Timing and magnitude of systolic stretch affect myofilament activation and mechanical work

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Dyssynchronous electrical activation of the ventricles, due to conduction defects such as left bundle branch block or ventricular pacing of structurally normal hearts, leads to abnormal systolic stretch (2). During ectopic ventricular pacing, early contraction near the pacing site stretches remote sites that have not yet begun to contract (17). Transient stretching of late-activated regions has been referred to as “prestretch” (1, 5, 12) and can reach magnitudes of up to 20% (20). Conversely, early activated sites shorten prematurely and stretch during erection (8). Dyssynchronous activation due to ventricular pacing of the normal heart also results in regionally heterogeneous distributions of local myocardial work (4, 13), O2 uptake, myocardial blood flow (4) and, if sustained, asymmetric hypertrophy (19).

Because dyssynchronous systolic stretch is caused directly or indirectly by the contraction of earlier or later activated regions of the wall, its duration is relatively long and typically about half the normal systolic interval (2). Its magnitude and timing relative to local electrical activation depend on location relative to the stimulus site, with the largest and earliest systolic stretches occurring in the latest activated regions where premature lengthening has peaked and largely recovered by the time local depolarization occurs. How dyssynchronous systolic stretching affects acute myocardial tension development and whether late versus early systolic stretches affect mechanics by similar or different mechanisms remain poorly understood, in large part because it is not possible to measure regional contractile tension development in the intact heart. The aim of this study was to investigate the mechanical effects of acute systolic stretches (representative in timing and magnitude of those seen during dyssynchronous ventricular activation in vivo) on cardiac contractile mechanics and the mechanisms by which these physiological stretches alter tension development. Isolated mouse right ventricular (RV) papillary muscles were stretched to mimic the magnitude, timing, and duration of systolic fiber stretch observed during ventricular pacing in vivo (2). Since different regions of the ventricles experience different timings and magnitudes of systolic stretch, the effects of these variables on twitch tension and work were systematically investigated.

Physiological stretches had different effects on twitch tension depending on stretch timing. Compared with muscle isometric twitches, premature stretches (peaking at or before electrical stimulation) resulted in lower peak tensions, whereas later stretches resulted in significantly increased contractile tension development. The relatively small deactivating effects of early stretches were found to be dominated by the effects of shortening during the development of twitch tension and readily explained by the force-velocity relation. However, the length-tension and force-velocity relations alone substantially overestimated tension responses to late systolic stretches, by twofold or more, suggesting an additional deactivating mechanism was involved. Using brief length transients to determine the deactivation time course, we found that physiological systolic stretches that peaked after the peak of the intracellular Ca2+ transient caused significant stretch deactivation, dissociating ~50% of cross-bridges. We conclude that the effects of systolic stretching, representative of dyssynchronous ventricular activation in vivo, are highly dependent on stretch timing relative to twitch tension onset and that late, but not early, stretches are sufficient to cause significant myofilament deactivation even though peak tension is increased.
METHODS

Muscle isolation and mounting. All experimental procedures were carried out following Institutional Animal Care and Use Committee-approved protocols in Association for Assessment and Accreditation of Laboratory Animal Care-approved facilities at the University of California-San Diego in accordance with National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Male 129/SvJ mice were anesthetized using isoflurane followed by cervical dislocation. The chest was then opened, and the heart was arrested via intracardiac injection of a cardioplegic solution (14). The heart was rapidly excised, cannulated, placed in a bath with cardioplegic solution, and retrogradely perfused through the aorta with the same solution. Incisions were then made in the RV free wall to allow for access to the RV papillary muscles. Long, unbranched papillary muscles were dissected.

The preparation was placed in a chamber (model 801C, Aurora Scientific) mounted on an inverted microscope (Nikon Eclipse TE300). The septal end of the muscle was attached to a force transducer (model 405A, Aurora Scientific), and the chordae tendineae was pierced with a hook attached to the lever arm of a high-speed, servo-controlled motor (model 322C, Aurora Scientific). The muscle chamber was constantly superfused with a modified Krebs-Henseleit solution (pH 7.35) (14) bubbled with 95% O₂ and 5% CO₂ in a reservoir immediately before being gravity fed into the muscle chamber. A peristaltic pump was used to recirculate the superfusate.

The muscle was paced at a constant rate of 2 Hz using platinum electrodes mounted inside the chamber. Each muscle was allowed to equilibrate for at least 30 min or until it was able to pace steadily. All stretching was imposed using the computer-controlled high-speed motor. A high-speed charge-coupled device (model IP-VGA210, Imprerx) camera, calibrated to determine pixel size, was used to record muscle lengths. Cross-sectional area was also recorded from the top and side views using a small angled mirror. Cross-sectional area was used to calculate tensile stresses from forces.

Strain tracking. Strains were measured using 7–10 titanium dioxide particles arrayed on the surface of the muscle near the central portion. Uniaxial Lagrangian strain (unitless) was calculated as follows: 

\[ E = \frac{1}{\lambda} (\lambda^2 - 1), \]

where \( E \) is uniaxial Lagrangian strain and \( \lambda \) is the ratio of stretched to slack muscle segment length. The charge-coupled device camera was used to track the marker displacements at a frame rate of up to 300 frames/s.

Ca²⁺ imaging. Ca²⁺ transients were imaged in a subset of muscles loaded with the ratiometric fluorescent dye fura-2 AM and excited alternately at 340 nm 380 nm via a fast filter switcher (Lambda DG-4, Sutter Instrument) (15). The loading solution containing fura-2 AM was infused into the muscle chamber in a dark room and allowed to load for 30 min. After the dye had sufficient time to penetrate cell walls, excess dye was washed out. The experiment then proceeded with the predetermined protocol, and ratiometric measurement of fluorescence emission was captured using a photomultiplier tube system (PMT-100, Applied Scientific Instrumentation).

Stretch protocol. Custom muscle testing control software was used to vary the timing and magnitude of stretches during stimulated twitches at a pacing rate of 2 Hz. Stretch waveforms were half sine waves with a fixed duration if 150 ms. The protocol consisted of 30 stretches, in which the timing was varied relative to the twitch stimulus time. Muscle length changes of 5%, 10%, and 15% were applied. These magnitudes were chosen as they fall within the range of systolic stretches observed during dyssynchronous activations in vivo (20). Each experiment consisted of three sequences: an isometric sequence, an actively stretched sequence, and a passively stretched sequence. Five isometric twitches were performed between each stretched twitch to allow the muscle to recover before the next sequence of measurements. After each stretched sequence was a sequence that was stretched but not stimulated, which was used to measure the passive tension due to the stretch. Work was calculated here as the area inside the fiber stress-fiber strain loop for a single complete twitch.

Time-varying stiffness. Instantaneous muscle stiffnesses at 30 different intervals throughout the twitch time course were measured by performing rapid 10% step stretches at intervals of 30 ms during the twitch. The local strain in the center of the muscle caused by the lengthening step was measured using the surface markers, whereas the tension due to the step stretch was measured using the force transducer. From the instantaneous changes in strain and tension due to the stretch, the instantaneous time-varying stiffness was calculated as follows (7):

\[ S = \frac{\Delta T}{\Delta e} \]

where \( S \) is instantaneous muscle stiffness, \( T \) is tension, and \( e \) is local strain. This time-varying stiffness was used to estimate the tension time course due solely to time-varying elastance by multiplying the measured stiffness time course by the strain (\( e_s \)) imposed on the muscle during an imposed stretch, as follows:

\[ T_{TVS} = S \times e_s = \frac{\Delta T}{\Delta e} \times e_s \]

where \( T_{TVS} \) is time-varying tension.

Deactivation protocol. An experimental protocol was used to assess how deactivation due to muscle length change varies at different times during a twitch. Muscle length impulses of 10-ms duration (triangle waveform with 5-ms stretch, 5-ms release to the initial length) and a stretch magnitude of 5% of the initial muscle length were applied to muscles at eight different times during a twitch, similar to previous protocols (11). The 5% stretch was designed to detach as close to 100% of the bound crossbridges as possible without damaging the tissue. Muscles were only included in the analysis if the 5% stretch caused active tension to drop to <10% of peak isometric twitch tension.

RESULTS

Effects of stretch timing. The timing of systolic stretches relative to stimulation (Fig. 1) had a significant effect on peak tension production (\( n = 5, P < 0.05 \)). The earliest stretches, which peaked before the peak of the Ca²⁺ transient, had an inhibitory effect on tension. Intermediate stretches peaking at the same time as the Ca²⁺ transient exhibited the largest increase in maximal tension compared with muscle isometric twitches and then fell below isometric as the stretch ended, during the shortening segment of the stretch protocol. The latest stretches, peaking after the peak of the Ca²⁺ transient, exhibited a slight increase in tension, late in the twitch. These stretches did not affect the magnitude or duration of the Ca²⁺ transient (Fig. 1D).

We generated a more detailed view of the effects of stretch timing relative to the time of peak isometric tension (Fig. 2A) by initiating stretches at 30 different start times relative to the stimulus. For stretches peaking between 0 and 25 ms after stimulation, peak tension decreased by at least 25%. Stretches that peaked 40 ms after stimulation neither increased nor decreased the peak tension compared with isometric. Stretches that peaked 60–125 ms after stimulation increased the peak tension by at least 200% (\( n = 4 \)). Consistently, the largest peak forces (Fig. 2B) were developed for stretches that peaked before the peak of the isometric twitch, during the plateau of the Ca²⁺ transient. Mechanical work was zero for early
stretches, peaking before the Ca\textsuperscript{2+} transient (Fig. 2C). For stretches peaking during the plateau of the Ca\textsuperscript{2+} transient, external mechanical work was significantly increased. For stretches peaking later, during the decline of the Ca\textsuperscript{2+} transient, work decreased sharply and became negative as the stretch did more work on the muscle than the muscle performed.

**Effects of stretch magnitude.** The effect of stretch magnitude on tension production was investigated by stretching to 5%, 10%, and 15% of total muscle length and measuring tension. Stretch magnitude had little effect on peak tension if the stretch peaked before electrical activation. When the peak stretch was at the same time as electrical stimulation, an increase in stretch magnitude reduced peak tension development. Early stretches inhibit peak tension, and this inhibition increases as stretch magnitude increases, as shown in Fig. 3, A and C. Thus, stretch not only altered the magnitude of peak tension but also influ-

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**Fig. 1.** A: timing of prescribed stretches with magnitudes based on total muscle length. B: measured uniaxial Lagrangian strain (unitless) responses to three different stretches. C: three tension responses to stretches with their timing varied in relation to stimulation (time 0). Tension values normalized to the peak tension produced by a nonstretched twitch (solid line). Tension trace line style matches corresponding stretch trace line style. D: measured Ca\textsuperscript{2+} transients for each stretch as well as nonstretched beat.

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**Fig. 2.** A: isometric tension from eight different papillary muscles normalized to peak tension. B: peak tensions (normalized to peak isometric tension) produced by 30 different stretches. The x-axis corresponds to the timing of peak stretch, whereas the y-axis corresponds to the peak tension resulting from that stretch normalized to the peak tension of a nonstretched beat. The vertical line shows that the peak effect of stretch occurs before the peak of isometric tension. The open square data point is the same stretch as the dotted trace in Fig. 1 (second stretch), which corresponds to stretch timing seen in late activated regions in vivo. The open triangle data point is the same stretch as the dashed trace in Fig. 1 (third stretch), which corresponds to stretch timing seen in early activated regions in vivo. C: external work done by the muscle calculated as a stress-strain loop. The vertical line occurs after the peak effect of stretch, meaning stretches occurring during the time of peak isometric tension do not generate the most work. Error bars represent SEs.
enced the tension time course. When the peak of the stretch occurred after stimulation, an increase in stretch magnitude increased tension development (Fig. 3, B and D). Comparison of five variably timed stretches with magnitudes of 5%, 10%, and 15% of total muscle length revealed that the effect of stretch magnitude on peak tension was highly dependent on stretch timing (Fig. 4).

**Time-varying stiffness.** To determine the extent to which time-varying stiffness alone could explain the effects of stretch timing on peak tension development, instantaneous stiffnesses throughout the twitch were computed from step stretch measurements (Fig. 5, A and B). Comparison of the normalized time-varying stiffness and muscle-isometric twitch tension (Fig. 5C) showed a very similar time course, suggesting that muscle isometric twitches behave largely like a time-varying elastance, similar to the intact ventricles (16). The time of the peak stiffness and time course of stiffness corresponded well with that of the peak twitch tension and tension time course of a nonstretched cycle. Hence, the results shown in Figs. 1 and 2 indicate that the timing of stretch that produces the largest effect on both tension and work production, which also occurred before peak stiffness, suggesting that time-varying stiffness of the muscle is not the only factor modifying tension and work.

**Deactivation.** To quantify the deactivating effects of stretching or shortening transients as a function of stretch time in our preparation, a series of muscle length transients (rapid stretch followed by release) were performed at eight different phases during the twitch cycle. These muscle length transients caused active tension at all time points in the twitch to drop below 10% of its maximum value, indicating that nearly 100% of cross-bridges were detached by the length transient. Muscle length steps occurring early in the twitch resulted in nearly 100% tension redevelopment after the impulse, whereas later transients after the peak of the Ca\(^{2+}\) transient resulted in progressively lower force development (Fig. 6), as previously reported (11). Expression of the peak redeveloped tension for each length transient timing as a fraction of the isometric tension at that same point in time (Fig. 6B) was used as a measure of deactivation due to a transient muscle length change.
Combined time-varying stiffness, force-velocity, and deactivation analysis. Time-varying stiffness calculations substantially overestimated the increased twitch magnitudes during late stretches compared with the experimental results (Fig. 7A). The time-varying stiffness analysis overestimated peak tensions the most for later stretches, as illustrated by the differences between the peak tensions due to experimental stretch and those of the time-varying stiffness analysis (Fig. 7B).

The tension redevelopment results from the rapid length transient protocol were used to show the potential deactivating effects of stretch at various times during a twitch. For each stretch, the percent deactivation was multiplied by the peak tension produced by the time-varying stiffness analysis. This results in a decrease in the peak tension from the time-varying stiffness analysis, with the decrease being the most dramatic for the later stretches. This analysis was done for two different scenarios, where stretch was assumed to deactivate 100% or 50% of cross-bridges. For the 50% deactivation analysis, the deactivation curve shown in Fig. 6B was scaled so that maximum deactivation was 50%. The 100% deactivation analysis greatly underestimated the peak tensions produced by experimental stretch, whereas the 50% deactivation analysis was very close (Fig. 7A). The peak tension from the 50% deactivation analysis was much closer to the peak tension produced by experimental stretch than those of just the time-varying stiffness alone. For the latest three stretches, the peak tensions from the 50% deactivation analysis were significantly different from those of the time-varying stiffness analysis ($P < 0.05$).

A nonlinear force-velocity relation was used with the shape of the curve based on a previous study (3). The measured stiffness values were multiplied by the measured muscle isometric strain to get an estimate of isometric twitch tension. The time-varying stiffness-predicted tension values were then scaled based on the shortening velocity at each time point throughout a cycle, with larger shortening velocities having a greater inhibition on tension. This analysis was combined with the 50% deactivation analysis to see if the force-velocity relation could explain any of the remaining discrepancy with the experimental results. The force-velocity analysis had little effect on peak tension values (Fig. 7C).

DISCUSSION

In this study, the effects of timing and magnitude of relatively slow systolic stretch on developed twitch tension were measured in mouse papillary muscles. The study was designed to simulate tissue systolic stretch seen in the dyssynchronously activated intact heart (2) and thus to understand better the mechanisms of regional changes in contractile stress development and mechanical work output associated with electromechanical dyssynchrony. In the dyssynchronously activated myocardium, early activated regions shorten early in systole, lengthen late, and do little or no external work (13). Conversely, late activated sites are stretched early, lengthen late...
against higher load and do substantially elevated work. This work heterogeneity may be an important stimulus for asymmetric hypertrophy.

Early stretches (dotted trace in Fig. IA) mimicked the stretch seen in late activated regions (stretch comes early with respect to local activation), and late stretches (dashed trace in Fig. IA) mimicked early activated stretch (stretch comes late with respect to local activation). We used muscle-length isometric papillary muscle twitches. Because the ends of the muscle are stretched as the central portion contracts, this preparation shortens significantly in the central region where strains were measured and then relengthens in this region during relaxation. The magnitude and timing of shortening are not dissimilar to normal systolic fiber shortening in vivo. By applying relatively slow sine wave stretches, we could approximate regional loading conditions occurring during dysynchronous activation in the intact heart (2). Stretches that peaked relatively early (after stimulation but before the time of peak isometric tension) significantly augmented tension and work, similar to late activated regions in the dys synchronously contracting myocardium. These changes were largely explained by the change in local muscle segment length alone due to the time-varying stiffness of the muscle during the rise of twitch tension. However, later stretches, peaking at or after the time of peak isometric tension, resulted in zero or negative external work even though peak muscle tension was still increased. For these later stretches, the observed changes in muscle tension were much less than those predicted by the time-varying muscle stiffness and strains alone. These measurements support the interpretation that later stretches, peaking during the decline of the intracellular Ca\(^{2+}\) transient, cause significant cross-bridge detachment and myofilament deactivation.

The force-velocity relation is a well-known deactivating mechanism in the myocardium. We sought to investigate its effects on our findings. There was a modest reduction in peak tension development that could be explained by the force-velocity relation, but this was only significant for very early stretches that started before stimulation so that the muscle was being unstretched during the rise of isometric tension. Stretches at times more representative of the late activated myocardium were not significantly affected by the force-velocity relation. Further analysis suggested that transient deactivation could help explain most of the role of stretch timing on contractility that could not be explained by the time-varying stiffness and force-velocity analyses.

**Effects of stretch timing.** Our results show that systolic stretch timing has a significant effect on muscle fiber tension production. This is significant because different regions of the heart experience systolic stretch at different times in relation to local tissue activation. It is not surprising that stretch affects tension production in cardiac muscle, as length-dependent activation has been studied in detail (9), and it is well known that stretch increases the affinity of troponin C for Ca\(^{2+}\) and increases cross-bridge formation (10). Nevertheless, little is known about the effects of systolic stretch in vivo on tension production. The ability to have precise control over stretch timing, magnitude, and shape was made possible by the computer-controlled system designed for these experiments.

The results of this study could not be explained by any single mechanism. Based on the well-known Frank-Starling mechanism, muscles stretched to longer lengths during activation would be expected to produce more tension than those activated at shorter lengths (9). Owing to the timing and velocity of stretch, muscles stretched at the peak of stretch actually show a reduction in peak tension compared with nonstretched beats, emphasizing the role of other mechanisms such as the force-velocity relationship and transient deactivation.

**Work.** The timing of stretch determines the amount of external work done by the muscle (Fig. 2C). Previous studies have concluded that late activated regions of hearts undergoing ventricular pacing do more external work and also have an increased demand for O\(_2\) (4, 13), where the early activated left ventricular free wall becomes significantly thinner and the late activated septum becomes significantly thicker (19). The work calculated in the previous studies was based on approximations of fiber stress. In the present study, both fiber stress and fiber strain were measured directly, an advantage of working with isolated tissue. Stretch timing that mimics systolic stretch in late activated regions in vivo causes increased external work.
performed by the muscle specimen. These results agree with those seen in vivo (4, 13) and also show that systolic stretch may be a large contributor to the work imbalance observed in vivo during regional ventricular pacing.

**Time varying stiffness.** Time-varying stiffness has been shown to play a substantial role in cardiac muscle mechanics, especially in modeling ventricular function. As a muscle is activated, its mechanical stiffness increases. Therefore, when a muscle is stretched during contraction, the total force of the muscle will increase more than if it was passively stretched. As a means of determining the contribution of the change in stiffness, an analysis was performed to determine what forces would have been produced if time-varying stiffness was the only contributor to changes in tension. The open circles in Fig. 7A show the peak tension values that would be produced simply due to stretching the tissue while the stiffness is changing using experimentally measured stiffness values. The results from this analysis show that while time-varying stiffness contributes to the general response of the tissue to stretch, it cannot completely reproduce the experimental stretch results. This distinction is important because time-varying stiffness is used to model ventricular contractility (16). Here, we show that time-varying stiffness is not sufficient in explaining the tension response to physiological stretches of isolated cardiac muscle.

When looking at the differences in the peak tensions produced by the stretch experiments and those that arose through the time-varying stiffness analysis, as shown in Fig. 7B, there is an obvious difference, implying that time-varying stiffness does not completely explain the measured time course of tension. As shown in Fig. 7, the time-varying stiffness analysis predicts more peak tension for all stretches. This implies that in tissue experiencing systolic stretch, there is also a deactivating effect occurring.

**Force-velocity effects.** The analysis of the stretch experiments demonstrate that the velocity of shortening and lengthening influence tension development in mouse cardiac papillary muscles. Another mechanism that was investigated as a possible means of explaining the role of stretch timing on contractility is the force-velocity relation. A force-velocity analysis was performed using measured shortening velocities and a force-velocity relation that was fit to literature values, with maximum shortening velocity as an adjustable parameter (3). Maximum shortening velocity was set to a value previously measured in rat trabeculae (3). The results shown in Figs 7A and B, demonstrate that the force-velocity relation has a larger impact on stretches 4–7. This is due to the fact that for those stretches, the muscle is shortening near the time of peak tension, thus decreasing the peak tension by the inhibition of tension due to higher shortening velocities. For the earliest and latest stretches, force-velocity has less of an effect on peak tension because the muscle is not shortening during peak tension; it is either lengthening or peak tension coincides with the peak of the stretch, meaning the muscle is not shortening and thus tension is not being inhibited. This analysis shows that there is another mechanism of deactivation that is present, one that deactivates even after all stretching has ceased.

**Transient deactivation.** Another mechanism that can explain some of the overestimation of tension predicted by the time-varying stiffness and force-velocity mechanisms is transient deactivation (6). Length transients have been shown to have a deactivating effect on tension production, as they can cause bound cross-bridges to detach, and cross-bridges are not able to rebind to regain previous levels of bound bridges (6), ultimately preventing tension from reaching magnitudes possible if the shortening had not taken place. An estimate of the impact of transient deactivation at different times during a twitch is shown in Fig. 6. These results indicate that any stretch that occurs later into a twitch can have a significant deactivating effect. This is of importance to this study because it was observed that a time-varying stiffness analysis alone overpredicted peak tension values, especially for later stretches.

A very small portion of the tension overestimation in the time-varying stiffness analysis was resolved by including the force-velocity relation, but for the majority of stretches, tension was still greatly overestimated. The addition of transient deactivation mechanism was able to account for the majority of the remaining overestimation of peak tension. Assuming that the stretches detached 100% of cross-bridges, the analysis predicted a significant underestimation of peak tension. This is not surprising because if the stretches had caused 100% detachment, tension would have dropped to zero, at least momentarily, after each stretch. Since this was not the case, assuming <100% cross-bridge detachment is more realistic. The analysis that assumed the stretches caused 50% deactivation of cross-bridges produced the results that matched the experimental stretch values the best.

**Limitations.** While all possible efforts were made to ensure that this study simulated systolic stretch and analyzed its effects in the best way possible, there are some inherent limitations. One limiting factor is the use of mouse papillary muscles. These muscles generally do not have the ideal characteristic of long parallel fibers that can be seen in cardiac trabeculae, so there are some inherent assumptions that take place with the use of papillary muscles. Due to the attachment method of the papillary muscle to the muscle chamber, there is some compliance of the tissue that cannot be avoided, which can affect the amount of stretch in the muscle portion of the specimen. By tracking the strain at the center of the muscle, as well as mounting the specimen to reduce the series compliance, these effects are minimized. Ultimately, papillary muscles were used due to their ability to withstand stretch without damage as well as the fact that they more closely resemble ventricular wall tissue undergoing systolic stretch in vivo. While papillary muscles mimic ventricular wall tissue better than trabeculae, they limit the extent to which this study can provide insights into the three-dimensional nature of dyssynchrony. This study, along with previous studies of dyssynchrony in the intact myocardium, help paint the entire picture.

Another limiting factor is that the experiments were not extended to diseased or failing myocardium, as this is often where dyssynchrony is observed. Future studies would involve applying similar experimental conditions to the failing myocardium. However, dyssynchrony is also observed outside of heart failure in patients with left bundle branch block or those undergoing cardiac resynchronization therapy. The present study is more relevant to these clinical scenarios.

**Conclusions.** In this study, the timing and magnitude of stretch on mouse papillary muscles were found to influence twitch tension and work. The time-varying stiffness analysis suggests that while the stiffness changes during contraction substantially contribute to the twitch tension, it does not fully explain the tension developed with stretch. Further analysis...
suggests that the force-velocity relationship plays a minor role in the tension development with stretch, whereas transient deactivation contributes greatly to tension production when length transients are present. These findings suggest that mechanisms involving activation and deactivation are needed to explain the resulting tension profiles, and thus systolic stretch is likely influencing activation of the myofilaments. This work has implications for continuum models of ventricular electromechanics in the dys synchronously activated heart, as it emphasizes the importance of modeling transient deactivation, which is not generally done. Dys synchrony is a major concern in heart failure, and the failing myocardium is known to have impaired Ca\(^{2+}\) handling and myofilament activation; hence, it would be important to extend this study to failing tissue. Dys synchrony is not always associated with altered electrical activation; these other forms of dys synchrony are often times related to ischemia, which has been previously studied (18). This study is relevant to dys synchrony in which the contractile state is altered, regardless of the cause of the dyssynchrony, because altered contractile states are mimicked by stretching instead of abnormal electrical activation. The present study gives insights into the effects of systolic stretch in the intact heart and that the timing of regional stretch plays a critical role in mechanics and work distribution as observed during dys synchrony and resynchronizing therapies.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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