction is a consistent feature of HCM, subtended by marked remodeling of the small coronary vessels, which appears to be genetically regulated and relatively independent of hypertrophy.[7,9,32] Although a powerful long-term predictor of progression to LV dysfunction and failure, microvascular dysfunction is not a sign of disease progression per se and, in "classic" HCM, it is not associated with evidence of permanent ischemic damage and replacement fibrosis.[7,9]

Clinical Course and Outcome

Once the "classic" HCM phenotype has developed, most patients experience long periods of clinical stability and may never undergo significant degrees of adverse remodeling or disease progression during their lifetime[7,10] (Figure 3A and 3B). Rather, a slow, almost imperceptible remodeling process occurs over the decades, overlapping changes related to physiological ageing.[33] Symptoms may vary and include dyspnea on effort, angina, atypical chest pain, syncope, and palpitations.[10,34] However, severe functional limitation is generally limited to individuals with severe LV outflow obstruction or restrictive physiology[24] (Figure 3E). Life expectancy is relatively favorable, with an annual cardiovascular mortality around 1%.[7,10,34] Although SCD rates are low in this subset, a subgroup of patients remain at high risk and should be identified by appropriate workup.[4,5,10]

Targets for Management and Research: Preserving Stability

Management in this stage focuses on relief of LV outflow obstruction and prevention of SCD. A detailed analysis of these issues goes beyond the scope of the present work: both have been the object of ongoing debate over decades and are extensively reviewed elsewhere.[4,5,10,12,34] Furthermore, long-term management strategies in patients with "classic" HCM include regular clinical scrutiny for signs of disease progression, prevention of cardiac comorbidity, and control of conventional risk factors such as sedentary lifestyle, hypertension, dyslipidemia, and diabetes.[10,19] In selected patients, such as those with exercise limitation and angina in the absence of obstruction, evaluation of microvascular function by PET may prove valuable in order to assess risk of long-term disease progression.[9]

Pharmacological treatment in this stage is mostly based on the time-honored use of β-blockers, calcium channel blockers, disopyramide, and amiodarone for control of symptoms, dynamic LV obstruction, and arrhythmias.[10,34] Specific
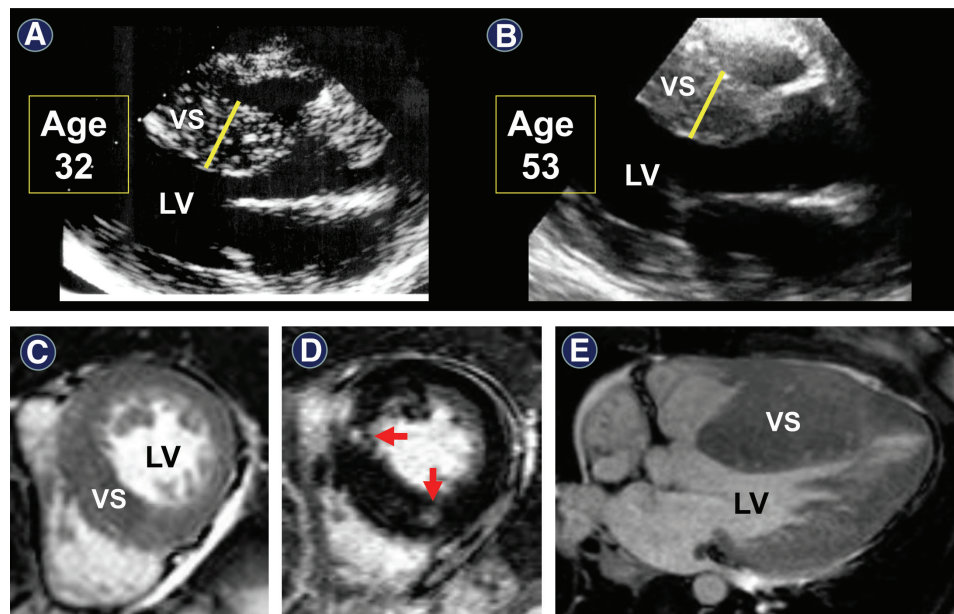
Figure 3. "Classic" hypertrophic cardiomyopathy (HCM) phenotype. **A** and **B**, This adult female patient with unknown genetic status remained totally asymptomatic over more than 2 decades, without treatment. Except mild left atrial remodeling, no changes in cardiac morphology or function were evident. **C** and **D**, Cardiac magnetic resonance (CMR) short-axis spin-echo (**C**) and delayed enhanced images (**D**) from a 66-year-old female HCM patient with the MYBPC3 mutation Tyr340X (NM_000256.3 c.1020C>G). Asymmetrical septal hypertrophy is evident, with limited areas of LGE at the right ventricular junction (**red arrows**). **E**, CMR long-axis image from a severely symptomatic 27-year-old male HCM patient with the MYH7 mutation Arg694Cys (NM_000257.2 c.2080C>T), massive LV hypertrophy, small left ventricular (LV) cavity size, and dynamic outflow obstruction. VS indicates ventricular septum.

treatments targeting cardiomyocyte energy deficiency and microvascular dysfunction are being investigated.[20,21,35] However, patients with "classic" HCM phenotype are not ideal candidates for the assessment of therapeutic interventions aimed at improving long-term outcome because of the low event rate, requiring large patient populations and very extended observation times.[36] More rewarding efforts are directed at investigating the effects of treatment on symptomatic status, myocardial energetic profile, microvascular function, and development of fibrosis.[3,20,22,26,35]

Stage III: Adverse Remodeling

Definition and Diagnosis

Adverse remodeling is defined by the presence of unfavorable structural modifications, superimposed to the "classic" HCM phenotype, translating into increasing LV fibrosis and worsening function (ie, an LVEF in the low-normal range of 50% to 65%), with relatively preserved clinical and hemodynamic balance. Rather than being an "average" process, this seems to represent a selective pathway followed by about 15% to 20% of HCM patients, a smaller proportion of whom will ultimately progress to overt dysfunction and heart failure[6-8,23] (Figure 1). Both the extent and time-course of LV remodeling are extremely heterogeneous: adverse changes may be observed at any age, including infancy and adolescence, and may lead to overt dysfunction and advanced HF in a brief span of time[37,38] but more often occur gradually over years or decades.[7,8]

The definition of this intermediate stage of disease progression is based on a combination of several structural and functional features including an LVEF in the low-normal

range,[23] moderate to severe diastolic function,[24-25] marked atrial dilatation,[39] moderate areas of LGE,[7,16,23,40] severe microvascular dysfunction,[9] thinning of the LV walls,[8] onset of atrial fibrillation (AF),[41] spontaneous reduction or loss of LV outflow obstruction,[8,42] and LV apical aneurisms.[43] Each of these features has been described separately in HCM cohorts, generally associated with adverse outcome. However, they show a consistent trend to cluster in individual patients, as though representing different aspects of disease progression in the same subset (Figure 5 and Figure 6). Because HCM is extremely heterogeneous, not all these "red flags" are expected to coexist in single patient and at the same time.[6,7] Rather, they might be seen as elements of an ideal cumulative score: the higher the score, the more likely the departure from a "classic" HCM phenotype toward adverse remodeling and progression.[6–9,23–25,39–41,43,44]

Adverse LV remodeling in HCM patients is subtended by variable and sometimes striking patterns of intramyocardial fibrosis, visualized by CMR as LGE, varying from moderate to large, confluent, infarct-like patches occupying significant proportions of the LV.[7,9-11,16,23,40] LGE generally shows a typical midwall localization, with sparing of the subendocardial region, but may be transmural when severe (Figures 5 and 6).[44] When substantial, the extent of LGE is inversely related to LVEF, supporting the view of discrete fibrosis as an expression of cardiomyocyte loss followed by a reparative process, ie, a scar.[23,44]

In HCM patients with low-normal LVEF values of 50% to 65% (representing 15% of the total cohort in one study), LGE was present in 67%, and constituted a median of 5% of the LV mass, with an interquartile range of 2% to 20%.[23] Such values
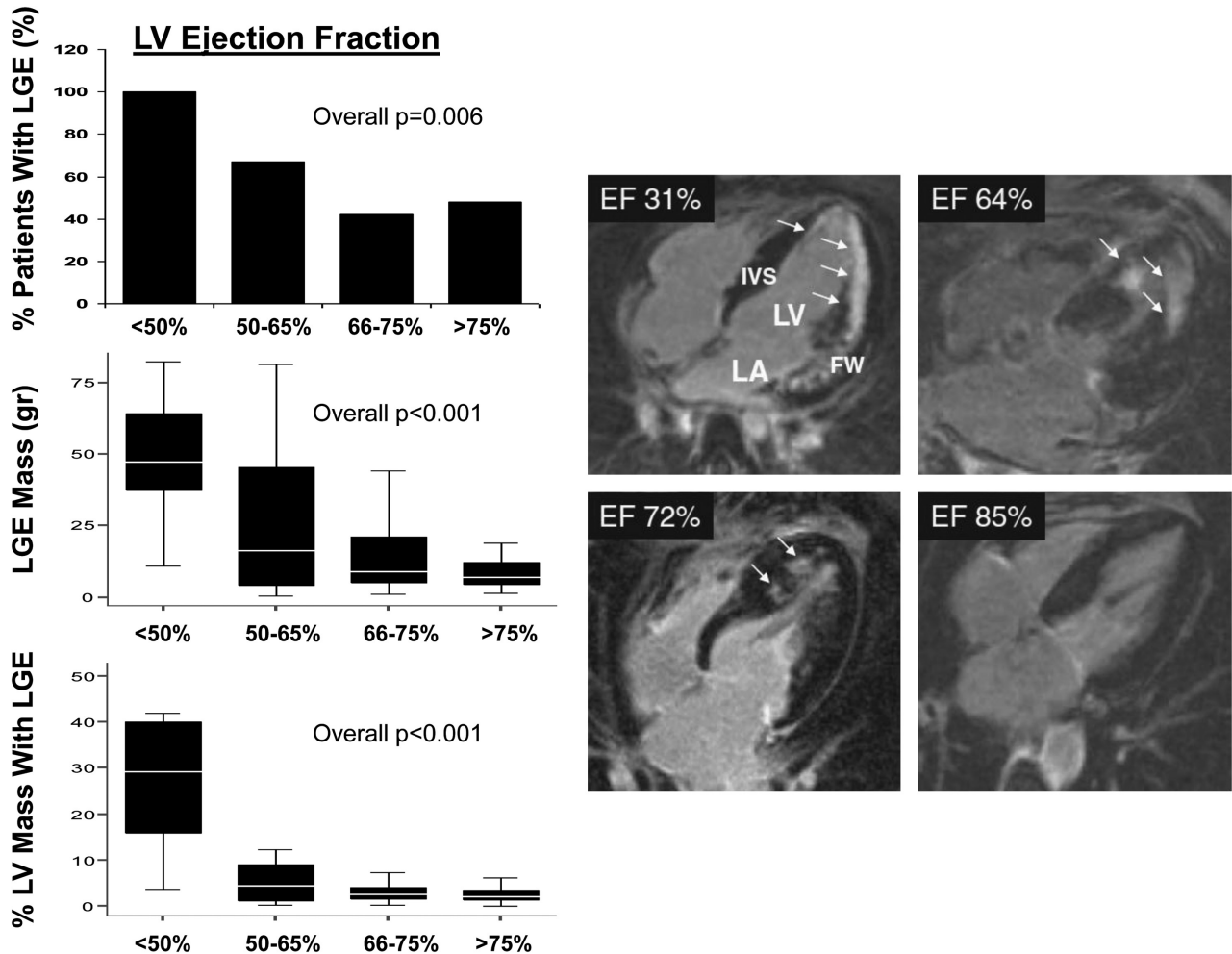
Figure 4. Relation of left ventricular (LV) ejection fraction (EF) to frequency and extent of cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) in 310 patients with hypertrophic cardiomyopathy (HCM). **Left panel: top**, Prevalence of LGE in 4 LVEF subgroups. **Center**, Box plot representing extent of LGE expressed as absolute mass in grams. **Black boxes** represent interquartile range; **horizontal white lines** represent median for each subgroup. **Bottom**, Box plot representing LGE expressed as percentage of overall LV mass. **Right panel**, LGE in 4-chamber vertical long-axis images of representative patients from the 4 LVEF categories. **Top left**, Twenty-year-old woman with end-stage progression showing extensive transmural myocardial fibrosis (LGE occupying 43% of LV wall; arrows). **Top right**, Sixty-one–year-old woman with low-normal EF showing transmural LGE occupying 24% of the LV. **Bottom left**, Thirty-five–year-old man with preserved systolic function showing limited nontransmural fibrosis occupying 8% of the LV. **Bottom right**, Forty-five–45-year-old man with supernormal systolic function showing absence of LGE. FW indicates free wall; LA, left atrium; and VS, ventricular septum. Reproduced from Olivotto et al.[23]

significantly exceeded those seen in patients with hyperdynamic LV and overlapped with patients exhibiting overt systolic dysfunction and LVEF <50% (Figure 4), suggesting that HCM patients with adverse LV remodeling and low-normal systolic function represent the reservoir from which advanced disease progression and the so-called "end-stage" disease will evolve.[6–8,23]

Mechanisms of Disease

Adverse LV remodeling in HCM appears triggered from within and probably reflects the interplay of microvascular ischemia, cardiomyocyte energy depletion and apoptosis, leading to progressive myocyte loss and fibrous substitution of the myocardium.[2,3,6,9,21,26] Of note, severe HCM progression is distinctively more prevalent in patients with complex genotypes, reflecting profound derangement of sarcomere mechanics and cardiomyocyte energetics.[3,15,16] Conversely, external triggers of adverse remodeling are seldom evident; factors such as viral myocarditis or epicardial coronary disease have been emphasized but are only anecdotally associated with disease progression.[7]

Clinical Course and Outcome

The clinical correlates of adverse remodeling may vary widely, ranging from mild to severe manifestations. Congestive symptoms may become evident, in the absence of LV outflow obstruction, paralleled by marked impairment of cardiopulmonary exercise testing and elevated titers of natriuretic peptides.[45] However, symptoms can be deceivingly mild and hinder the fact that disease progression has begun.[7,25] The onset of AF, relatively frequent in this phase, represents both an epiphenomenon and an important determinant of further cardiac remodeling and functional deterioration.[41,46]
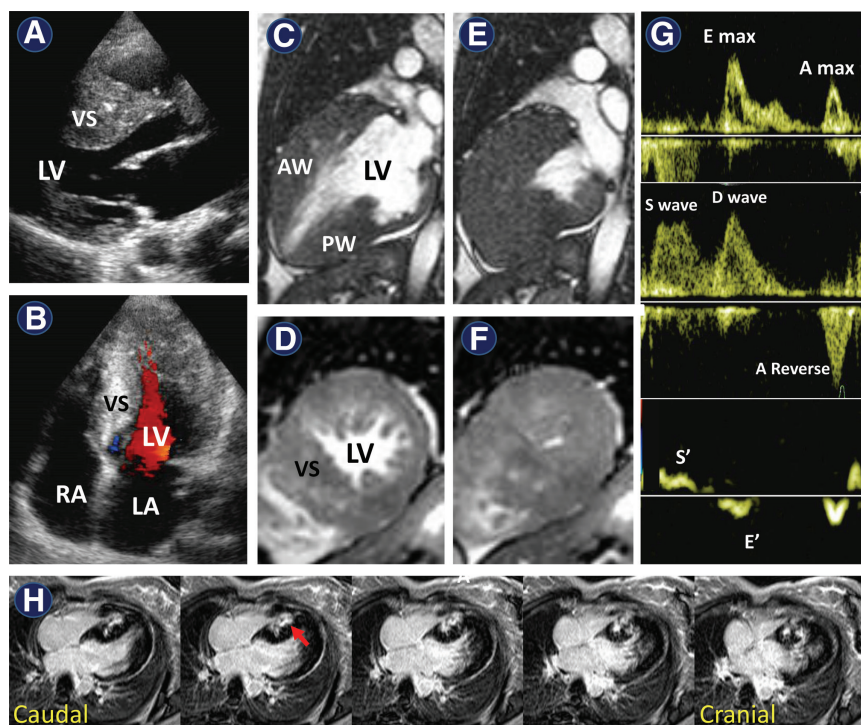
Figure 5. Adverse remodeling. Thirty-two–year-old woman with unknown genetic status and history of increasing dyspnea on effort. End-diastolic echocardiographic (**A** and **B**) and cardiac magnetic resonance (CMR) views (**C** and **D**) showing severe left ventricular (LV) hypertrophy, prevalently localized at the midapical portions, and left atrial dilatation. End-systolic CMR images (**E** and **F**) show preserved systolic function causing cavity obliteration. Diastolic function is markedly impaired (**G**), with pseudonormalized, triphasic LV filling pattern (**top**), prominent pulmonary vein reverse A wave (**middle**), and severely reduced mitral annulus tissue Doppler imaging velocity (**bottom**). End-diastolic long-axis images in **H** show substantial LGE involving the septum. AW indicates anterior wall; PW, posterior wall; and VS, ventricular septum.

The present attempt to describe a specific subset of HCM patients with early evidence of disease progression represents a novel concept which has not been assessed in longitudinal studies. As a result, the long-term outcome of this subset is unresolved. Based on studies addressing individual features of disease progression such as LA dilatation, AF, microvascular dysfunction, and LGE, it is plausible to expect cardiac mortality rates of about 3% to 5% per year, intermediate between the low risk associated with "classic" HCM phenotype, and the high risk associated with overt LV dysfunction.[9,24,25,39–41]

Targets for Management and Research: Opposing Deterioration
HCM patients with adverse cardiac remodeling should be considered at risk of further progression toward overt dysfunction and HF. Because such progression may occur over very extended periods of time,[7,9] close clinical surveillance with CMR, cardiopulmonary testing, and serial proBNP titration may prove valuable, potentially allowing for preventive treatment.[20,35] Specifically, the information provided by contrast-CMR is crucial for the identification of patients in transition from stages II to III and from stages III to IV,[23] although the advisable frequency of scans during follow-up remains to be determined.[10]

Adequately designed, prospective trials are urgently required to test which therapeutic strategies may have a potential impact on HCM progression.[3] Because of higher expected rates of cardiac events and HF-related complications, longitudinal studies focusing on patients with evidence of adverse remodeling may allow sufficient statistical power to assess outcome.[36] At present, it is plausible to consider timely implementation of treatments that have proven effective in other causes of LV dysfunction, such as modulators of the renin-angiotensin-aldosterone system.[10,34] The timing of therapy switch from "classic" HCM pharmacopea to antiremodeling HF treatment is challenging, and should take in account all the clinical "red flags" delineated above.[7,23] Too often, HF therapy is withheld in HCM patients until overt systolic dysfunction is evident, and the greatest potential is probably lost.[37,38] Such delay is often due to the fact that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are known to worsen LV outflow obstruction in patients with "classic" phenotype, and therefore considered inappropriate in HCM at large. Conversely, preclinical evidence suggests that these agents may exert beneficial effects at various stages.[20,47] Furthermore, intracellular metabolic modulators such as perhexiline and ranolazine have recently emerged as promising treatment options in this setting.[3,35]

Finally, aggressive management of AF is likely to play an important role in preventing functional and clinical deterioration in HCM patients.[41] Current strategies include pharmacological treatment with amiodarone and warfarin as well as with catheter-based techniques.[10,41,46] However, available evidence is limited and further research is warranted in the field.

Stage IV: Overt Dysfunction

Definition and Diagnosis
Overt dysfunction is an uncommon but challenging clinical evolution of HCM, characterized by severe functional deterioration of the LV (defined by an LVEF <50%), subtended by extreme degrees of fibrosis and remodeling and generally associated with hemodynamic decompensation and adverse outcome (Figure 7).[6–8,16,15,37,38] This subset coincides with so-called "end-stage" HCM, representing about 5% of patients in most cohorts. Maron and Spirito[8] masterfully
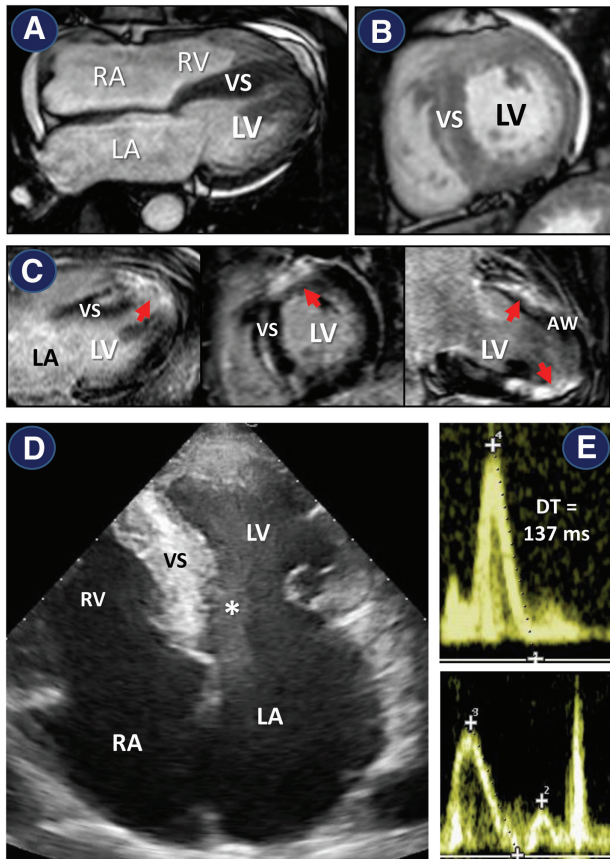
Figure 6. Adverse remodeling. **A** through **C**, Thirty-two–year-old man with unknown genetic status and paroxysmal atrial fibrillation. Four-chamber and short-axis cardiac magnetic resonance views (**A** and **B**) show marked biatrial dilatation, mild left ventricular (LV) hypertrophy with normal cavity dimensions, and low-normal LV ejection fraction (EF) (56%). Delayed-enhanced images (**C**) show substantial late gadolinium enhancement (LGE) involving the ventricular septum (VS), apex, and free wall (**red arrows**). **D** and **E**, Fifty-seven–year-old man with the MYBPC3 mutation c.407 to 1G>A. Echocardiographic 4-chamber view shows biatrial dilatation and smoke effect in diastole (**asterisk**). A restrictive LV filling pattern is evident (**E, top**), reflecting significant progression compared with the pseudonormalized pattern documented 4 years previously (**bottom**). LVEF was 62%. RA indicates right atrium; RV, right ventricle; AW, anterior wall; and DT, deceleration time.

Figure 7. Selected gross and histopathologic features of patients with the end-stage of hypertrophic cardiomyopathy. **A** and **B**, Distal cross-sectional views of explanted hearts with systolic dysfunction but persistent and marked left ventricular (LV) wall thickening in the absence of cavity dilatation; in **B**, transmural scarring (white areas) is diffuse and circumferential involving virtually the entire LV wall. **C** and **D**, Low-magnification views of LV myocardium shows large areas of replacement fibrosis, which in **C** contains abnormal intramural coronary arteries with thickened walls and narrowed lumen (**arrowheads**). Trichrome stain; magnification ×40 and ×20, respectively. **E**, Area of cardiac muscle cell disorganization in which adjacent myocytes are arranged at perpendicular and oblique angles; one abnormal intramural coronary artery (**arrow**) is evident. Hematoxylin and eosin stain; magnification ×200. **F**, Fibrotic area of LV myocardium, including trabeculations. Trichrome stain; magnification ×40. Reproduced from Harris et al.[37]

described this process in 1998: "…the typical clinical profile of the individual patient with HCM evolving through the end-stage emerges as that of a young or middle-aged adult (age 20–40 years) in whom accelerated clinical deterioration occurs over approximately 5 to 6 years. During this period, LV wall thickness regresses about 25% (from 20–15 mm, on average) at a rate of 1.0 to 2.0 mm per year, LV end-diastolic cavity dimension increases about 20% (from 45–55 mm, on average) at a rate of 1.0 to 1.5 mm per year, and up to 3 to 4 mm per year, and is accompanied by a parallel increase in end-systolic dimension. Ejection fraction may decrease substantially from supranormal values (>70%) to <45%, but often only to slightly below the lower limits of normal subjects."

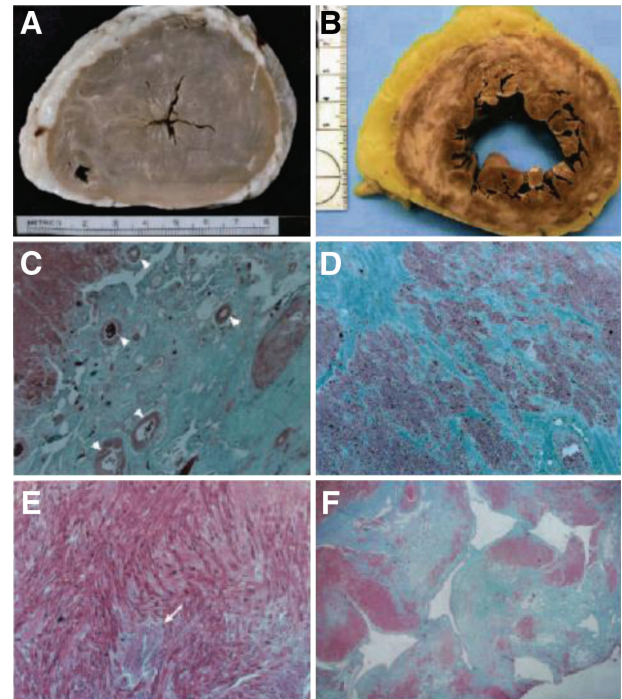The morpho-functional manifestations of HCM in this advanced stage span between two extremes. The first can be defined as the *hypokinetic-dilated* form, characterized by volume increase and spherical remodeling of the LV. In the most severe cases, this variant may be hard to distinguish from a primary dilated cardiomyopathy, and the diagnosis of HCM relies either on prior documentation of asymmetrical LV hypertrophy or family history.[7,37,38,48] However, such diagnostic dilemma is uncommon, as the degree of dilatation in HCM is virtually never as marked as that of dilated cardiomyopathy, and residual, focal hypertrophy is often retained (Figure 8A through 8D). Additional features such as right ventricular dilatation/dysfunction, pulmonary hypertension, and functional mitral regurgitation may be observed in variable degrees; conversely, LV outflow obstruction is always absent.[10,16,37,38]

The other variant, which can be denominated *hypokinetic-restrictive* (Figure 8E through 8I), is characterized by a small and stiff LV with extreme diastolic dysfunction, resembling primary restrictive cardiomyopathy; in contrast, systolic function is only mildly or moderately impaired.[24,38,49] Some degree of residual asymmetrical hypertrophy is evident although generally mild, as a consequence of progressive
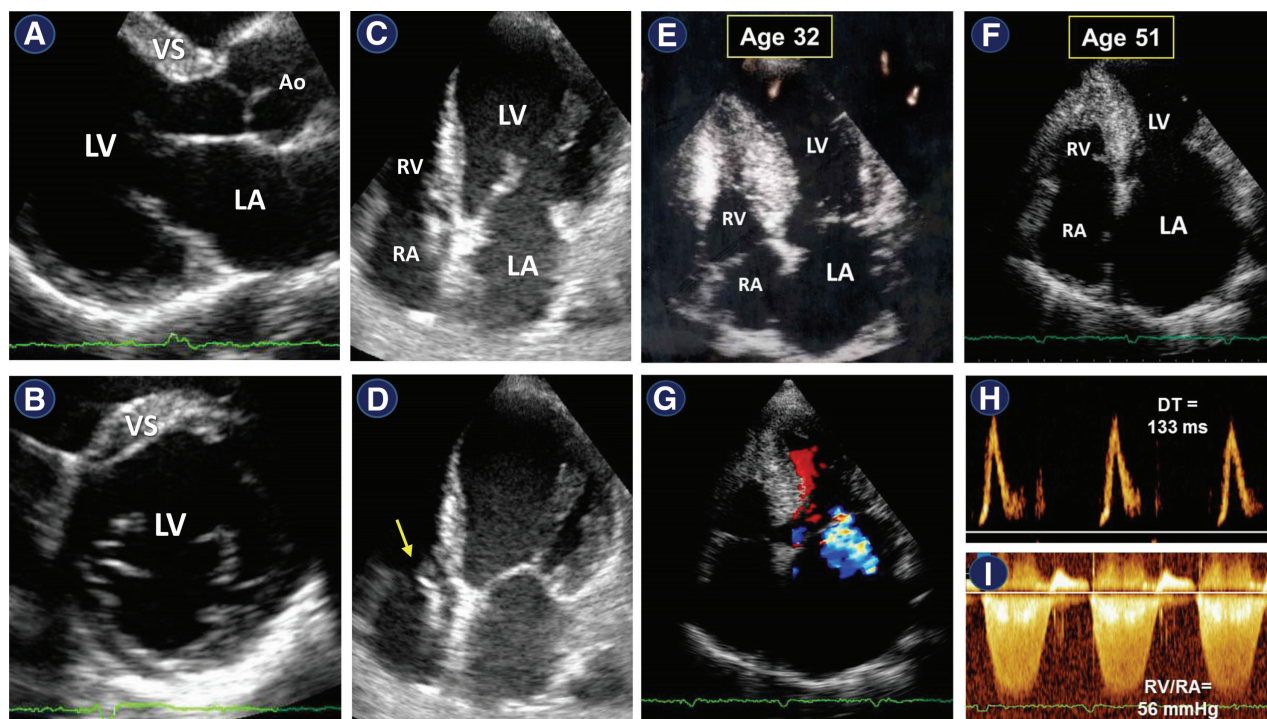
Figure 8. Overt dysfunction. **A** through **D**, Hypokinetic-dilated hypertrophic cardiomyopathy (HCM): 58-year-old female patient with family history of sudden cardiac death, diagnosed at age 31 years. After recurrent sustained ventricular tachycardia, she received an implantable cardioverter-defibrillator (ICD) at age 51 years. At last evaluation, she showed marked left ventricular (LV) dilatation and severe systolic dysfunction (LV ejection fraction [EF],18%). Currently awaiting cardiac transplantation, she has had an episode of appropriate ICD discharge caused by ventricular fibrillation. **A** and **B**, End-diastolic parasternal long- and short-axis views. **C** and **D**, End-diastolic and end-systolic apical 4-chamber view. **Arrow** indicates the ICD catheter. E through I, Hypokinetic-restrictive HCM: female patient with family history of HCM, carrying the MYBPC3 mutation Glu258Lys (NM_000256.3 c.772G>A). At age 32 years, she had typical asymmetrical septal hypertrophy with hypercontractile LV and labile outflow obstruction (**E**). Over 2 decades, she developed heart failure, thinning of the septum, loss of LV outflow gradient, marked biatrial dilatation (**F**), moderate mitral regurgitation (**G**), severe diastolic dysfunction, and pulmonary hypertension (**H** and **I**). Final LVEF was 42%. After the onset of permanent atrial fibrillation, she had a cardioembolic stroke, and at age 52 years she died suddenly, having refused an ICD. VS indicates ventricular septum; LA, left atrium; Ao, aorta; DT, deceleration time; and RV/RA, peak right ventricular/right atrial gradient.

fibrous substitution and thinning; marked biatrial dilatation and AF are almost invariably present.[9,49] This phenotype can be associated with most known HCM-causing sarcomere genes, although possibly more common in patients with thin filament mutations. In addition, the London group has demonstrated in 2007 that β-myosin heavy chain and cardiac troponin I mutations can rarely cause a primary restrictive cardiomyopathy phenotype that appears to represent a different entity from HCM.[49] Very recently, Caleshu at al[50] have reported that mutations in TPM1, MYL3, and MYL2 can be associated with primary, nonhypertrophied restrictive cardiomyopathy, providing further evidence that mutations in sarcomere genes can cause a spectrum of phenotypes besides HCM, including also dilated cardiomyopathy and isolated LV noncompaction.[2]

Mechanisms of Disease

Overt dysfunction represents the extreme consequence of adverse remodeling in HCM patients and is therefore subtended by the same mechanisms.[3,6,7,9,16,17,23,25,32,40,44] In the most severe cases, the process is so advanced that structural and molecular changes in the myocardium represent terminal manifestations overlapping those of other failing hearts.[37,48] Thus, a major challenge is represented by the identification of an ideal "tipping point" separating reversible from irreversible stages

of dysfunction.[6] Important insights might be gained by comparing myocardial global gene expression in different phases of HCM with that of other states, such as severe HF and recovery of ventricular function after HF reversal. Indeed, reversible changes in the expression of genes encoding sarcomeric and nonsarcomeric cytoskeletal and linker proteins, integrins, calcium-handling proteins, extracellular matrix components and regulators, metabolic enzymes, and others have been demonstrated to progress in severe HF and reverse during recovery.[6,51]

Clinical Course and Outcome

The terms *end-stage* and *burned-out phase* have entered common use for HCM patients with overt dysfunction, largely for lack of a better term.[3,6,10,34] In our opinion, such denomination is often inappropriate, in that it evokes a terminal state, which must necessarily proceed to refractory HF and heart transplantation or death. Indisputably, the outcome of HCM patients in this stage is severe, not only due to high rates of HF-related complications and mortality but also because of a considerable incidence of SCD exceeding 10% per year.[10,25,37,38,48] However, rates of clinical deterioration and clinical fate, even in the presence of severe LV impairment, may vary considerably.[6,7]

At the most severe end of the spectrum, there are patients who rapidly develop the full-fledged syndrome of congestive

HF and face adverse outcome; however, such occurrence is rare in HCM cohorts. For example, at our institution, less than 2% of patients have required cardiac transplantation or have died in refractory HF before the age of 50 over the last 3 decades (unpublished observation); similar rates are reported by other referral centers performing cardiac transplantation.[48] On the other hand, the decline in LV function and progression of symptoms may be slow, particularly in older individuals, and many patients can be stabilized for years, benefiting from the full armamentarium of HF treatment.[10,34,52] Of note, the hypokinetic-restrictive subtype constitutes a larger percentage of advanced heart failure HCM patients than the dilated type.[49] These patients do not typically present in overt heart failure with clinical signs of congestion but rather with low cardiac outputs on the basis of restrictive filling.[24,38] Therefore, they are more challenging to recognize and manage, as they do not tolerate nor benefit from the standard heart failure therapies. Furthermore, most are not candidates for left ventricular assist devices (LVAD) because of small cavities and relatively preserved contractile function.[51] Early hemodynamic assessment and oxygen consumption stress testing is crucial to avoid missing a window for transplant listing.[48]

Targets for Management and Research: Reversing Failure

Overt dysfunction is a challenging but self-declaring condition, in which clinical severity is evident and management necessarily aggressive, based on standard guidelines for HF.[10] Commonly accepted measures include ACE inhibitors and angiotensin receptor blockers, HF-specific β-blockers, spironolactone, loop diuretics, and, in the presence of AF or an apical aneurysm, oral anticoagulants for cardioembolic prevention.[10,34,37,38,41] In addition, overt LV dysfunction should be considered a potential indication for primary arrhythmic death and implantable cardioverter-defibrillator implantation.[37]

Biventricular pacing for cardiac resynchronization therapy has been anecdotally reported as effective in HCM patients with systolic LV dysfunction.[52] However, there are no standardized criteria for implantation, and identification of potential responders remains empirical. It is unlikely that criteria developed in postinfarction or dilated cardiomyopathy patients may be applicable to HCM, given its peculiar LV geometry and pathophysiology. Nevertheless, resynchronization represents a very promising option for the improvement of LV efficiency and symptoms in HCM patients with overt dysfunction and should be specifically investigated.[3,10,52]

Finally, tailored surgical options may be present in individual cases. These include mitral plasty to correct annulus dilatation and regurgitation, implantation of an LVAD, and cardiac transplantation.[48,51] Although specific data on HCM patients are not available, the concept of myocardial recovery after LV unloading deserves investigation in HCM patients with advanced disease.[51]

Conclusions: Understanding Diversity
Few cardiac diseases are as heterogeneous as HCM. Individual patient variability with regard to timing of onset, phenotype, and clinical course is extreme, constantly defying rigid classifications. The reasons for such diversity, even within

members of the same family, are poorly understood and potentially range from epigenetic to environmental factors. Although not uncommon in the general population, HCM is an orphan disease, in that most therapeutic decision are not evidence-based, and limited efforts are aimed at conducting properly designed clinical trials, for which the time is now ripe. Furthermore, there is limited awareness among patients and physicians regarding the risk of disease progression in HCM, and its recognition is therefore delayed—often to the advanced and truly "end-stage" phases. Further, extensive research is warranted in the field to identify treatment strategies that may effectively reverse such progression. It is hoped that a clinically meaningful definition of the stages of disease may represent an important prerequisite for future initiatives aimed at tailoring management to individual HCM patients' needs, in a concerted effort to improve quality of life as well as outcome.

Disclosures
None.

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Patterns of Disease Progression in Hypertrophic Cardiomyopathy: An Individualized Approach to Clinical Staging
Iacopo Olivotto, Franco Cecchi, Corrado Poggesi and Magdi H. Yacoub

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Supplemental Material

Movie 1. At admission. Subcostal view: pericardial tamponade with compression of the right ventricle

Movie 2. MRI-scan 20 days after heart rupture. Apical-midventricular view, SSFP (cine).

Movie 3. Day 17 after ECMO explant. Subcostal view: regress of tamponade and compression of the right ventricle

Movie 4. Day 17 after ECMO explant. Left parasternal short axis view: inferoseptal left ventricle wall rupture

Movie 5. Day 17 after ECMO explant. Colour Doppler in left parasternal short axis view: inferoseptal left ventricle wall rupture

Movie 6. MRI-scan 4 months after heart rupture. Apical-midventricular view, delayed enhancement (DE).