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How myofilament strain and strain rate lead the dance of the cardiac cycle

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Abstract

Movement of the myocardium can modify organ-level cardiac function and its molecular (crossbridge) mechanisms. This motion, which is defined by myocardial strain and strain rate (muscle shortening, lengthening, and the speed of these movements), occurs throughout the cardiac cycle, including during isovolumic periods. This review highlights how the left ventricular myocardium moves throughout the cardiac cycle, how muscle mechanics experiments provide insight into the regulation of forces used to move blood in and out of the left ventricle, and its impact on (and regulation by) crossbridge and sarcomere kinetics. We specifically highlight how muscle mechanics experiments explain how myocardial relaxation is accelerated by lengthening (strain rate) during late systole and isovolumic relaxation, a lengthening which has been measured in human hearts. Advancing and refining both *in vivo* measurement and *ex vivo* protocols with physiologic strain and strain rates could reveal important insights into molecular (crossbridge) kinetics. These advances could provide an improvement in both diagnosis and precise treatment of cardiac dysfunction.

Keywords

Strain; strain rate; relaxation; systole; diastole; striated muscle

One might elicit many differing thoughts when asked to combine the terms “motion” and the “heart”, but a classical focus is on moving blood rather than moving the myocardial tissue. This is unsurprising since maintaining cardiac output (moving blood through the body) is essential and changes in left ventricular blood volume after activation are a key component of the Wiggers’ diagram [1], which is often a first introduction into cardiac function (Figure 1). Ejection fraction, a measure of how much blood moves out of the left ventricle, was measurable *in vivo* from the early 1900s using radiographic, then ultrasonic techniques; ejection fraction also correlated well with abnormal left ventricular function [2, 3]. However, movement of blood is no longer sufficient to characterize cardiac function in diseases such as the syndrome known as Heart Failure with preserved Ejection Fraction (HFpEF).

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DISCLOSURES

None

Advances in clinical imaging have previously pushed cardiac function analysis from blood flow to myocardial motion-based indexes such as myocardial torsion, strain, and strain rate. For example, diastolic function was originally assessed non-invasively via transmitral Doppler blood flow imaging, but Tissue Doppler Imaging of the motion of the mitral annulus has become a more important measure [4, 5]. Both ultrasound and MRI have been used to measure the torsion (or twist) of the ventricle, which is associated with contractile dysfunction [6]. A more recent measure of motion is myocardial strain, or the change in a muscle segment's length from its original length divided by its original length ($\text{strain} = (L - L_0)/L_0$). Global Longitudinal Strain imaging in HFpEF patients is beginning to reveal abnormal myocardial strain [7]. Clinical measurements of myocardial strain are primarily done in principal myocardial axes (long, short). Of note, these axes typically only report a component of the shortening of sarcomeres, the muscle contractile units, because the sarcomeres within the multi-cellular myofibers are aligned in helical and circumferential bands [8, 9]. Nonetheless, the relationship between myocardial motion and cardiac function has long been considered important [10].

It is generally understood that the molecular mechanisms driving cardiac function are near or within the sarcomere [11–15]. Muscle contraction occurs when calcium is first released from the sarcoplasmic reticulum to increase the cytosolic calcium. Calcium then binds to troponin to open up myosin binding sites, and myosin-actin crossbridges form to generate force. Ex vivo mechanical experiments applying tissue strain are currently used to characterize cardiac muscle function (for example cardiac power [16]). Unfortunately, many parts of the relationship between myocardial motion (strain and strain rate) and both the molecular (crossbridge) mechanisms and physiology remain unknown.

This review seeks to highlight the continuous and dynamic motion of the myocardium throughout the cardiac cycle, describe known mechanisms, and introduce some of the remaining unknown functional relationships between motion and function (Figure 2). We do so by stepping through the cardiac cycle from isovolumic contraction through filling. *In vivo* myocardial strain and strain rate along with related *ex vivo* myocardial functional experiments will be described. Understanding how *in vivo* and *ex vivo* studies of myocardial strain are linked- and the resultant physiology of each- may reveal new insights into molecular mechanisms and new ways to diagnose and treat cardiac dysfunction.

1. Systole

1.1 Isovolumic Contraction is Not Static

Even though blood is not entering or exiting the left ventricle, the myocardium is dynamic during isovolumic contraction. Apical rotation occurs during isovolumic contraction [17], and Tissue Doppler imaging reveals rapid basal then apical movement of the mitral annulus [18] (Figure 2). These clinical findings can be explained by muscle mechanics experiments because a contracting muscle fiber cannot be held isometric along its entire length. Either a muscle fiber's end-to-end length or a portion of its sarcomere length can be held isometric, but not both at the same time. Studies using laser and x-ray diffraction techniques provide fine detail of how the internal sarcomeres shorten in muscles with fixed ends [19, 20], and internal shortening and contraction can be visualized using optical microscopy [13]. The

internal sarcomeres can be held isometric by stretching the ends of the fiber during contraction. Both of these situations reveal that the ends of the muscle effectively act as a series elastic element, stretching slightly to accommodate changes in length [11, 21]. The heterogeneous contraction (that exists for all striated muscles) means that some segment of the muscle is undergoing a change in strain during all muscle contractions, even if internal segments or the ends of the muscle are held isometric [13, 14, 22].

Whether the ends or the central sarcomeres of a muscle are held fixed has an impact on force generation. In skeletal muscle, the descending limb of the length-tension relationship is curved in muscle-length isometric preparations, but more linear in sarcomere length isometric preparations, as predicted by filament overlap [23]. In myocardial muscles, sarcomere-isometric muscles generate more force than muscle-fiber isometric muscles [24].

Because the muscle fiber also shortens as the force (pressure) increases during this phase, isovolumic contraction might be better described as auxotonic contraction. Auxotonic contractions occur when both force and length change during a contraction (in contrast to isometric/isovolumic contraction where length/volume is held constant or isotonic contraction where the tone (pressure/force) is held constant). Measurement of *in vivo* sarcomere length strain is probably not feasible in the clinic, but open questions remain. For example, sarcomere isometric muscles are known to generate more force and attenuate the peak calcium release compared to fiber isometric muscles [24], therefore, shortening strains during isovolumic contraction would suggest further reduced peak force. How does *in vivo* myofiber strain during isovolumic contraction modify the rate of pressure development? Tissue Doppler Imaging reveals biphasic isovolumic contraction waveforms of the mitral annulus reflective of the transmural electrical activation pattern [18]. Given this, one might ask, could measuring myocardial strain rates during isovolumic contraction using Tissue Doppler assist in monitoring myocardial electrical synchrony?

1.2 Ejection, Contractility, and Myocardial Strain

Maintaining cardiac output and ejection is key to maintaining homeostasis, but myocardial strain is responsible for important physiologic responses as the left ventricular chamber becomes smaller (Figure 2). When an activated (contracting) striated muscle is shortened, fewer crossbridges remain bound and forces are reduced [25]. The systolic myocardial contractility is typically assessed using permeabilized (or chemically ‘skinned’) muscle fibers. Permeabilized muscles are activated using exogenous calcium, and the muscle may be shortened while being isotonically load-clamped - e.g. it is shortened to maintain a specific force. These techniques provide key contractile measures, such as cardiac power, but also induce crossbridge detachment during the change in strain [11, 16, 26]. Integrated to the *in vivo* condition, fewer crossbridges remain bound during ejection and shortening, which allows the left ventricular pressure to match the arterial afterload, instead of far exceeding it. (In contrast, when the myocardium doesn’t shorten, such as in aortic stenosis, the left ventricular pressure can rise well above the aortic pressure [27].) It also means that an ejecting and straining ventricle does not generate as much force as it would if the aortic valve didn’t open [28].

Ex vivo myocardial mechanics measurements that include shortening strains and strain rates provide essential information about muscles, but physiologic improvements might still be available. A limitation of permeabilized measurements is that they use a constant calcium and isotonic force, whereas *in vivo* cytosolic calcium and arterial afterloads are rapidly changing [24]. Load clamp protocols can mimic ejection and shortening in intact cardiac trabeculae [29] but it is yet known how load clamping against physiologic afterloads (Windkessel models) would impact shortening strains and crossbridge attachment.

2. Diastolic Relaxation

Clinically, the relaxation phase of the left ventricle begins when blood flow ceases at aortic valve closure. Cardiac motion suggests, however, that relaxation normally begins earlier and that relaxation is tightly coupled to systole. Based on a visual observation of epicardial motion, Wiggers and others observed that “there can be no doubt, however, that ventricular contraction ceases” (peak shortening strain occurs) before the aortic valve closes [1]. *In vivo* strain measurement suggests that this proto-diastolic period, a period of lengthening starting after peak strain but during ejection, is lost in cardiomyopathies and diastolic dysfunction [30, 31] (Figures 1–3).

2.1 Biochemical Control of Relaxation

The biochemical and molecular processes of force generation and relaxation are tightly coupled. To relax, a muscle must reverse the biochemical process of calcium, i.e. cytosolic calcium must be reduced, binding sites begin to deactivate as troponin returns to its inhibited state, and fewer crossbridges remain attached [15]. Calcium and binding site deactivation must begin before the muscle relaxes and dysregulation can cause diastolic disease [32, 33]. However, sarcomeric properties themselves appear to be a strong regulator of relaxation coupled to contraction. For example, Janssen showed that the rates of force development and relaxation are highly related in fixed end isometric muscles and suggest that crossbridge properties (not calcium) control the rate of relaxation [12]. While these properties are increasingly well characterized, their response to motion is not.

2.2 Introduction to Mechanical Control of Relaxation

While sarcomeric properties likely define the close coupling between rates of force development and relaxation [12], relaxation may be de-coupled from contraction by mechanical changes. Reducing afterload (e.g. blood pressure *in vivo* or the peak contractile force *ex vivo*) was commonly thought to accelerate relaxation, thus providing a mechanical way to uncouple relaxation from the biochemical rate [26, 34]. To understand this and its (improper) physiologic application, it is useful to return to the original studies of Brutseart and others that suggested that afterload would modify relaxation using load clamps on paced intact cardiac trabeculae [33]. After activation, the myocardial fiber was held isotonically (load clamped) by first shortening it, then fully relengthening it back to its original length where the ends were then held isometric *before* the force was allowed to relax. At reduced afterloads, this stretch was followed by a faster force relaxation. The relengthening strain (then called ‘relaxation loading’) was shown to be necessary to modify the relaxation rate

(Fig. 3B) and was speculated to “prematurely abbreviate the lifetime of the crossbridges”, which more rapidly reduced the force [35].

In vivo, the myocardium does not fully relengthen in systole before relaxing. If it did, the ventricle would have fully re-filled, meaning that the heart ejected and refilled from the aortic blood pool. Besides the non-physiologic net zero cardiac output, the aortic valve rectifies the flow to prevent significant amounts of blood from returning into the ventricle in systole. Partial lengthening *is* physiologic and measureable using MRI and ultrasound measurements of torsion and myocardial strain [31, 36, 37]. The essential finding in these human studies is that peak strain (shortening) occurs before the aortic valve is closed in normal hearts. Wiggers called this period of lengthening strain after peak shortening strain but before aortic valve closure the ‘proto-diastolic’ period. During this time the heart begins to lengthen, which will try to draw blood back into the ventricle, accelerating closure of the aortic valve [1, 38].

Lengthening at end systole is sufficient to modify the relaxation rate, no matter the afterload or strain magnitude (Fig. 3C) [26], using load-clamp protocols in cardiac trabeculae similar to the method above [33, 35]. It is not surprising that lengthening might accelerate relaxation. Indeed in the k_{tr} maneuver, which rapidly shortens and lengthens a calcium-activated, permeabilized muscle [25, 39], the rapid lengthening strain is thought to detach nearly all of the bound crossbridges. Lengthening at end systole may be related to a biomechanical study that showed that length can also accelerate the relaxation of an isolated myofibril [14]. Myofibrils exhibit a two-phased relaxation after calcium is removed [13, 14]. The initial slow phase is a homogeneously isometric phase, whereas the later fast phase is highly dynamic with heterogeneous sarcomere lengths. The duration of the slow phase is determined by thin filament deactivation and crossbridge kinetics [11, 13, 14]. In contrast, the fast phase begins when a single half-sarcomere suddenly undergoes a lengthening; a strain that quickly propagates down the length of the myofibril to rapidly relax it [13]. A stretch during the slow-relaxation phase caused myofibrils to transition more rapidly to fast relaxation [14].

Interestingly, our *ex vivo* myocardial mechanics studies and computational modeling revealed that the myocardial strain rate (the speed of lengthening), not strain, modifies the relaxation rate (Fig. 3D) [26]. Relaxation rates did increase with large strains, but were not sensitive to low strains; in contrast, relaxation rates were correlated to all myocardial strain rates. Computational modeling shows that faster strain rates led to a faster rate of crossbridge detachment and relaxation rate [26], which supports the hypothesis of Brutsaert that the lifetime of crossbridges was reduced upon lengthening [35]. These data are consistent with the following response: as the myocardium stretches more rapidly during relaxation, crossbridges are detached and are unable to re-attach as most binding sites are rapidly being inhibited [11, 13, 14, 26]. Calcium is also being removed from the cytosol making it increasingly difficult to replace the bound bridges (in contrast to permeabilized load-clamp protocols where calcium is constant). The exact mechanisms that control how sensitive crossbridge detachment and cooperative de-activation are to strain rate are not yet elucidated, but future studies may reveal new opportunities for treatments of diastolic dysfunction.

2.3 Contractile Coupling and Clinical Relevance of Strain Rate Control of Relaxation

If the myocardium doesn't shorten in systole, it can't relengthen and therefore will relax more slowly. In our muscle mechanics studies, we showed that muscles that shorten less have slower strain rates during lengthening, despite a preserved systolic duration [26]. In vivo, a canine study showed that a ventricle that is not allowed to shorten/twist relaxes more slowly than one allowed to shorten/twist [40]. Global longitudinal strain is reduced in the myocardium of patients with HFpEF [7], which would exacerbate any impaired relaxation. These data suggest that a subtle dysfunction in systolic strain may have important impacts during diastole, but to our knowledge, this effect requires further study. A better understanding of *in vivo* strain and strain rate patterns could be applied to *ex vivo* myocardial mechanics studies to better elucidate the mechanisms underlying the dysfunction.

Furthermore, the timing of peak shortening strain (and initiation of the lengthening strain) can also impact the heart's ability to relax. In Patients with cardiomyopathies and diastolic dysfunction, shortening is prolonged, sometimes continuing until after the aortic valve closes [30, 31]. Muscle mechanics experiments showed that lengthening at end systole was both necessary [33] and sufficient [26] to modify the subsequent relaxation rate. Thus, the myocardium in these patients could not accelerate the relaxation rate. The cause of the loss of this proto-diastolic period, and the mechanisms underlying how sensitive crossbridge detachment to strain rate is not yet known. Therefore, additional experiments using protocols that better mimic cardiac ejection and *in vivo* myofiber strain and strain rates, whether the motion is measured at the ends of the muscle fibers or internal to the sarcomeres, could enhance our understanding of the control of myocardial and ventricular relaxation.

2.4 Isovolumic (Auxotonic) Relaxation

The *in vivo* myocardium does not stop lengthening when the aortic valve closes (Figure 2). Even in our *ex vivo* experiments where the end-to-end length was isometric during relaxation, some segment of the muscle is undergoing a lengthening strain (Figure 3). Like during isovolumic contraction, short basal, then apical strain rates related myofiber lengthening can be detected via tissue Doppler imaging that suggest the myocardium is moving during relaxation [18], and may represent a pattern of deactivation. Tissue torsion measures show rapid changes during isovolumic contraction which also suggests that the muscle moves while the pressure (and myocardial forces) decline during isovolumic relaxation. Because the myocardial forces and lengths are changed simultaneously, isovolumic relaxation must also be auxotonic.

Interestingly, a faster rate of myocardial untwisting torsion itself correlates with a faster relaxation rate *in vivo* [40, 41] and the ventricular-atrial pressure gradient that drives early filling [42, 43]. Thus, myocardial strain is associated with pressure changes and could be a non-invasive diagnostic marker for slow pressure relaxation. It is also possible that the larger magnitude torsion in the left ventricle would correlate with more rapid crossbridge detachment and faster relaxation rates, similar to what we see with end systolic strain rates. The full implication of these relationships (first to pressure decline, second to crossbridge

detachment) are not yet fully characterized. However, faster strains during auxotonic relaxation may reduce the crossbridge population, which may reduce impaired relaxation phenotypes during the subsequent diastolic filling period.

3. Diastolic Filling

Myocardial lengthening strains and strain rates are also known to be important during diastolic filling (Figure 2). A large strain and strain rate of the myocardium is associated with a large atrioventricular pressure gradient [42, 43]. Strain and strain rates also reveal abnormal stiffness and relaxation (viscosity) in the left ventricle [4, 5, 44]. Strain rates during early filling (tissue Doppler e') are reduced in patients with impaired relaxation [4, 5]. *Ex vivo* mechanical studies in intact cardiomyocytes also revealed that bound crossbridges contribute to myocardial stiffness throughout diastole [45].

At the end of diastole stress-strain measurements and active changes in strain also have important physiologic effects. Titin (and to a lesser extent the collagen-rich extracellular matrix) in myocardium modifies the end diastolic pressure volume relationship [46], a measure of stiffness that is directly related to myocardial force and strain [47]. While this is an important predictor of exercise tolerance both *in vivo* and *ex vivo* [48], the active straining of the left ventricle during atrial filling is also important. *Ex vivo* mechanics experiments confirm that this end diastolic strain primes the myocardium for a stronger contraction [49]. While both muscle mechanics and *in vivo* clinical physiology reveal the importance of strain and strain rate, muscle mechanics studies may provide insight into whether the crossbridge response to strain could be used to help enhance the subsequent ventricular contraction.

4. A Translational Perspective on Myocardial Motion

Myocardial strain and strain rate can have important implications upon *in vivo* cardiac function. As noted above for example, the torsion rate during isovolumic relaxation correlates with the intraventricular pressure gradient that drives filling [42, 43] and ventricular stiffness and relaxation [44, 50]. This likely means that reduced early systolic and isovolumic strain rates are not able to detach crossbridges, which would contribute to the impaired relaxation phenotype. Separately, in a dog model where apical rotation was limited, peak pressure development and relaxation rate was correlated with myocardial motion (torsion) [40]. This result shows that preventing shortening attenuated relaxation *in vivo*. This finding might have clinical relevance for heart failure treatment with left ventricular assist devices. Most devices are fixed to the ventricular apex [51], which can attenuate torsion, and might modify the mechanics of the failing heart. It is unclear how this strain limitation impacts myocardial function and recovery *in vivo*.

Advances in *in vivo* and clinical studies may be needed to more completely understand how strain and strain rate regulate cardiac function. Currently, *in vivo* strain and strain rate are measured in the principal axes of the ventricle (longitudinal, radial, etc), which do not reflect the shortening and lengthening of the myofibers that are helically aligned [9]. Similarly, torsion reflects shortening of the helically-aligned subendocardial and subepicardial

myofibers (and their activation pattern) that causes the left ventricle to twist in a motion akin to wringing out a towel [8, 52]. Thus, while current clinical measures of myocardial strain and motion have value, they typically represent only components of the shortening of a myofiber. For example, Global Longitudinal Strain is reduced in cardiac hypertrophy; but myofiber remodeling reduces the helix causing more circumferential and radial motion, than longitudinal motion [53, 54]. Since cellular contractility is not suppressed, reduced longitudinal strain reflects a change in the helical myofiber architecture, not a change in myofiber strain or function.

We hypothesize that measuring myofiber-direct strain, as opposed to principal ventricular axis strains, might help design mechanical experiments that would better mimic physiologic myofiber strains and strain rates, including in the context of increased fibrosis common in diastolic dysfunction [30, 34]. Myofiber strain is more complicated to measure because MRI or ultrasound techniques must be used to first measure the helical myofiber architecture [10, 55, 56]. These measures might validate predictions from *ex vivo* studies. For example, non-uniform segmental strains have also long been thought to help modify relaxation [33] but, as noted above, non-uniform strain of small segments (individual sarcomeres) is responsible for the fast phase of myofibril relaxation [13]. In the whole heart, it is unclear how much non-uniform strain might benefit cardiac function instead of representing pathological dyssynchrony, where ill-timed strain reduces force generation [57]. Thus, myofiber directed strain might provide a measure of dyssynchrony throughout the cardiac cycle, in addition to the Tissue Doppler Imaging measurement proposed for isovolumic contraction [18].

Ex vivo mechanical studies already utilize strain and strain rate changes to reveal important parameters, such as myocardial power, but additional advances will reveal additional insights into the molecular mechanisms underlying contraction and relaxation. Applying a physiologic strain profile (and calcium activation profile) could, for example, help describe crossbridge dynamics as they respond to physiologic strains and strain rates. Such studies may also provide insight into how other molecular components that stretch during contraction (the series elastic elements above) regulate the response to strain or possibly even how fibrosis could modify myocardial strain, strain rates, contraction, and/or relaxation.

5. Summary

Myocardial strain and strain rate not only reflect changes in myocardial function but modify the function of the heart and couple the phases of the cardiac cycle (Figure 2). During isovolumic contraction, the myocardium shortens and twists slightly, which might attenuate force production. Shortening is enhanced during ejection, which detaches crossbridges. If shortening finishes before the aortic valve closes, relaxation can be accelerated by a fast lengthening strain rate. Lengthening strain and strain rate during isovolumic relaxation may also modify the pressure decline and early diastolic filling. The impact of both passive elastic strain and strain-rate dependent crossbridge detachment continues throughout the entire duration of diastolic filling, including the atrial contraction where a late diastolic stretch can prime isovolumic contraction. Clinically, strain and strain rate are of increasing importance as indexes of cardiac function. Current and future experiments that elucidate the

relationship and mechanisms that link force and strain and strain rates in the heart will enhance our ability to diagnose and treat cardiovascular disease.

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Figure 1. Wiggers' Diagrams with Strain and Strain Rate Signals.

A) Wiggers' description of the consecutive phases of the cardiac cycle. Notably, a proto-diastolic period is described before isometric (now isovolumic) relaxation, i.e. before the closure of the aortic valve. (Reprinted with permission from [1]) B) A schematic of the modern Wiggers' diagram typically includes left ventricular pressure and volume (often along with other parameters like heart sounds); here we include strain and strain rate. The pressure and volume signals can be measured using many methods including catheterization, ultrasound, MRI and angiography. Myocardial strain and strain rate traces are typically not

included in the Wiggers' diagram, but imaging (typically strain ultrasound and tissue tagged MRI) show that the myocardium is dynamic throughout the cardiac cycle. The L_0 for strain is typically taken as the end diastolic length. In many (mostly healthy hearts, blue strain), a proto-diastolic period is seen, where shortening strain peaks, and the myocardium begins to relengthen before isovolumic relaxation begins. In many hearts with diastolic dysfunction, the peak strain is reduced and peak strain occurs near or after aortic valve closure, causing the proto-diastolic period to be lost (discussed in Section 2.2). Myocardial strain rate (as would be measured via Tissue Doppler Imaging of the mitral annulus in an apical view) reveals that the isovolumic periods are auxotonic (discussed in Section 1.1) and is commonly used to help diagnose diastolic dysfunction (discussed in Section 3).

Figure 2. An overview of *in vivo* ventricular motion throughout the cardiac cycle.

Motion is revealed by multiple imaging modalities such as ultrasound and tagged MRI.

Insights from *ex vivo* mechanical studies and open questions are discussed throughout this Review.

Figure 3. Control of Relaxation Rate.

A-C. Load clamp experiments in intact cardiac muscles. The force and length traces in Panel A most closely mimic the pressure and volume traces in the Wiggers' diagram. Brutsaert and others showed that myocardial lengthening strain ('relaxation loading') was necessary to modify the relaxation rate using the protocol shown in Panel B [33, 35]. In these works, the muscle was typically fully relengthened back to its diastolic length before relaxation. We showed later that lengthening was sufficient to modify the relaxation rate using protocols shown in Panel C by performing load clamps where the muscle was partially lengthened towards its diastolic length. We concluded that the relaxation rate, measured during end to end isometric relaxation, was dependent on the strain rate at end systole as shown in Panel D [26]. Note that three of the four points were all taken at the same afterload, but were either not relengthened (red), partially relengthened (purple), or fully relengthened (blue).