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LV twisting and untwisting in HCM: Ejection begets filling. Diastolic functional aspects of HCM

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Abstract

Conventional and emerging concepts on mechanisms by which hypertrophic cardiomyopathy (HCM) engenders diastolic dysfunction are surveyed. A shift from familiar left ventricular (LV) diastolic function approaches to large-scale (twist-untwist) and small-scale (titin unfolding-refolding, etc.) wall rebound models, incorporating interaction and dynamic distortions and rearrangements of myofiber sheets and ultrastructural constituents, is suggested. Such an emerging new paradigm of diastolic dynamics, emphasizing the relationship of myofiber sheet and ultraconstituent distortion to LV mechanics and end-systolic shape, might clarify intricate patterns of early diastolic rebound and suction, needed for LV filling in many of the polymorphic phenotypes of HCM.

Janus was a Roman deity with 2 faces (*Janus bifrons*), looking backward and forward simultaneously just as gates look in both directions (Figure 1). He too watched entrances and exits, and his shrines were located at crossing places or intersections.

The left ventricle as Janus bifrons

The pumping left ventricle forms the intersection or central link (Figure 1) between the low-pressure and the high-pressure systems of the circulatory ensemble.¹ It is a suction-compression positive-displacement pump, exhibiting both self-regulating properties as an independent organ and dependent properties as part of the overall circulation. In diastole, it adapts to the low-pressure system from which it draws blood, whereas, in systole, it adjusts to the high-pressure system into which it must force blood. For that reason, it needs to alternate between the widely disparate functional-structural requirements of systole and diastole.¹

Since like Janus it can look directly backward and forward, into the low- and high-pressure systems, it displays remarkable Janus-like characteristics. Hence, it subserves at times incongruous functions, such as when excessive wall hypertrophy in response to a systolic pressure overload is associated with diminished diastolic distending wall stress levels and, not uncommonly, with increased muscle stiffness, both of which may then be responsible for impaired left ventricular (LV) diastolic filling.^{2–4} Almost all forms of heart disease and most strikingly hypertrophic cardiomyopathy (HCM) alter ventricular structure. The changes in

LV configuration may in themselves set the stage for cardiac dysfunction, by disturbing the dynamics of the interaction of the ventricle with the diastolic and/or systolic components of the circulation. A companion survey addresses systolic peculiarities of LV dynamics in HCM.⁵ Here we examine filling dynamics and diastolic function. More extensive and in-depth discussions can be found elsewhere.^{1,6}

What goes out must come back in—before it can go out again

What goes out must first come back into the ventricle. Thus, maintenance of stroke volume and cardiac output depends not only on systolic performance but also on the capacity for adequate diastolic LV filling. This is influenced by diastolic duration, venous return,^{7,8} the interplay of active myocardial relaxation and passive diastolic properties,^{3,9–12} by systolic torsion release and diastolic recoil,^{13–18} by external constraints including the pericardium and pleural pressures,^{7,8,19,20} coronary flow and vascular turgor (“erectile effect”),^{21–25} and atrial contraction. Since at end-diastole the atrium is ordinarily about one third the LV size, atrial contraction can contribute 15% to 35% of LV end-diastolic blood volume, depending on heart rate and other applying conditions.^{26–31} Diastolic function and its interacting determinants are systematically explored in previous reviews.^{3,9,15,32–40}

When heart rate increases, diastolic filling time decreases and, for adequate stroke volume and cardiac output maintenance, filling rates must rise; for example, with a resting rate of 60 beats/min, up to 500 ms is available for filling, but with an exercise tachycardia surpassing 160 beats/min, the full stroke volume must be replenished in 100 ms or less.⁴¹ This demands a speedier energy-dependent myocardial relaxation and accentuated atrial topping off (atrial kick) of end-diastolic ventricular volume. Ventricular pumping problems and heart failure may reflect compromised filling and are elicited or accentuated by exercise or by a dobutamine stress test if ergometric exercise is unfeasible.⁴²

LV diastolic dysfunction in HCM demonstrated by multisensor left heart catheterization

As early as 1962, it was already recognized that hypertrophy in HCM “could disable a patient more from poor ventricular filling in diastole, than from obstruction to outflow in systole.”⁴³ Subsequently, our understanding of diastolic HCM pathophysiology has been promoted by modern invasive and noninvasive instrumentation, including imaging modalities.⁴⁴ Their utilization has been facilitated by digital data acquisition and signal processing⁴⁵ and by high-power digital computing methods,⁴⁶ which have made possible detailed assessments of ventricular function. As an example of advanced instrumentation, Figure 2 illustrates severe diastolic dysfunction in HCM revealed by multisensor left heart catheterization during supine ergometer cycle exercise.⁴⁷ Particularly striking in Figure 2 during exercise is the persistently downsloping in HCM micromanometric LV pressure throughout the diastolic period up to the ensuing atrial contraction. This is to be contrasted with the exercise-induced sharp upslope of LV diastolic pressure in the juxtaposed normal, catheterized for angina symptoms, in whom no disease was found. This raises the question: why such a striking difference?

It has been known since the cardiac cycle observations of Wiggers⁴⁸ in the 1920s that, during early rapid filling (from mitral opening to minimum diastolic pressure), a paradox is observed: LV dimensions are increasing while pressure is declining. How can this be? Anomalies, or paradoxes, do arise in medicine, which the prevailing tenets cannot resolve and, in time, some new conceptual approach resolves the paradox by a paradigm change. Wiggers' paradox led me during the late 1970s to formulate a mathematical model in which the processes transpiring during early diastole are neither purely passive nor purely active. This diastolic relaxation-passive filling (RPF) model accomplishes evaluation of passive wall stiffness in intact beating ventricles by single-beat analysis (ie, using multiple pressure-volume coordinates from a single beat); before it, related evaluations required multiple beat analysis (ie, end-diastolic pressure-volume coordinates from multiple beats). In it, the total (micromanometric) measured ventricular diastolic pressure, P_M , is determined by 2 overlapping processes: (a) the ongoing decay of actively developed pressure, P_R , and (b) the progressive buildup of passive filling pressure, P^* , as shown in Figure 2, bottom right. The degree of impairment of the relaxation rate compared with the rapidity of pressure rise with passive filling determines the slope exhibited by P_M .

The RPF model was introduced at the American Heart Association's 53rd Scientific Sessions in Miami Beach, FL, in November 1980.⁴⁹ It took several years of effort before the full paper presenting the new paradigm⁵⁰ was eventually accepted and published in *Circulation*. As emphasized by Thomas Kuhn in *The Structure of Scientific Revolutions*, dialogue can become difficult between the adherents of different paradigms. Here, "different paradigm" implies a different way of understanding based on different fundamental concepts; these giving rise to different kinds of questions and of acceptable answers. The RPF model has guided observations by imposing order on the complexity of (early) diastolic filling and indicating which parameters are important for study.^{49,50} This has allowed evaluation of the roles of interacting active and passive dynamic factors in cardiac diastolic mechanics in numerous studies extending to the present.³²⁻³⁷

Diastolic dysfunction and signs of impeded filling in HCM

Diastolic LV dysfunction is a key determinant of symptoms in HCM, including breathlessness, orthopnea, paroxysmal nocturnal dyspnea, angina accompanying impaired diastolic relaxation, and exercise limitation. Wide variation exists in phenotypic expressions of genetic mutations underlying HCM, with corresponding symptom variability. Consequently, underpinnings of diastolic LV dysfunction in HCM are multifactorial and several mechanisms may participate, including increased pericardial constraint from massive cardiomegaly.^{3,12,51} Specifically, abnormal myocardial calcium fluxes and kinetics, reflecting proliferation in sarcolemmal Ca^{2+} channels or delayed Ca^{2+} reuptake into the sarcoplasmic reticulum and resulting in raised intracellular $[Ca^{2+}]$, may produce cardiomyocyte hypertrophy and cellular disarray.⁵²⁻⁵⁴ A clinical implication is that early pharmacologic intervention to improve Ca^{2+} dysregulation may improve the natural history of HCM.⁵⁵ Successful intervention would represent development of a new Kuhnian treatment paradigm: attenuation of penetrance and expressivity of genetic HCM mutations by altering a disease mechanism.

Myocyte and massive global or localized wall hypertrophy^{56,57} and cellular and myofibrillar disarray reflecting, in part, abnormal mutated sarcomeric proteins⁵⁴ distort cardiac geometry and encroach on the LV chamber. Moreover, intramural coronary arterial wall thickening with luminal narrowing are implicated in myocardial ischemia.⁵⁸ Diastolic dysfunction is best assessed noninvasively by Doppler echocardiography, remembering that “pseudonormalization” of the transmitral filling pattern can occur with passive atrial distension accompanying mitral regurgitation linked to systolic anterior motion of the mitral valve (SAM)—the Valsalva maneuver acutely decreases atrial filling in phase 2 (reduced venous return) and may unmask the abnormal relaxation and inflow pattern. Admittedly, diastolic dysfunction’s relation to particular patient symptoms is difficult to ascertain.⁵⁹ Nevertheless, there is evidence that time to peak filling rate may be a determinant of exercise tolerance,⁵⁷ and an improvement in indices of ventricular filling during therapy with calcium antagonists (eg, diltiazem) results in improved exercise capacity.^{60,61}

Remarkably, diastolic HCM abnormalities may be more or less prominent. This might be expected for a disease characterized by profound genetic and epigenetic phenotypic heterogeneity, with substantial variation in expressivity and age-dependent penetrance.^{62–65} Abnormalities span the gamut, starting from those that can accompany substantial physiologic remodeling hypertrophy as seen in some athletes. They develop in a quantitatively more severe progression through derangements that come with compensatory reactive adaptations to pathological systolic pressure overloads (eg, in hypertension and aortic stenosis). Such adaptations bring about transition to pathologic diastolic changes that impair the intrinsically Janus-like characteristics of the left ventricle embodied in Figure 1. In many patients, they may transition into distinctive qualitatively new problems peculiar to HCM. I have already referred to helpful reviews of typical diastolic abnormalities in concentric LV hypertrophy that are shared to variable extents by HCM; accordingly, I now focus on the distinctive, qualitatively new, transitions to diastolic pathology that are *peculiar* to HCM.

Interaction of the diastolic LV flow field and restricted chamber compliance

Heart sounds should be regarded as vibrations of the cardiohemic system attendant to flow acceleration or deceleration.⁶⁶ Within this concept of sound generation, mitral inflow deceleration in early and late diastole underlies the third (S3) and fourth (S4) heart sounds. With normal sinus rhythm, an S4 is the norm in HCM, resulting from an energetic atrial contraction into the noncompliant LV cavity.⁶⁷ Most provocative is that an S3 is also found regularly in HCM.⁶⁸ The S3 gallop can appear as a rumble in both sinus rhythm and atrial fibrillation, often having vibrations of considerable duration.⁶⁹ An S3 in HCM can resemble the “knock” of pericardial constriction, when pericardial thickening or calcifications interfere with chamber expansion and filling. Such titillating diastolic sounds are common in HCM.^{69–73} They reveal extreme filling opposition, secondary to the seriously compromised by the massive hypertrophy effective LV compliance.

Acceleration of a laminar fluid flow has a stabilizing and deceleration a destabilizing effect. Generally, intracardiac flows, being strongly time-dependent and nonuniform in space, can have complicated stability characteristics.^{1,6,74–77} Figure 3, top, is adapted from a systolic

companion survey⁵ and shows representative instantaneous velocities and streamlines in the systolic ejection flow field of HCM progressing toward LV cavity obliteration. Figure 3, bottom, subpanel *a*, displays what one might, based on the top panel, expect the inflow field to look like in the ensuing early filling: similar velocity vectors but pointing in reverse. Blood flowing in the flow field depicted in the long axis in subpanel *a* and in the short axis in *b* is subject to strong dynamic convective deceleration,⁵ with decreasing velocities as it flares out toward the actinomorphic (Gk., with radial symmetry) receding chamber walls. This brings about a Bernoulli pressure rise downstream.⁵

This adverse dynamic situation yields a powerful instability that leads to a breakdown of the diverging streamline pattern and a highly disturbed, eddying flow regime, as is illustrated in subpanel *c*. These eddies are a “sink” for flow momentum and kinetic energy associated with the inflow. Inflow kinetic is thus converted into turbulent kinetic energy and ultimately into heat (viscous dissipation). Eddying flow regimes generate audible murmurs and rumbles, which explains the S3 rumble simulating mitral stenosis referred to above. These phenomena represent pseudosound, uninfluenced by compressibility and consisting of pressure disturbances generated by rapid fluctuations of the local velocity field of turbulent eddies.⁷⁴ It is through the recognition that deceleration has a flow destabilizing effect leading to eddy generation, that the diastolic HCM rumbles make fluid dynamic sense!

Eddying flow regimes generally consist of a hierarchy of eddies of various orders⁷⁴; there is an irregular “eddy cascade” in which the energy of the overall flow is transmitted to eddying motions of progressively diminishing size, down to the smallest possible scale, which is stable.⁷⁴ To be stable, these extremely small eddies must represent a low-inertia and low-Reynolds number regime. Now, viscosity plays an important role, and there is dissipation of the kinetic energy of inflow into heat.⁷⁴

Mutually counteracting local acceleration and convective deceleration effects in mitral inflow with diverging streamlines

I have previously demonstrated and explained in depth^{75–78} that, during the E-wave upstroke, the total pressure gradient along the inflowing stream is the algebraic sum of a downstream pressure decrease contributed by local acceleration (time derivative of velocity)⁴⁵ and a pressure rise contributed by convective deceleration⁴⁵ that partially counterbalances the local acceleration gradient. This counteracting action in the flow field with diverging streamlines (see Figure 3, bottom, subpanels *a* and *b*) is what underlies the peculiar apparent smallness of early diastolic intraventricular pressure gradients in both cardiac ventricles.^{76–78} On the other hand, in the flow field with converging streamlines (Figure 3, top) during ejection, throughout the upstroke of the ejection waveform both convective and local acceleration effects act in the same sense, actually reinforcing each other.^{1,46,47,74,75}

With a compliant LV, during the normal early gushing E-wave upstroke the flow kinetic energy is converted by Bernoulli energy interchange into wall-distending static pressure. In the HCM situation depicted in Figure 3, bottom, the inflow kinetic energy is diverted into deflected eddies and is merely degraded into wasted heat. This process and its repercussions are not at all negligible in the context of diastolic filling.

Peculiarities of LV diastolic filling hindrance in HCM

Inspection of the muscle-bound left ventricle (end-systolic configuration in rigor mortis) in Figure 3, bottom, subpanel *d*, which incorporates features from classic anatomic photographs,^{79–81} suggests that any inception of filling of such a structure under diastolic transmural pressure levels should be unattainable—what with the very small chamber radius and surrounding massive walls! The geometric repercussions of the end-systolic HCM geometry for wall stress and the effective transmural pressure required to initiate distension and filling are daunting: remember, by Laplace’s law (Figure 3, bottom, subpanel *d*), wall stress decreases with radius and wall thickening—and this without even taking into consideration the relaxing, incompletely decayed, contractile wall stresses discussed earlier in the context of the RPF model.^{49,50} The auscultatory S3 gallop described above is evidently a manifestation of the difficulty to expand the end-systolic ventricle, with inflow energy diverted into dissipative eddies.

Beyond any doubt then, should there not be some exceptional distinctiveness in the LV filling dynamics of HCM, which does not need come into play in other—normal or abnormal—settings? Despite an increasing number of papers devoted to diastolic dynamics in various HCM phenotypes, this is a question that has up until now escaped any mention in the literature.

The preceding considerations lead me to infer that, in some HCM phenotypes, the initial LV chamber enlargement needed to allow initiation and further progression of diastolic filling must be directly or indirectly dependent on active forces. This dependency on active forces is absolute and essential even for the *inception* of LV diastolic filling in cases with LV cavity obliteration (with nearly or virtually complete end-systolic emptying). It should not necessarily conjure up active muscular contraction in the sense of the action of antagonist extensors opening a fist closed by flexor muscles (see Figure 4, bottom). Nonetheless, the functional anatomist Torrent-Guasp has argued that the anatomy of the ventricular myocardial band (VMB), which he described, and its segmental electrical and mechanical activation indicate that normal filling is the consequence of such an active muscular contraction.^{13,15,16,82}

What is needed for filling in the peculiar situation of HCM is not merely auxiliary recoil forces coming into play at end-systolic volumes smaller than a so-called equilibrium volume,^{83–85} obtained with a ball-in-cage mitral anulus occluder in anesthetized open-chest dogs, for which no evidence was found using Inoue transvenous mitral commissurotomy balloon catheters to occlude mitral inflow in human multisensor catheter investigations.⁸⁶ In any event, this related concept has no bearing on the situation under consideration, in view of the myocardial anatomic and histoarchitectonic aberrations that render meaningless any notion of an “equilibrium volume.” However, the fundamental idea of a release of strain energy stored during systolic myocardial contraction, as depicted in Figure 4, top, dominates the dynamics.

Diastolic rebound in HCM

Figure 5, I, schematically highlights the basic concept allowing inception of filling in HCM cases exhibiting angiographically virtual LV cavity obliteration and muscle-bound end-systolic lumen. Two masses interconnected by a spring are compelled toward each other by some force, squeezing the spring in the process; if the force is subsequently removed, the spring rebounds, accelerating the masses away from each other. Clearly, neglecting dissipative effects, work performed by the squeezing force was stored as spring compression strain energy, which subsequently was converted into kinetic energy of motion of the separating masses, stretching the spring and becoming converted again into spring expansion strain energy. Such bidirectional interconversion cycles would continue indefinitely in absence of energy-dissipating (frictional) effects or with periodic active force reapplication. Focusing on the initial squeeze and rebound phases, the force driving the coming together of the masses is also responsible for their subsequent separation! Such a mechanism involving the muscular LV walls would bring about some diastolic expansion as a consequence of their preceding systolic contraction, as Figure 5, I, insinuates.

Strain energy, the energy of elastic spring deformation, is indispensable in fathoming the diastolic reexpansion of the muscle-bound *end-systolic* LV lumen shown in Figure 3, subpanel *d*. In Figure 4, the spring is simply an energy reservoir that enables strain-energy changes attendant to myocardial contraction during ejection to be stored temporarily in LV walls, ready to bring about abrupt early chamber expansion in diastole. The amount of strain energy that can be stored in a load-bearing elastic structure without causing permanent damage to it may be defined as its “resilience.” Resilience may also be thought of as the capability of a strained body to recover undeformed size and form after release.

Some helpful biomechanics

Young’s modulus is a measure of the stiffness of an elastic material. It is determined from the slope of a stress-strain curve generated during tensile tests on a material sample. Materials of low Young’s modulus can stretch or contract more in relation to their length than stiffer ones, and so can store more strain energy per unit volume. This is a very important albeit generally unrecognized concept.

Longer materials will deform further and will therefore store more strain energy before sustaining permanent damage, even though the force that is applied and the stress that is in the material remain the same. This may be pertinent in the functional anatomy of Torrent-Guasp’s ventricular myocardial band.⁸² Although low stiffness and high extensibility promote strain energy absorption and transient storage, it is easy to end up with a structure that is too floppy for its purpose. This limits the resilience that can be implemented into the Janus-faced left ventricle and explains why meat counters do not offer hearts: they are too tough to chew even after long moist cooking that converts collagen into gelatin.

Myocardial fiber histoarchitectonics

In the cardiac walls, there has to be a compromise between stiffness with strength and resilience, and the achievement of the best compromise entails the intricate design in the

histoarchitectonics of myofiber sheets. The optimum arrangement may vary depending on loading and pumping demands and on necessary (patho)physiologic phenotypic adaptations. Comprehension of ventricular pumping in HCM requires an elucidation of structural-functional correlations. Figure 5, II, subpanel *a*, schematically demonstrates how LV myofiber sheet geometry changes smoothly across the wall thickness: it shifts from a slightly oblique orientation in the subendocardium to a circumferential orientation in the midwall and again to an oblique (nearly perpendicular to the subendocardial) orientation in the subepicardium.^{87,88}

Molar (large-scale) LV wall twist and untwist processes

The arrangement of myofiber sheets within the wall gives rise to torsion, akin to wringing a towel (Figure 5, II, subpanel *b*), during the systolic contraction of the oppositely oriented helical fibers; this torsion follows the subepicardial layers because of their longer lever.⁸⁹ As indicated in Figure 5, II, subpanel *a*, when viewed from the apex, the systolic rotation of the base is clockwise and that of the apex counterclockwise, so that the resulting upward swing of the apex produces the precordial cardiac impulse.

Consequently, the twisting mural deformation during systole results not only in ejection but also in the storage of a significant amount of strain energy. The rotated fibers behave like a wound-up torsion coil that, during the ensuing isovolumic relaxation and early diastole, swiftly unwinds while releasing its strain energy, as the torsion coil in mechanical watches. The process may be actively reinforced by persisting contraction of still depolarized subendocardial myofibers that, in contrast to the earlier systolic stage, are no longer opposed by contraction of subepicardial ones.

Such filling abetting mechanisms are crucial for initiating filling of the muscle-bound end-systolic lumen, although they can be inconsistently compromised in HCM, as indicated in Figure 5, II, subpanel *c*, because of incongruous global and regional hypertrophy patterns. These are typified by disproportionate involvement of the interventricular septum and anterolateral wall encroaching on a virtually emptied end-systolic chamber (Figure 3, subpanel *d*). Functional consequences of septal histoanatomy have not been a subject of study until recently.⁹⁰ Other plausibly implicated histoarchitectonic aberrations include irregular myocyte hypertrophy and disarray,^{54,91} and patchy fibrosis that may form grossly visible scars.^{92–94}

Accordingly, patients with HCM demonstrate decreased longitudinal and increased circumferential systolic and early-diastolic strains,^{95,96} suggesting subendocardial myofiber dysfunction with relative sparing of other myocardial layers. The decreased longitudinal mechanics imply a compromised left atrioventricular plane piston function,¹ with relative sparing of circumferential and twist mechanics. LV ejection in HCM is therefore strongly dependent on circumferential wall strain with short-axis area reduction.

HCM patients show relatively preserved net LV torsion (see Figure 5), although the base-to-apex distribution of the twist is changed from normal: rotation at the mid-LV level becomes clockwise (ie, similar in sense to basal rotation).^{97,98} The ring of null rotation, which represents the LV region where rotation crosses over from clockwise into counterclockwise,

is displaced apically (Figure 5, II, subpanel *c*). This diminishes the rotation gradient for most of the left ventricle, while exaggerating the twist near the apex.⁹⁶ Such changes may accrue from asymmetric hypertrophy, myofiber disarray, fibrosis and wall stiffening, which render most of the wall rigid as a pipe, supplanting its normal more twistable structure.

As noted earlier, compliant materials can store more strain energy per unit volume than stiffer ones. Wall stiffening in HCM will therefore impair optimal storage of strain energy into systolic LV twisting and its diastolic conversion into kinetic energy of wall rebound. Indeed, it has been shown that LV untwisting is delayed and its rate reduced in many HCM patients.⁹⁹ Slowed untwisting may be related to decreased elastic recoil and retarded myocardial relaxation. Because untwisting rate can be increased despite impaired LV relaxation embodied in prolonged pressure decay (Figure 2), untwisting and relaxation rates do not hinge on the same mechanism.⁹⁷ Consequently, augmented untwisting rate might be a *compensatory* mechanism for early filling in some HCM patients¹⁰⁰; this is a mechanism that merits comprehensive investigation.

Microscopic and submicroscopic (small-scale) wall deformation and rebound processes

When the organized larger-scale twist-untwist process is significantly compromised in HCM, smaller-scale strain energy storing and release mechanisms are likely to gain importance as a parallel factor abetting initiation of and early diastolic filling. Figure 6 exemplifies one way to understand this, by pretending that the myocardium is made up of a network of microscopic and submicroscopic masses and springs. Active systolic contraction deforms it to some end-systolic high-energy configuration. Removal of the contractile wall stresses is then equivalent to specifying a different target metric for the distances between the neighboring masses interconnected by the spring ensemble. This metric corresponds to the low-energy configuration sought by the rebounding LV wall, as indicated in Figure 6. In the process, suction is generated for initiation and early-stage development of inflow. This enlarges the LV lumen and reduces the relative wall thickness, allowing for higher wall-distending stress creation (Laplace's law) by the mitral inflow and applied intraluminal LV pressure.

Within the myocardium the smaller-scale strain energy storing and releasing mechanisms comprise elastic collagenous components of the interstitium and the intrasarcomeric giant protein titin (evoking the Titans of Greek mythology), which connects the Z line to the M line in the middle of the sarcomere (Figure 6, inset), so that a single titin molecule spans half a sarcomere.^{101,102} Titin functions as a bidirectional spring, conferring length-restoring myocardial elasticity.¹⁰³ With contraction or distension from resting sarcomere length, titin generates forces rapidly reestablishing resting sarcomere dimensions. It is composed of 244 individually folded protein domains joined by unstructured peptide sequences¹⁰⁴; these domains unfold when titin is stretched and refold when tension is removed.¹⁰⁵

Directions for future investigations

In future investigations, a shift from familiar approaches of LV diastolic function to large- (twist-untwist) and small-scale (titin unfolding-refolding, etc.) wall rebound models incorporating interactive dynamic distortions and rearrangements of myofiber sheets and

ultrastructural constituents is needed. Large-scale LV twist-untwist quantifications in patients with HCM can be accomplished by noninvasive methods: magnetic resonance imaging (MRI) tissue tagging and echocardiography. Major advantages of MRI include the spatial resolution and precision of tissue tagging and nonexistent acoustic window limitations. Motion analysis of tissue tags quantifies myocardial kinematics; indeed, MRI is the criterion standard for tracking twist and untwist processes throughout the cycle.^{17,98,106–109} However, its temporal resolution falls short of echocardiographic standards, and MRI is contraindicated in patients requiring pacemakers and ICDs. Recent developments in tissue Doppler, 2-dimensional speckle tracking, and video processing software deliver reliable echocardiographic measurements of torsion and rebound kinematics.^{14,18,89,99,100,110,111}

Within physiological volumes, titin is the dominant contributor to passive LV wall forces; extracellular matrix–based forces dominate at larger chamber volumes,¹¹² implausible in HCM at end-systole and incipient diastolic filling. Therefore, studies of small-scale wall rebound determinants in HCM should focus on titin as supplier of sarcomere length–restoring forces developed in systole and causing cardiomyocyte elastic recoil.^{113,114} Titin, through modulations in the expression of its isoforms (N2BA/N2B) and/or its phosphorylation state, has been shown to be important in the pathophysiology of several heart diseases.¹¹⁵ Both N2BA and N2B titin isoforms are coexpressed within human sarcomeres. Because N2B titin is much stiffer than N2BA titin, the passive stiffness and rebound forces of cardiomyocytes and LV walls are modulated by titin isoform switching (shifting N2BA/N2B ratio). Thus, cardiomyocytes extracted from endomyocardial biopsies of patients with diastolic heart failure exhibited a relative increase in the expression of the more rigid titin isoform, the N2B, whereas an increased ratio was found in patients with dilated cardiomyopathy.¹¹⁶ Alterations in titin phosphorylation may also induce short-term alterations in restoring force development.¹¹⁷ Initial intriguing work in HCM suggests that increased titin binding to α -actinin may lead to stiff sarcomeres, which could be highly susceptible to the hypertrophic response to mechanical stress, thus contributing to the pathology.^{118,119}

Advances in modern nanotechnology for biomechanical measurements allow direct investigation of mechanical forces of cellular and subcellular scale.¹²⁰ Emerging single-molecule nanoanalysis instruments for investigating titin dynamics open an era of true subcellular molecular biology. Ways to accurately manipulate titin molecules comprise optical magnetic tweezers and atomic force microscopy (AFM) cantilevers. In these techniques, a biomolecule, such as titin, has one end bound to a surface and the other to a force sensor—a micrometer-sized bead or a cantilever—whose displacement is measured to derive the force. Insights can be gained into titin unfolding-and-refolding dynamics using such nanoinstrumentation.^{105,121} Pulling on titin macromolecules using optical tweezers or atomic force microscopy, a sawtooth pattern is observed due to the sequential *unfolding* of multiple protein units, which I mentioned in the preceding section. Such emergent single-molecule methods currently provide unprecedented capabilities for investigating the structural properties and dynamics of titin and its bidirectional restoring force development.

Conclusions

Basic mechanisms by which HCM begets diastolic dysfunction have been surveyed. Myocardial ischemia, especially subendocardial, and intracellular processes, such as changes in Ca^{2+} homeostasis, contractile and cytoskeletal proteins, and myocyte disarray, all contribute significantly to abnormalities in myocardial relaxation and stiffness; so do also changes in the extracellular matrix and in fibrillar collagen, and patchy fibrosis. Principal among all diastolic anomalies, however, are the massive, asymmetric wall hypertrophy and commonly excessive ejection fraction, leading to virtually complete LV emptying or unduly reduced end-systolic chamber dimensions. By Laplace's law, wall stress decreases with radius and wall thickening. Consequently, this end-systolic geometry preempts development, with any attainable diastolic pressure levels, of Laplace wall stresses high enough for the inception and progression of passive early-diastolic wall expansion.

The emerging new paradigm of diastolic dynamics, emphasizing the relationship of myofiber sheet and ultraconstituent distortion to LV mechanics and end-systolic shape might explain intricate facets in patterns of diastolic rebound and suction needed for LV filling in many of the polymorphic phenotypes of HCM. It might also, as suggested in Figure 4, result in extraepicardial or intramural implantable recoil devices to promote diastolic elastic rebound in selected subsets of HCM patients: those with massive hypertrophy and excessive ejection fraction leading to virtually complete LV emptying or unduly reduced end-systolic chamber dimensions.

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Figure 1.

The “Janus-faced” pumping left ventricle forms the central link between the low-pressure and the high-pressure systems of the circulatory ensemble.

Figure 2.

Deep LV and aortic root pressures (LVP and AOP, respectively) in HCM at rest and during supine bicycle exercise, which elicits an abnormal LVP diastolic decay, suggesting impaired ventricular relaxation; LVP decays throughout diastole, in sharp contrast to the normal pattern. Adapted with permission of PMPH-USA from Pasipoularides A. *Heart's Vortex: Intracardiac Blood Flow Phenomena*. Shelton, CT: People's Medical Publishing House, 2010. 960 pp.

FLOW FIELD CHARACTERISTICS

*Stable
convectively
accelerated
laminar
outflow field
in LV cavity
obliteration*

Figure 3.

Top, Late systolic fluid dynamics in HCM with “cavity obliteration”—shrinking narrow tube with contracting walls. Local and dynamic convective (associated with wall collapse displacing sequentially increasing flow increments from apex to outlet) inertial as well as powerful viscous effects are salient. Bottom, The opposite flow pattern is not applicable in early filling because highly decelerated flows are unstable (see text for discussion).

INTERACTIVE LV DIASTOLIC REEXPANSION & RELAXATION

Might implants of elastic recoil-devices at different LV-levels promote diastolic rebound in HCM?

Figure 4.

Diastolic elastic rebound of relaxing myocardial walls is needed for LV chamber reexpansion and filling in HCM. Might implantable extraepicardial or intramural elastic recoil devices at different LV levels promote diastolic rebound in HCM?

Figure 5.

Molar (large-scale) LV wall twisting accompanies systolic contraction of oppositely oriented helical fibers; even if somewhat abnormal, untwisting during isovolumic relaxation and early diastole is a crucial filling abetting mechanism in HCM with virtually complete chamber emptying (see text for discussion).

Figure 6. Microscopic and submicroscopic (small-scale) cytoskeletal strain energy storing and releasing mechanisms can gain importance in abetting early diastolic filling in HCM, if larger-scale twist-untwist processes are significantly compromised.