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#### Slack Myocardium: A New Concept of Myocardial Function

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An increasing body of recent research at the molecular and cellular levels suggests that myocardial cells exhibit a transitional "slack" stage during the cardiac cycle when the sarcolemmal membrane and intracellular skeleton largely formed by the protein, titin, are neither stretched nor compressed, therefore being at rest. This article bridges this knowledge with clinical physiology by extrapolating molecular and cellular concepts with the idea of a "slack myocardium" as a physiological stage of cardiac cycle. Introduction of this term and incorporation of the concept in future research may help to explain a range of recent clinical studies and open new directions for future research and experimental work in cardiac physiology. J Clin Basic Cardiol 2006; 9 (online): 15–8.

Key words: myocardium, titin, echocardiography, diastole, physiology

R ecent advances in cellular and molecular myocardial research increasingly point to the importance of a "slack" state of cardiac sarcolemmal membrane [1] and intracellular structures in respect to the end-diastolic and end-systolic status. Arguably, the most significant influence on the evolving understanding of molecular structure, physiology and pathophysiology of the myocardium originates from research on the role of the structural protein, titin. This commentary attempts to bridge molecular and cellular research of "no-tension" or a "slack" period of the cardiac cycle with clinical cardiac physiology. Introduction of the "slack myocardium" concept may benefit clinical research and open new approaches for evaluation and qualification of myocardial functional abnormalities. The detailed description of titin, its physiological function and properties, was well described elsewhere [2].

Titin is the largest protein in man and is present in striated muscles, including the myocardium. Titin has multiple cellular functions, the most important being formation of a "structural skeleton" that also acts as a "molecular spring" [2].

Titin has several isoforms with the full-length titin isomers being the most relevant to this discussion. There are two major isoforms of full-length titin in human myocardium: N2B and N2BA. The primary difference in these isomers is in extendable elements of their structure, positioned within the I-band of the sarcomere. N2B isomers are shorter and stiffer, while N2BA are longer and more elastic [3]. Significant variation of cDNA sequence and exon-splicing patterns in the extensible I-band region of cardiac titin, related to the variation in passive myocardial tension, has been recently demonstrated in different mammalian species [4]. This discovery raises reasonable doubt about the validity of free extrapolation of related experimental animal data to humans. Different expression of titin isomers has been linked to a variety of physiological responses as well as certain myocardial pathologies [5-8]. Dynamic structural switch in expression of isomers has particular importance in human ischaemic heart disease [9].

Three regions of the myocardial titin protein are responsible for the "molecular spring" action. Application of relatively small forces results in minor-length distention of titin.

At this stage, multiple immunoglobulin-like (Ig-like) segments of titin are breaking hydrogen molecular bonds and unfold their complicated 3D-structure providing physical opportunity for stretching. As the stretch force increases, a unique proline-rich sequence called the PEVK domain of titin starts to elongate in order to accommodate moderate increases in sarcomere length. The cardiac PEVK domain acts as a random coil and exhibits a complicated interaction with actin [10]. Finally, with high force application resulting in high physiological sarcomere length, the N2B sequence becomes stretched in an attempt to accommodate the change in cellular structure. A unique N2B sequence exists only in cardiac titin and allows maximum physiological stretch of sarcomeres. Each of the above stretched segments expresses recoil forces in response to extension. These forces are nonlineally proportionate to the length of titin distention and compression [2, 11, 12].

The "slack sarcomere" concept is an outgrowth of recent titin research. Such a condition occurs when titin molecules are neither stretched nor compressed. At this stage, the "molecular spring" is "at rest" and does not exhibit entropic activity. The practical clinical importance of this new perception is the possibility to extend the significance of the existing concept from the level of the single molecule to the level of the myocardial cell and then to the myocardium as a whole.

Current concepts of cardiac mechanics are limited to the myocardial transitions from the end-diastolic to end-systolic state and back again, repetitively. Although such an approach appears logical, recent advances in the understanding of a cellular state of "slack sarcomere" present new opportunities to define an intermediate "slack myocardium" state for the heart as a whole. Such a state would take place twice during the traditionally described cardiac cycle: once during systole and then again during diastole.

Several interactive forces determine myocardial mechanics. Extracardiac forces play important roles but are outside the scope of this article and will not be reviewed. Intracardiac forces mostly consist of those generated by myocardial cells and the extracellular cardiac matrix.

Pressure differences between the cardiac chambers result in actual movement of blood between the chambers and consequently throughout the body. Such differences depend on preload and afterload, cardiac valve function, atrial and/or ventricular contractility and the suctioning force of the relaxing chambers, as well as chamber compliance to accommodate an incoming blood volume. These forces are constantly

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interactive and dynamic, which complicates the identification of specific causes of heart failure increasingly recognized as a multifactorial process [13].

The in vivo understanding of cardiac mechanics has been greatly enhanced with the development of echocardiography. This resulted in a massive amount of data on cardiac performance and function. Multiple echocardiographic parameters most often derived from 2D assessments were developed for the assessment of left ventricular systolic and diastolic functions. These parameters also include Doppler mitral inflow and aortic outflow profiles and Doppler assessment of myocardial tissue motion with derived parameters, such as tissue strain and its propagation rate. They are used to describe the normal state and to quantify and stage the degree of cardiovascular pathology. Such parameters helped to differentiate between the interactive forces within the myocardium that are responsible for blood flow within the heart and in the great vessels [14]. No "slack myocardium" state however has been correlated to date echocardiographically. In fact, no references to a "slack myocardium" at the level of the whole myocardium can be identified in the current literature

Ventricular systole is a dynamic and rapid stage of the myocardial cycle. In normal conditions, it occupies approximately 30 % of the total cardiac cycle time. Approximately an equal amount of blood is moved in and out of the ventricle during diastole and systole respectively, however, more force is obviously required to propagate this volume in the shorter systole against a large peripheral vascular resistor than in the longer diastolic period. It accordingly makes systole more energy consuming. The force in systole is achieved by a combination of active contraction of myocardial cells and recoil forces of both the titin and the extracellular cardiac matrix, which are stretched during diastole. Active contraction is a result of a complex energy-dependent, calcium-activated interaction between actin and myosin. The energy generated by the "molecular spring" action of titin complements active contraction when the initially stiff N2B domains, then PEVK regions and finally Ig-like segments restore the original 3D molecular structure from the stretched end-diastolic state [15, 16]. Such complementing interaction continues until the "slack" stage is achieved, after which continuation of active contraction has to work against the force of titin Ig-like segments to stretch them in the opposite direction. The extracellular matrix also contributes to the recoil force, though to a lesser extent than titin. The matrix consists of fibrillar proteins such as collagens and elastin, and basement membrane proteins including collagens, fibronectin and laminin, and proteoglycans. The status of the extracellular matrix during the "slack" stage remains unknown. End-diastolic ventricular stretch largely depends on the filling pressure difference between the atrium and ventricle. The extent to which titin is stretched plays a paramount role in the systolic Frank-Starling mechanism via several pathways, but primarily via recoil-dependent forces and alteration of actin-myosin coupling [17]. Coupling is altered by a complex process which brings actin and myosin closer to each other.

Diastole takes up approximately 70 % of the cardiac cycle time. The current physiologic concept divides diastole into four stages: isovolumic relaxation, rapid filling, slow filling (diastasis) and late diastolic filling (atrial filling). Ventricular diastole is a result of a complicated interaction of several forces. Obviously, the most important force is a pressure exhibited from the atrium across the atrio-ventricular valve. This force is complemented at the initial stage of relaxation by the recoil-generated force of titin's "molecular spring" due to the return of Ig-like segments (as far as we know presently, Ig-like segments are the only parts of titin to be stretched "inside" during end-systole) into the "slack" state [18]. Once "slack" status is passed, atrio-ventricular pressure must work to stretch titin's Ig-like segments in the opposite direction, followed by PEVK regions and, finally N2B domains (Fig. 1). During this stage, a progressive increase in resistance generated by titin must cause decreased filling. There is also an extracellular matrix-mediated force that works against the diastolic stretch. The extent and direction of this force at the beginning of diastole until the heart reaches "slack" state is unknown.

Diastole is regarded as an active process. Several mechanisms are responsible for energy consumption during cardiac relaxation. Adenosinetriphosphate (ATP) is required for disassociation of calcium and cardiac troponin C (TnC). Sarcoplasmic calcium ATP-ase and sodium-potassium channels function to restore the intracellular calcium concentration. It is likely that most of actin-myosin disassociation in normal conditions is done between end-systolic and "slack" phases. TnC binds calcium, resulting in conformationary changes that bring active heads of myosin in closer contact with actin. To facilitate the release of calcium from TnC, ATP is needed. Upon this, conformation of myosin head positioning develops, which enables disassociation of the actin/myosin complex. Equilibration of the cytosolic calcium concentration with related energy consumption probably extends throughout most of diastole.

When systole is completed and pressure inside the aorta exceeds left ventricular pressure, the aortic valve closes. The mitral valve still remains closed at this time. This is the beginning of the "isovolumic" relaxation phase. This term is partially misleading because Doppler analysis of the myocardial tissue motion confirms continuation of the systolic rigor at the initial part of this stage. It is only when actin-myosin disassociation begins that the real "isovolumic" relaxation



Figure 1. Movement from end-diastolic to end-systolic state of the sarcomere involves major changes in structural status of cardiac titin. Enddiastolic stretch requires uncoiling of Ig-like segments, PEVK sequence and N2B/N2BA regions. As the contraction starts with actin-myosin interaction, the recoil spring forces of stretched titin molecules support shortening of the sarcomere until the titin has no more stretched segments. At this moment, the "molecular spring" is inactive and the "slack sarcomere" status is achieved. Continuation of active contraction beyond this point requires Ig-like segments of titin to be stretched inwards, creating spring forces ready to initiate diastole when active actinmyosin interaction will cease.

starts and intraventricular pressure drops. While cardiac valves remain closed, no flow takes place between cardiac chambers, and therefore no intraventricular volume change occurs. When the wave of relaxation spreads from the basal ventricular segments towards the apex resulting in the drop of intraventricular pressure below atrial, the opening of the mitral valve and rush of the blood into the ventricle indicates the beginning of the "rapid filling" phase. The analysis of the mitral inflow profile shows initial acceleration of flow, which culminates with the peak of the early rapid filling "E" wave on Doppler echocardiographic assessment. The corresponding pressure-loop suggests a small negative pressure acting as a sucking force between the ventricle and the atrium during this acceleration stage in normal hearts. Subsequently the mitral inflow becomes decelerating on Doppler profiling with a corresponding disappearance of significant difference in pressure gradient between the atrium and the ventricle. This is followed by progression into the slow filling-stage and - finally - "atrial kick."

Myocardium consists of millions of sarcomeres. Sarcomeres cannot exhibit an absolute synchronicity in mechanics. Even within a few millimeters of myocardial tissue, each sarcomere would reach end-systolic and end-diastolic phases in slightly different millisecond timeframes. Such differences would greatly increase within the whole organ, especially in the presence of intraventricular conduction defects. The development of the "slack" state in systole and in diastole would also only occur during relative synchronicity of a mass of sarcomeres. The implication from this is that if we attempt to define the "slack" stage for the entire myocardium by echocardiographic parameters, we should accept that such a phase would not be instantaneous across all sacrcomeres, as it is not for end-systolic and end-diastolic stages. In fact, all cardiac stages are not instantaneous, but instead are dynamic processes spreading through the myocardial tissue and at times overlapping each other when analyzed at any given time.

When the mitral valve opens and the flow of blood from the left atrium into the left ventricle starts, it manifests with the appearance of the "E" wave on Doppler. A recent study by King and colleagues indicated that mitral annular diastolic peak tissue velocity occurs earlier than the peak of early mitral inflow velocity in normal human hearts [19]. This study also demonstrated that such a relationship may be altered in the presence of diastolic dysfunction and elevated atrial pressure. It is our understanding that during this stage in normal hearts, rapid "relaxation" results in creation of a negative sucking pressure inside the ventricle. Such effect must be largely determined by Ig-like segments of titin (with some contribution of extracellular matrix) exhibiting a recoil "spring" effect in addition to the pressure exhibited by the left atrium. Once the multitude of "molecular springs" returns to a neutral status, the propagation of blood between the chambers becomes only a function of the pressure gradient between the atrium and the ventricle. We postulate that the flow exhibits accelerating qualities once the stretch of the increasing multitude of molecular springs begins. It therefore seems logical to postulate that the tip of the "E" wave on Doppler analysis of mitral valve inflowprofile should correspond with the "slack myocardium" state for the majority of myocytes. It occurs within a period when a negative "suction" pressure within the left ventricle reaches its peak, which normally corresponds with the peak of ventricular inflow via the mitral valve. This peak inflow is registered as a peak of the E-wave on Doppler echocardiographic assessment.

Synchronized analysis of pressure loops inside the ventricle and the atrium obtained with high-fidelity catheters as well as synchronized assessment of Doppler flow profiles are needed to challenge this hypothesis.

Subject to confirmation that the tip of the "E" wave corresponds with the mechanical phase of "slack myocardium", the sum of the isovolumic relaxation time and "E" wave acceleration time is an important parameter to identify. It determines the time between end-systolic stage and "diastolic slack stage", while the remaining diastolic phase could be attributed to the "diastolic stretch" phase and be analyzed accordingly. When assessing regional diastolic function, the measurement of tissue acceleration time may be indicative of the speed with which the multitude of the molecular titin springs are released in that region of the tissue, until the "slack" state is achieved. Such measurements became possible with the introduction of tissue velocity imaging and guantitative strain imaging. It may therefore become a non-invasive indicator of the metabolic diastolic function related to the process of disassociation of Ca from TnC. Multiple regional measurements, coupled with the strain rate propagation velocity assessment, may help to establish global ventricular metabolic status in early diastole. Since an ability to reach high velocity depends largely on the quality of the spring, extrapolation of the resulting tissue velocity may be of interest to establish a non-invasive assessment of titin's isoform expression and switching [20] of the isoforms of titin under different pathophysiological conditions. An ability to measure "slack" myocardial volume could become valuable in the development of meaningful indices related to the relationships with end-diastolic and end-systolic volumes. This would help to establish parameters for quantitative assessment of the whole range of cardiac pathologies such as diastolic dysfunction, congestive heart failure and ischaemic heart disease, which have been shown to have close relationship with changes in titin isoforms and function [21].

Analysis of pressure loops inside the ventricle and the atrium obtained with high-fidelity catheters, along with synchronized assessment of Doppler mitral inflow profiles and myocardial strain measurements in different regions of the ventricle, are needed to challenge this hypothesis. Further studies involving assessment of the relationships between onset of myocardial tissue motion, strain and strain rate propagation, onset of mitral inflow with corresponding change of titin isoform expression, as demonstrated by myocardial biopsy, are needed for better definition of the "slack myocardium" state and its clinical significance.

In conclusion, we believe that incorporation of invaluable data recently collected from molecular and cellular research into cardiac clinical physiology warrants the introduction of the concept of the "slack myocardium phase" of myocardial dynamics. This may enhance our understanding of cardiac physiology and pathophysiology. This concept may also offer a unique means to diagnose cardiac diseases associated with abnormalities in cardiac size, compliance and performance.

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