Enhancement of Contractility With Sustained Afterload in the Intact Murine Heart
Blunting of Length-Dependent Activation

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Mark E. Steinhelper, PhD; Marc D. Feldman, MD

Background—It has been hypothesized that because of its rapid heart rate, the intact murine heart functions near maximal contractility in the basal state. If this hypothesis is correct, then the fast and slow components of myocardial length-dependent activation should be blunted compared with larger mammals.

Methods and Results—Mice (n=24) were anesthetized, and via an open chest, LV pressure-volume relationships were determined by a dual-frequency conductance catheter system. Baseline pressure-volume relationships were determined during transient occlusion of the inferior vena cava, and repeat measurements were made after 1 (n=10) and 7 (n=21) minutes of sustained aortic occlusion. Control experiments were performed in a subset of mice (n=3). For baseline to 1 minute, an increase in afterload (maximal pressure 95±9 to 126±7 mm Hg; P<0.001) and effective arterial elastance (5.9±3.1 to 9.2±3.9 mm Hg/μL; P<0.001) resulted in an increase in end-diastolic volume (31±8 to 35±9 μL; P<0.001). The result was maintenance of stroke volume (17±6 to 15±6; P=NS) owing to an increase in contractility (leftward shift in V100 [the volume of end-systolic elastance at 100 mm Hg], 24±9 to 16±5 μL; P<0.001). No additional augmentation of systolic function was found at 7 minutes.

Conclusions—This study demonstrates that the fast phase of length-dependent activation is intact but not the slow phase, consistent with murine myocardium functioning near maximal contractility in the basal state. (Circulation. 2003;107:2962-2968.)

Key Words: pressure ■ afterload ■ hemodynamics ■ contractility ■ diastole

The rapid rate of the murine ventricle has led investigators to postulate that in these small ventricles, determinants of myocardial contractility may be different from those of larger mammals. It is known that murine cardiac muscle is less sensitive to calcium than muscle from larger mammalian species, with lower Fmax and higher Ca 50.1 In addition, the sensitive to calcium than muscle from larger mammalian mammals. It is known that murine cardiac muscle is less myocardial contractility may be different from those of larger animals. The force-frequency relation in the intact murine left ventricle (LV) is flat at physiological heart rates,2 unlike the near doubling of contractility over a physiological range of heart rates in larger mammals. Finally, under physiological conditions, the murine heart has greater sympathetic stimulation and less vagal stimulation than do hearts of larger mammals.3,4 These findings have led to the hypothesis that the intact murine heart functions at or near maximal contractility in the basal state, such that there is an inherently limited cardiac reserve.5 If this hypothesis is correct, extrapolation of results on ventricular function of genetically altered mice to other species must be made with caution.

In the murine myocardium, length-dependent activation has been demonstrated conclusively in isolated skinned fibers.6 However, the use of detergents to permeabilize sarcolemmal and intracellular membranes has been shown to alter the Ca2+ responsiveness of the myofilaments.7 To date, no studies have examined whether length-dependent activation is present in the intact LV of the murine heart, in situ or ex vivo, and whether the phenomenon in murine myocardium is similar to that described in myocardium of larger mammals. Because mutations of troponin species in mice have been shown to alter calcium sensitivity6 and to be associated with specific cardiomyopathies,8–11 understanding the physiological response of normal mouse hearts to changes in myofilament length is important and will expand our ability to define the mechanisms underlying the changes induced by such genetic alterations.

Length-dependent activation of cardiac muscle has been shown to have both fast and slow components. The fast component is believed to be due to increased calcium sensitivity of the myofilaments induced by stretch and is

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thought to be the basis for the Frank-Starling relationship.\textsuperscript{12,13} The slow component has been attributed to a progressive increase in the magnitude of the calcium transient that follows the action potential.\textsuperscript{12-14} Whether these fast and slow components are present in murine myocardium has not been examined. We designed a study to define the magnitude of length-dependent activation in the intact murine heart and to assess both fast (1 minute) and slow (7 minute) components. The myocardium was stretched (LV end-diastolic volume was increased) by the sustained application of afterload (aortic occlusion). We tested the hypothesis that the murine heart functions at near-maximal capacity in its basal state and therefore anticipated that length-dependent activation would be blunted compared with larger mammals. Using the LV pressure-volume plane construct, the present results demonstrate that the end-systolic elastance of the intact murine LV undergoes a leftward shift ($V_{100}$) in response to sustained afterload but does not have further enhancement of contractility between 1 and 7 minutes. Thus, there is a fast but not a slow component to length-dependent activation in the in situ mouse heart.

**Methods**

**Conductance Technology**

A 1.4F miniaturized pressure-volume catheter (SPR-719, Millar Instruments) was used in these studies. A constant excitation current (17 μA root mean square) was applied to the outermost electrodes at 2 frequencies, 10 and 100 kHz, simultaneously. The device uses a custom signal generator/processor and bridge amplifiers developed by us and licensed to and subsequently modified by Millar Instruments, Inc. The 10- and 100-kHz frequencies are generated sequentially with a Signametrics Complex DDS Generator (SM-1030). The theory behind the determination of volume with the conductance catheter has also been described.\textsuperscript{15} The only instrumentation used in conjunction with the dual-frequency conductance system was an aortic flow probe, used to correct for electrical field inhomogeneity ($\alpha$).

**Animal Protocol**

The protocol was approved by the Institutional Animal Care and Use Committee at the University of Texas Health Science Center at San Antonio and conformed with "Guidelines for the Care and Use of Laboratory Animals" (NIH publication No. 86-23, revised in 1985) and "Principles of Laboratory Animal Care" (published by the National Society for Medical Research). Female CD-1 mice (n=24; Charles River Laboratories, Wilmington, Mass) weighing 20 to 30 g and aged 2 to 4 months were anesthetized by urethane (1000 mg/kg IP) and etomidate (25 mg/kg IP). These anesthetics were chosen because of their minimal negative impact on myocardial contractility. Respiration was controlled through a tracheotomy cannula, and the animals were mechanically ventilated with a rodent ventilator at 100 breaths/min supplemented with 100% oxygen. Physiological temperature was maintained with a Vesta heating operating table with rectal probe. The chest was entered by anterior thoracotomy. An apical stab was made in the heart with a 30-gauge needle, and the miniaturized mouse conductance catheter was advanced retrograde into the LV along the long axis with the proximal electrode just within the myocardial wall of the apex. The inferior vena cava (IVC) was isolated immediately below the diaphragm for transient occlusion. The descending thoracic aorta was dissected free, and a suture was placed around it and left under no tension.

Baseline LV pressure-conductance relationships at both 10 and 100 kHz were acquired at 1000 Hz and stored for offline conversion to pressure-volume relationships. Similar data were acquired during transient occlusion of the IVC. Next, tension was applied to the suture placed around the descending thoracic aorta to increase LV peak systolic pressure by a minimum of 25 mm Hg. LV pressure-conductance data were obtained again during the sustained increase in afterload both at baseline and during transient occlusion of the IVC. Atrial pacing was not performed as a means to standardize heart rate in this study.

Time points were chosen to examine both the rapid and slow phases of length-dependent activation.\textsuperscript{12-14} Previous studies have demonstrated both isolated papillary muscle\textsuperscript{15} and in the intact LV\textsuperscript{16} that the fast enhancement of tension development occurs immediately, and the slow response is maximal over 7 to 10 minutes. Therefore, 7 minutes was chosen to examine the slow response (n=24) and 1 minute to examine the fast response (n=13) because that was the earliest time that we could reproducibly record data during occlusion of the IVC.

In a subset of mice (n=5), steady-state LV pressure-volume relationships were also acquired at 2 and 4 minutes after aortic occlusion to evaluate the time course of changes in LV performance. In a second subset of mice (n=6), we applied transient complete aortic occlusion at 7 minutes of sustained afterload to maximally elevate LV end-diastolic pressure and volume. In a third group of mice to serve as a control (n=3), afterload was not applied.

To derive $\alpha$ at the end of the experiment, a small-animal blood flowmeter (T 106, Transonic Systems Inc) was placed around the aorta. The flowmeter was placed on the ascending thoracic aorta.

**Data Analysis**

The pressure-volume data were analyzed with software developed by us and licensed to and modified by Millar Instruments, Inc. (PVAN). The algorithms used are found in previous publications.\textsuperscript{20-23} Absolute volume measurements from the conductance catheter were calibrated with a correction for gain or $\alpha$. The volume signal was divided by $\alpha$, which was defined as the ratio of flow-probe stroke volume to the conductance stroke volume. The mean $\alpha$ for those mice that had afterload applied was 1.11±0.45 (n=21). The $\alpha$ for the subset of mice with baseline, 1-minute, and 7-minute data (n=10; $\alpha=1.15±0.56$) did not differ from that for the mice with baseline and 7-minute data (n=11; $\alpha=1.08±0.35$; $P=NS$).

**Statistical Analysis**

Baseline and 7-minute afterload data were compared by Student’s paired t test (n=21). Baseline, 1-minute, and 7-minute data were compared by repeated-measures ANOVA with contrast (n=13). The multiple comparisons for all differences with baseline used the Dunnett post hoc test. The transient aortic occlusion data generated during sustained aortic occlusion compared the first and last beats of these pressure-volume ramps by Student’s paired t test (n=6). Data are presented as mean±SD.

**Results**

Figure 1 shows representative raw data collected from a single mouse during this study. The application of afterload produced an increase in the end-diastolic and end-systolic 10- and 100-kHz conductance (G) signals ($G_{da}$ and $G_{es}$, respectively). Figure 2 shows typical data collected from a different mouse. There was an increase in LV end-systolic pressure ($P_s$) and end-diastolic volume, but interestingly, no significant increase in LV end-diastolic pressure. A leftward shift of the line that defined end-systolic elastance ($E_{es}$) was evident by 1 minute, with no additional leftward shift between 1 and 7 minutes.

The effects of 7 minutes of sustained afterload on systolic and diastolic function in 21 mice are shown in Table 1. Afterload was increased as evidenced by increases in maximum LV pressure ($P_{max}$), $P_s$, and effective arterial elastance.
Figure 1. Representative data collected from single mouse. Left, Data acquired at baseline; second panel, during application of sustained afterload for 1 minute; third panel, after application of sustained afterload for 7 minutes; and right, addition of flow probe to determine α. Each panel displays 10- and 100-kHz signals. Top row is real-time 10-kHz signal, and next row is 100-kHz signal. Note higher instantaneous conductance of 100-kHz signal measured in microsiemens (μS) because of contribution of myocardium. Next row is LV pressure (LVP). Bottom row is instantaneous aortic flow, which could only be determined at end of experiment. As is visually evident, there is an increase in Pes and end-diastolic pressure; Ees, end-systolic elastance; V100, volume of 10-kHz signal; and dP/dt-EDV, a measure of LV contractility.

Table 1. Effects of Sustained Afterload on Systolic and Diastolic Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Afterload 7 min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>482±43</td>
<td>449±41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vtd, μL</td>
<td>33±10</td>
<td>38±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vae, μL</td>
<td>18±7</td>
<td>22±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pmax, mm Hg</td>
<td>92±8</td>
<td>118±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pes, mm Hg</td>
<td>84±10</td>
<td>114±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ees, mm Hg/μL</td>
<td>12±2</td>
<td>11±3</td>
<td>NS</td>
</tr>
<tr>
<td>SV, μL</td>
<td>18±6</td>
<td>18±7</td>
<td>NS</td>
</tr>
<tr>
<td>EF, %</td>
<td>53.4±9.9</td>
<td>47.1±9.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CO, μL/min</td>
<td>8845±3330</td>
<td>8056±3253</td>
<td>NS</td>
</tr>
<tr>
<td>SW, mm Hg/μL</td>
<td>1296±403</td>
<td>1561±590</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ea, mm Hg/μL</td>
<td>5.4±2.6</td>
<td>7.5±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dP/dtmax, mm Hg/s</td>
<td>8738±1659</td>
<td>10 707±2506</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>dP/dtmin, mm Hg/s</td>
<td>−6857±990</td>
<td>−9368±1836</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dV/dtmax, μL/s</td>
<td>1029±469</td>
<td>1106±738</td>
<td>NS</td>
</tr>
<tr>
<td>dV/dtmin, μL/s</td>
<td>−686±476</td>
<td>−697±471</td>
<td>NS</td>
</tr>
<tr>
<td>Ees, mm Hg/μL</td>
<td>3.3±1.9</td>
<td>4.3±2.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Ees</td>
<td>0.98±0.01</td>
<td>0.99±0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Vtd</td>
<td>26±10</td>
<td>19±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dP/dt-EDV, mm Hg/s</td>
<td>193±124</td>
<td>225±143</td>
<td>NS</td>
</tr>
<tr>
<td>fPVR-EDV</td>
<td>0.89±0.11</td>
<td>0.93±0.06</td>
<td>NS</td>
</tr>
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</table>

Values are mean±SD. Vtd indicates LV end-diastolic volume; Vae, LV end-systolic volume; Pmax, maximum LV pressure; Pes, LV end-systolic pressure; Pmin, LV end-diastolic pressure; SV, stroke volume; EF, ejection fraction; CO, cardiac output; SW, stroke work; Ees, effective arterial elastance; dP/dtmax and dP/dtmin, first derivative of LV pressure rise and fall; dV/dtmax and dV/dtmin, first derivative of LV volume filling and emptying; Ees, end-systolic elastance; V100, volume of the Ea at a pressure of 100 mm Hg; dP/dt-EDV, a measure of LV contractility; and r, the correlation coefficient of the data used to generate the two measures of contractility examined.

Paired Student’s t test: P<0.05 is significant. n=21.
The effect of sustained afterload on the early (1 minute) and late (7 minute) time points for the subset of 10 mice is shown in Table 2. The impact of 1 minute of sustained afterload was a leftward shift of V100, which was similar to that found at 7 minutes. The alterations in steady-state and caval occlusion parameters found at 7 minutes had already been approached by 1 minute. In control mice (n=3), there was no change in end-diastolic volume (22±7, 21±6, and 22±9 μL), Ees (2.4±0.9, 2.5±0.8, and 2.6±1.1 mm Hg/μL), or V100 (16±4, 19±5, and 19±3 μL; P=NS for all by ANOVA) when baseline, 1-minute, and 7-minute times, respectively, were examined in the absence of afterload.

To be certain that the changes seen at 1 minute were consistently sustained until 7 minutes, additional time points at 2 and 4 minutes after the application of afterload were examined. Steady-state LV pressure-volume relationships were recorded, and the point that defined the upper-left corner was examined relative to the 1- and 7-minute lines that defined Ees. An example from a single mouse is shown in Figure 2. A more detailed analysis was performed in a subset of mice (n=5). In all 5 mice, the 2- and 4-minute points fell on the line that defined 1- and 7-minute Ees, and not farther to the left.

The effect of a complete transient aortic occlusion on LV pressure-volume relationships is examined in Table 3. These studies were performed because the anticipated alternations in diastolic function, such as a prolongation in τ (data not shown) and rise in Pd with an increase in Vd did not occur in the 21 mice examined (Table 1). To maximize the load applied to the LV, complete aortic occlusion was applied after 7 minutes of sustained afterload (n=6). Single-beat comparison was made between the first beat and the beat with peak pressure. Under this augmented load, there was a further increase in Vd, Pmax, Pd, and Ees as well as an increase in Pd and τ.

To determine whether homeometric autoregulation was a more dominant mechanism for enhanced LV contractility, we examined how quickly end-diastolic volume increased as transient aortic occlusion was applied to this same subset of mice (Table 3). Over 3.7±1.6 seconds, as Pd increased from 118±13 to 162±12 mm Hg (P<0.05), end-diastolic volume increased from 29±11 to 33±11 μL (P<0.05). The inset figure in Table 3 makes the same point, where end-diastolic volume can be seen to increase beat by beat as transient aortic occlusion is applied. Furthermore, closer scrutiny of Figure 2 demonstrates that for any matched end-diastolic volume, sustained afterload loops shortened to a lower end-systolic volume and larger stroke volume than baseline loops.

**Discussion**

This study demonstrates for the first time that a sustained increase in afterload results in improved contractile performance of the intact CD-1 murine LV. In response to an
average 26-mm Hg increase in systolic pressure, there was a substantial leftward shift of the end-systolic pressure-volume relation. This shift appeared within 1 minute of the increase in afterload and was maintained, with no augmentation, for 7 minutes. These findings indicate that in the intact CD-1 murine heart, length-dependent activation exists as a monophasic process, without the rapid and slow components previously described in larger species.\textsuperscript{12-14} Although the rate of isovolumic relaxation did not slow and LV end-diastolic pressure did not increase with sustained afterload, these parameters did increase during the application of extreme afterload (transient aortic occlusion after sustained partial aortic occlusion). These results are consistent with the hypothesis that the intact CD-1 murine heart functions near maximal contractility in the basal state and thus does not have a large cardiac reserve.\textsuperscript{5}

Alvarez et al\textsuperscript{12} and Cingolani and coworkers\textsuperscript{13} demonstrated that mechanical stretch produces autocrine release of angiotensin II, which via stimulation of AT\textsubscript{1} receptors induces the formation and release of endothelin. Endothelin stimulates the Na\textsuperscript{+}-H\textsuperscript{+} exchanger, increasing intracellular Na\textsuperscript{+}, which in turn activates the Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger, with subsequent elevation in intracellular Ca\textsuperscript{2+} and augmented contractile performance. In the murine myocardium, however, sarcoplasmic reticular Ca\textsuperscript{2+} recycling is the dominant mechanism for Ca\textsuperscript{2+} handling, accounting for >90% of the Ca\textsuperscript{2+} available for each cardiac contraction\textsuperscript{2,29} (compared with 50% in larger mammals\textsuperscript{2}). Thus, in mice, the Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger handles <10% of activator Ca\textsuperscript{2+} for each action potential, and the proposed mechanism for the slow phase of length-dependent activation has a minimal role. Whether this fully explains the lack of a second phase in the mouse heart will require further studies.

Numerous prior studies have assessed the impact of increased afterload on performance of the intact LV in larger mammals. Studies in isolated cross-perfused canine hearts showed that increases in simulated aortic impedance led to leftward shifts of the P\textsubscript{es}-LV end-systolic volume (V\textsubscript{es}) relation.\textsuperscript{30} Likewise, prior work from Sodums et al\textsuperscript{31} in intact closed-chest dogs showed that when afterload was increased by angiotensin II infusion, the P\textsubscript{es}-V\textsubscript{es} relation underwent a parallel leftward shift. These results were subsequently reproduced in this model during phenylephrine infusion by Little et al\textsuperscript{32} and in our laboratory during nonpharmacological increases in afterload induced by inflation of a balloon in the proximal descending aorta.\textsuperscript{33} Klautz and coworkers\textsuperscript{34} showed in newborn lambs that increased afterload led to an increase in E\textsubscript{a} and a leftward shift of the pressure-volume relation. Our results in the intact murine LV are consistent with these studies, where again the dominant demonstration of length-dependent activation was via a leftward shift of the line that defined end-systolic elastance. None of these larger mammalian studies, however, examined the time dependence (fast and slow components) of length-dependent activation.

The time constant of isovolumic relaxation was not prolonged under conditions of sustained increased afterload. It was not until the application of excessive load (transient aortic occlusion added to sustained aortic occlusion) that there was a prolongation of isovolumic relaxation. Prior studies of larger mammals have demonstrated that the time constant of relaxation was prolonged after the application of as little as 12 mm Hg of afterload,\textsuperscript{25,34-36} far less than achieved in the present study. Why was it so difficult to demonstrate the afterload dependence of \(\tau\) in intact murine myocardium? The rate of LV pressure decline is directly related to the force generated during contraction,\textsuperscript{34} and in most studies, increased afterload has been associated with an increase in the time constant of relaxation. In the mouse, the rate of Ca\textsuperscript{2+} reuptake by the sarcoplasmic reticulum\textsuperscript{1} is exceedingly rapid, which accounts for the rapid rate of mechanical restitution. Likewise, despite the addition of up to 8 mmol/L Ca\textsuperscript{2+} to isolated murine myocardium, Gao and colleagues\textsuperscript{1} found no increase in diastolic tone, aftercontractions, or other manifestations of Ca\textsuperscript{2+} overload. In contrast, isolated rat myocardium demonstrates Ca\textsuperscript{2+} overload much more readily.\textsuperscript{1} Our observation that there was a prolongation of \(\tau\) only after extreme

<table>
<thead>
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<th>TABLE 3. Effect of Transient Aortic Occlusion</th>
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<tr>
<td>(V_{es}), (\mu L)</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Beat\textsubscript{dash}</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>(\pm SD)</td>
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For abbreviations, see Table 1. Beat\textsubscript{dash} indicates first beat; Beat\textsubscript{bold}, beat with peak pressure, illustrated in the inset figure; and \(\tau_{isovol}\), time constant of isovolumic relaxation.

\(P<0.05\) vs Beat\textsubscript{dash}, paired Student’s \(t\) test. \(n=6\).
afterload (124 to 172 mm Hg) is consistent with mice having faster Ca\textsuperscript{2+} reuptake capability than larger mammals, such that much higher calcium transients would be needed to saturate the uptake mechanism.

A second observation on diastolic performance was that despite substantial elevation of end-diastolic volume after sustained afterload, the anticipated increase in end-diastolic pressure did not occur. Only after the complete additional transient aortic occlusion did LV end-diastolic pressure increase. This appears not to have resulted from volume depletion, because the mean baseline LV end-diastolic pressure was 12 mm Hg. We speculate that operating on the flat portion of the diastolic pressure-volume relationship may be advantageous in hearts with high rates, because heart rate is a determinant of myocardial oxygen demand. Wall stress, which incorporates chamber pressure, chamber radius, and wall thickness, is also a determinant of myocardial oxygen demand. Although increased end-diastolic volume will lead to increased wall stress because of increased radius and reduced thickness, this is minimized if chamber pressure is not also elevated. Moreover, when wall stress is elevated, coronary resistance is elevated as well,\textsuperscript{17} and at very high heart rates there may be limited ability to meet the needs of increased myocardial oxygen demand, such that working at low diastolic pressures may be advantageous. Additional studies will be needed to address this question.

There are 2 limitations to the present study that require further comment. Reflexes were not blocked in the preparation and are the explanation for the slight reduction in heart rate with sustained afterload at 1 and 7 minutes (Table 2). However, it is unlikely that the absence of a slow component of length-dependent activation is due to enhanced vagal tone in the present preparation. The decrease in heart rate occurred at 1 minute and persisted at the same heart rate at 7 minutes. Thus, the same vagal tone present at 1 minute was probably present at 7 minutes. Furthermore, previous investigators have shown that in the intact preparation, improved LV contractility in response to afterload was not abolished by sympathetic and parasympathetic denervation.\textsuperscript{18}

The second limitation is that sustained afterload can increase contractility by other mechanisms besides length-dependent activation. Homeometric autoregulation may occur in response to sustained afterload.\textsuperscript{26–28} However, the significant increase in end-diastolic volume in the present preparation, coupled with a lower end-systolic volume and increased stroke volume at matched preload in Figure 2, supports a lesser role for homeometric autoregulation compared with length-dependent activation. Further evidence is provided by the immediate linkage between increased afterload and increased end-diastolic volume, which suggests that the presence of homeometric autoregulation was not the dominant mechanism for increased contractility. Increased coronary perfusion secondary to increased afterload also is known to increase LV contractility\textsuperscript{39} and probably made some contribution to the enhancement of contractility that was seen.

In conclusion, our results show that a sustained increase in afterload leads to an increase in end-diastolic volume and a leftward shift of the $P_{EDV} - V_{ED}$ relation at 1 minute, which is evidence of length-dependent activation. There was no further leftward shift at 7 minutes, which demonstrates the lack of a second, slow phase to this phenomenon. Of note, increases in LV end-diastolic pressure and $\tau$ appeared only during extreme afterload elevation. Thus, the physiology of this increasingly important research model has unique features that reflect highly efficient calcium-handling mechanisms and unique chamber properties.

Acknowledgments

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References

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