Myocardial cross-bridge kinetics in transition to failure in Dahl salt-sensitive rats

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McCurdy, Daniel T., Bradley M. Palmer, David W. Maughan, and Martin M. LeWinter. Myocardial cross-bridge kinetics in transition to failure in Dahl salt-sensitive rats. Am J Physiol Heart Circ Physiol 281: H1390–H1396, 2001.—The role of altered cross-bridge kinetics during the transition from cardiac hypertrophy to failure is poorly defined. We examined this in Dahl salt-sensitive (DS) rats, which develop hypertrophy and failure when fed a high-salt diet (HS). DS rats fed a low-salt diet were controls. Serial echocardiography disclosed compensated hypertrophy at 6 wk of HS, followed by progressive dilatation and impaired function. Mechanical properties of skinned left ventricular papillary muscle strips were analyzed at 6 wk of HS and then during failure (12 wk HS) by applying small amplitude (0.125%) length perturbations over a range of calcium concentrations. No differences in isometric tension-calcium relations or cross-bridge cycling kinetics or mechanical function were found at 6 wk. In contrast, 12 wk HS strips exhibited increased calcium sensitivity of isometric tension, decreased frequency of minimal dynamic stiffness, and a decreased range of frequencies over which cross bridges produce work and power. Thus the transition from hypertrophy to heart failure in DS rats is characterized by major changes in cross-bridge cycling kinetics and mechanical performance.

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Two-dimensional long-axis and short-axis views of the LV were recorded, with the short-axis at the level of the tips of the papillary muscles. After gain settings were optimized, M-mode tracings were recorded at the same level. and posterior wall thickness at end diastole (PWT) was measured. LV internal dimensions (end-diastolic diameter (LVEDd) and end-systolic diameter (LVESd)) were measured using the leading edge-to-leading edge convention. LVEDd measurements were made at the time of maximal diastolic dimension, whereas LVESd was measured at the point of greatest anterior systolic excursion of the posterior wall. Values from all measured beats in each animal were averaged. LV percent fractional shortening (%FS) was calculated as \[\frac{[(LVEDd - LVESd)/LVEDd] 	imes 100}{\text{observer with no knowledge of the animal's study group analyzed the echocardiographic images.}]

**Dissection and strip preparation.** After 6 or 12 wk of the diet, the rats were anesthetized with isoflurane (1%), and the heart was rapidly removed and immediately placed in a standard Krebs solution containing 30 mM 2,3-butanedione monoxime (BDM) and gassed with 95% O_2-5% CO_2. Subsequent procedures have been published in detail previously (2). Briefly, LV papillary muscles were disintegrated in BD-M-Krebs solution to yield thin strips (diameter \(\approx 0.125\) mm; length \(\approx 1.0\) mm) with parallel fiber orientation. The strips were transferred to a vessel containing relaxing solution composed of 5 mmol/l MgATP, 40 mmol/l phospho-creatine, 240 U/ml creatine kinase, 1 mmol/l free Mg_2, and 0.11 mmol/l CaCl_2, 5 mmol/l EGTA, and 20 mmol/l phospho-creatine. 2-hydroxyethyl)-2-aminoethanesulfonic acid buffer (pH 7.0), ionic strength 190 mmol/l with added sodium methan-sulfonate. The strips were then demembranated (skinned) by the addition of Triton X-100 to a final concentration of 1% wt/vol and 50% glycerol wt/vol (with 10 \(\mu\)g/ml leupeptin, a protease inhibitor), and incubated overnight at 4°C. Strips were then transferred to a vessel with a solution of the same composition except for Triton and stored at \(-20°C\) until used within 1 wk.

At the time of study, the strips were placed in a vessel containing relaxing solution. Aluminum T clips were attached to the ends producing a uniform strip with a between-clamp length of \(\sim 0.5\) mm. The clipped strip was transferred to a 30-\(\mu\)l drop of relaxing solution on a glass-bottomed, temperature-controlled aluminum chamber filled with mineral oil and attached to a strain gauge and piezoelectric motor (2). A strip-chart recorder and digital storage oscilloscope monitored analog displacement and strip force signals. A Peltier-effect thermoelectric device maintained oil and solution temperature at 22°C. Attached strips were incrementally stretched to and then maintained at a sarcomere length of 2.2 \(\mu\)m (measured using an inverted microscope and filar micrometer). Strip tension (kN/m²) was calculated by dividing force by the cross-sectional area of the strip. Strip cross-sectional area was calculated as the product of \(\pi \cdot a \cdot b\), where \(a\) and \(b\) are the major and minor radii of the strip. Calcium activation of the strips was achieved by exchanging equal volumes of relaxing solution for activating solution and incrementally increasing the free calcium concentration from pCa 8.0 to pCa 4.5. Activating solution had the same ionic composition as relaxing solution except that the total CaCl_2 was 5.03 mmol/l (pCa 4.5). Solutions were formulated by solving equations describing ionic equilibria (7). Isometric force measurements were analyzed by a nonlinear least-squares fit of the isometric force data using the Hill equation (SigmaPlot, Jandel Scientific, SPSS; Chicago, IL).

**Sinusoidal length perturbations.** Small amplitude sinusoidal length perturbations of the skinned strips (sinusoidal analysis) was used to obtain information about diet-induced alterations in myocardial mechanical properties and cross-bridge kinetics at varying calcium concentrations. Details have been described previously (2, 14). Briefly, after steady-state isometric tension was reached at each calcium concentration, sinusoidal perturbations of 0.125% strip length (amplitude) were applied at 42 discrete frequencies (\(f\), 0.125–100 Hz). The length and force signals were digitized and normalized to the initial length and cross-sectional area of the muscle strip (Fig. 1A). The complex stiffness modulus obtained from the data provides a measure of the relative magnitudes (dynamic stiffness, kN/m²) and phases of the fractional length and tension sinusoids. The phase shift (\(\theta_s\)) corresponds to a time shift (\(t_s\)) between the two sinusoids, where \(t_s = \theta_s/2\pi f\). Figure 1B is a representative Nyquist plot of the viscous and elastic moduli at each frequency under activated (pCa 5.0) conditions. Maximal oscillatory work production by the strip corresponds to the complex modulus data point with the lowest viscous modulus in the Nyquist plot. The strip produces maximal oscillatory power at the data point with the maximal product of frequency and work, which occurs at or near the frequency producing the lowest viscous modulus.
The observed complex modulus was fit to the following complex modulus equation

\[ y(f) = A(2\pi f)^\alpha - (B_if + iC_if) \]

where \( y \) is the complex modulus at frequency \( f \) (in Hz), with real and imaginary (elastic and viscous) components; \( \alpha \) has a value of 1 and units of radians; \( A, B, \) and \( C \) are the magnitudes of processes \( A, B, \) and \( C \), as defined in the model (in kN/m²); kinetic parameters \( b \) and \( c \) are defined as the characteristic frequencies for processes \( B \) and \( C; i = -1^{1/2} \), and \( k \) is a unitless exponent. Figure 1C shows the complex modulus with the three respective processes labeled. The sum of the three moduli is displayed as the solid line in Fig. 1B (i.e., the curve fit to the complex modulus equation). Process \( A \) is hypothesized to be a measure of the viscoelastic response of parallel passive elements of the strip. Values for the hemispherical processes \( B \) and \( C \) are thought to reflect the number and the unitary stiffness of cycling cross-bridges per cross-sectional area, with \( B \) representing a work or force-producing process and \( C \) representing a work-absorbing process in the cross-bridge cycle (15, 16). Maximum oscillatory work production by the cross bridges occurs at the nadir of process \( B \), corresponding to frequency \( b \). \( 2\pi b \) is the apparent rate constant for the work-producing step and power \( = \pi fE_v(\Delta f/L_v)^2 \), where \( E_v \) is the viscous modulus, \( \Delta f \) is the amplitude of sinusoidal length perturbation, one-half peak to peak; and \( L_v \) is the strip length. Maximum oscillatory work absorption occurs at the apex of process \( C \), corresponding to frequency \( c \), with \( 2\pi c \) the apparent rate constant of the work-absorbing step (14).

Statistics. Data are reported as means ± SD unless indicated. Two-way analysis of variance (ANOVA) was used to detect differences. A Student-Newman-Keuls test was used for multiple comparisons. A value of \( P < 0.05 \) was taken to indicate significance.

RESULTS

Body weight, LV-to-body weight ratio, and mortality. Table 1 shows the effects of diet on body weight (BW), LV-to-BW (LV/BW) ratio, and mortality. Initiation of the HS diet when the animals were 8 wk old rather than 6 wk old resulted in a greatly reduced mortality (20% vs. ~80%) compared with our previous report (13), whereas still causing a marked increase in LV/BW ratio at 6 wk. LV/BW ratio then decreased at 12 wk as the animals progressed toward heart failure. LV/BW ratio was significantly higher in HS-6 and HS-12 compared with age-matched LS controls. Previous studies from our laboratory as well as others have documented that between the sixth and twelfth week of the HS diet there are significant increases in mortality, wet lung weight, blood urea nitrogen, and creatinine consistent with a transition to heart failure (11, 13). BW of LS-12 rats was slightly larger than HS-12 rats.

Table 1. Effect of dietary salt on body weight, LV-to-body weight ratio, and mortality

<table>
<thead>
<tr>
<th></th>
<th>BW, g</th>
<th>LV/BW, g/kg</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-6</td>
<td>339 ± 9</td>
<td>2.56 ± 0.20</td>
<td>0</td>
</tr>
<tr>
<td>HS-6</td>
<td>342 ± 23</td>
<td>4.05 ± 0.37</td>
<td>0</td>
</tr>
<tr>
<td>LS-12</td>
<td>460 ± 7</td>
<td>2.27 ± 0.10</td>
<td>0</td>
</tr>
<tr>
<td>HS-12</td>
<td>433 ± 7e</td>
<td>3.38 ± 0.17</td>
<td>20</td>
</tr>
</tbody>
</table>

Data are means ± SD. LV, left ventricular; BW, body weight; LV/BW, LV weight-to-BW ratio; LS-6 and HS-6, low-salt and high-salt diet for 6 wk; LS-12 and HS-12, low-salt and high-salt diet for 12 wk. *\( P < 0.05 \) vs. age-matched LS.

Echocardiographic variables. Echocardiographic assessment was performed after 4, 6, 9, and 12 wk of the diet. LVEDd was significantly larger in the HS-9 group compared with both age-matched LS controls and the previous HS-6 measurement. LVEDd continued to increase such that the HS-12 group had a significantly larger LVEDd than either HS-9 or LS-12 groups (9 2.56 vs. LS 5.32). The LS group maintained a constant LVEDd and LVSDd throughout. LVSd was significantly greater in the HS-12 compared with that of the HS-9 or the LS-12 group. PWT was increased by HS diet at 6, 9, and 12 wk compared with that of the LS controls. However, the HS-12 group PWT was smaller than that in the HS-9 group, consistent with progressive dilatation without additional hypertrophy. LS-6 %FS was ~40% and remained at about this value during the study. HS-6 %FS was increased compared with LS-6 and, in combination with the increased PWT, indicates compensated hypertrophy. At 9 wk %FS had decreased compared with HS-6 and was similar to the age-matched LS controls. This change in function at 9 wk, along with the increased LV dimension in diastole and systole, suggests that HS-9 hearts are starting to undergo a transition to failure. At the 12 wk time point, %FS in the HS group (32%) was greatly reduced compared with both LS controls and the previous HS time point. In conjunction with major increases in LVEDd and LVSDd (~25%), this indicates LV decompensation.

Isometric tension-calcium relation. There were no significant differences in the absolute relaxed (pCa 8.0) or maximal tension (pCa 5.0) after 6 wk of the diet. The calcium concentrations producing half-maximal relative (percentage of maximal) tension generation (pCa50) were equivalent after 6 wk of the diet (HS 5.28 ± 0.02 vs. LS 5.32 ± 0.02). Figure 2 illustrates the isometric tension-calcium relation in strips from the 12-wk diet groups expressed both as absolute (kN/m²) tension values (Fig. 2A) and as a percentage of maximal tension (Fig. 2B). The regression lines in Fig. 2 represent the data fit to a modified Hill equation. There was a significant increase in pCa50 in the HS-12 group assessed from the pCa-absolute tension relationship (LS 5.14 ± 0.05 vs. HS 5.29 ± 0.03, \( P < 0.03 \), Fig. 2A) and from the pCa-relative tension relationship (LS 5.28 ± 0.03 vs. HS 5.39 ± 0.02, \( P < 0.001 \), Fig. 2B), indicative of increased calcium sensitivity. The trend toward higher maximal tension in the LS-12 group (Fig. 2A) was not statistically significant.

Sinusoidal analysis. In Fig. 3 A Bode plot of the dynamic stiffness-frequency relation from the sinusoidal analysis is illustrated for the 12-wk diet groups. When the muscle is relaxed (pCa 8.0) there is a roughly linear relationship between dynamic stiffness and the frequency of length perturbation (Fig. 3A). With activation (Fig. 3, B and C) there is an increase in the magnitude of dynamic stiffness that reflects an increased number of force-generating cross bridges. In addition, the dynamic stiffness-frequency relation be-
comes more complex, with relatively low dynamic stiffness at low frequencies that decreases to a minimum as the frequency increases. The nadir of dynamic stiffness is referred to as \( F_{\text{min}} \) or the “dip” frequency. At frequencies greater than \( F_{\text{min}} \) there is a dramatic increase in stiffness because an increasing number of attached cross bridges are unable to complete the transition to the postforce producing state. There was no difference in the magnitude of minimal dynamic stiffness or \( F_{\text{min}} \) in LS-6 and HS-6 groups at pCa 5.0 or 5.5. At pCa 5.0, \( F_{\text{min}} \) was significantly lower in the HS-12 group than the LS-12 group (3.30 ± 0.79 vs. 4.98 ± 1.28 Hz, Fig. 3C, \( P < 0.05 \)). The magnitude of minimal dynamic stiffness was 35% less in the HS-12 group, although this difference did not reach statistical significance (\( P = 0.084 \)). The difference between LS-12 and HS-12 is accentuated when dynamic stiffness is examined at a submaximal calcium concentration of pCa 5.5 (Fig. 3B), which is closer to normal in vivo systolic calcium levels (6). HS-12, which has greater calcium sensitivity (Fig. 2), displays the characteristic dip frequency observed in maximally activated strips, whereas a clearly defined dip in dynamic stiffness is absent in the plot for LS-12 (Fig. 3B). At pCa 5.5 HS-12 dynamic stiffness was significantly less than LS-12 between 2.6 and 6.0 Hz and is attributed to an increased sensitivity of the cross bridges to length perturbation.

The phase-frequency relation shown at pCa 5.0 for the 12-wk diet groups in Fig. 4 represents the \( \theta_{\text{e}} \) of the recorded force sinusoid relative to the length sinusoid and corresponds to an actual \( t_{\text{e}} \) in the two sinusoids. A negative phase shift indicates a negative viscous modulus and that work (net mechanical energy) produced by the strip over one complete perturbation cycle is

![Fig. 2. Tension-pCa relationship of skinned papillary fibers from Dahl salt-sensitive rats on specified diet for 12 wk. Data are means ± SD. 1 kN/m² = 1 mN/mm².](image)

![Fig. 3. Dynamic stiffness-frequency relation after 12 wk of diet with varying levels of calcium activation. A: pCa 8.0; B: pCa 5.50; C: pCa 5.0. Lines are fits to complex modulus equation (Eq. 1) using values (see Table 3) for model-defined processes. See RESULTS for description. Data are means ± SE; n = 9 for each group.](image)
greater than that absorbed by the strip from the apparatus. A positive phase shift indicates net absorption of energy by the strip from the apparatus. There was no difference between groups in the phase shift after 6 wk. However, the frequency at which the phase shift was most negative was lower in the HS-12 group (1.62 ± 0.017 Hz vs. LS-12 2.57 ± 0.024 Hz, Fig. 4, P = 0.005). In addition, the HS-12 peak positive phase shift (net energy absorbed by the strip) also had a substantially lower frequency (HS-12 6.45 ± 0.43 Hz vs. LS-12 11.42 ± 0.99 Hz, P < 0.001). These findings indicate that there are fundamental differences in the frequency-dependent viscoelastic properties of the HS-12 strips.

The oscillatory power output of the strip reflects the active viscous component supplied by the strip over and above the passive viscous property of the strip. There were no significant differences in the oscillatory power output frequency distribution in the 6-wk diet groups (data not shown). Figure 5 shows the frequency-oscillatory power relation for frequencies 0.0125 to 4 Hz at maximal activation (pCa 5.0) for the 12-wk diet groups. The HS-12 strips produce power over a substantially lower range of frequencies (≤2.0 Hz) than LS-12 (approximately <3.0 Hz).

Mean values for the processes (coefficients) A, B, and C and kinetic parameters b and c (in Hz) obtained by solving the complex modulus equation are presented in Table 2. There was a small but statistically significant increase in c in LS-12 compared with LS-6. The reason for this increase is unclear, although neither LS time point was significantly different from the corresponding HS value. Of greater significance was the lower b value in HS-12 compared with LS-12 (2.20 vs. 3.56 Hz, P < 0.01). Therefore, according to our model, the apparent rate constant (2πb) of cross-bridge force generation (and work production) was also lower. Thus kinetic processes attributable to cross-bridge function are altered in muscle strips from hearts undergoing a transition to failure.

DISCUSSION

To understand the mechanisms responsible for the transition from compensated cardiac hypertrophy to myocardial failure, it is important to measure functional characteristics during each of these phases. Such information is unavailable from patients, because myocardial tissue is not ordinarily available during the compensated or transition phases. The DS rat model is well suited to address this problem because it undergoes a well-characterized, predictable transition from compensation to failure. Thus 6 wk of the HS diet induces compensated hypertrophy with normal chamber diameter and %FS (Tables 1 and 3). In skinned strips, we found that the isometric tension-calcium relation, dynamic stiffness, and complex modulus model parameters were unchanged at this time (Table 2). After 12 wk of the HS diet, the hearts had undergone a transition to a decompensated state accompanied by LV dilatation and a decrease in %FS (Tables 1 and 3). In HS-12 skinned strips, an increase in calcium sensitivity of isometric tension was observed, with no change in maximal tension (Fig. 2). Sinusoidal analysis indicated that there is a decrease in Fmin, a reduced frequency range for oscillatory power output, and a decrease in the apparent rate constant for the work-producing step in the cross-bridge cycle (Table 2). Corresponding to the changes in Fmin and power frequency range, the maximum positive and negative phase shifts occur at lower frequencies in HS-12 rats. Thus, whereas there are no significant changes in myofilament viscoelastic properties in the compensated state, the transition to the decompensated state is associated with major viscoelastic alterations involving depression of both cross-bridge cycling and mechanical performance.

We previously reported that compensated hypertrophy in DS rats is associated with a relatively modest increase in the percentage of V3 isomyosin (from 10 to 44%) and a 25% decrease in maximum myofibrillar ATPase (13). With decompensation, V3 isomyosin increases to about 75% and myofibrillar ATPase decreases by 44%. Consequently, it is unlikely that myofilament alterations that occur during the transition to failure are attributable entirely to the isomyosin shift.
and reduced ATPase, because both are significantly altered in the compensated phase. Furthermore, V3 isomyosin expression per se does not necessarily result in myocardial failure as evidenced by animals rendered hypothyroid who convert to 100% V3 isomyosin (18).

We also previously documented a small change in troponin T isoform distribution and a decrease in troponin T phosphorylation in failing Dahl rats (13). More recently, we reported a decrease in troponin I (TnI) phosphorylation and, using a combination of isolated native thin filaments and skeletal muscle myosin in the in vitro motility assay, a reduction in calcium sensitivity of unloaded velocity in failing DS rats (28). The latter finding indicates that a change in the thin filament contributes to the altered cross-bridge kinetics in the failing state. The decreased phosphorylation of TnI is likely due at least in part to decreased β-adrenergic responses. However, this effect may not be a primary cause of the transition to failure, because there is a decreased β-adrenergic response independent of β-adrenergic receptor density or L-type Ca\(^{2+}\) channel function in the compensated heart (3, 12, 21). Thus it may not be possible to ascribe the transition from compensated hypertrophy to failure to a simple alteration in thin filament proteins.

We found striking reductions in the frequency of maximal work and power generation by the myofilaments during the transition to failure. An impairment of both excitation-contraction coupling, the latter related to depressed sarcoplasmic reticulum calcium pumping (8, 26). However, our observation of a decrease in characteristic frequency \(b\) and apparent rate constant \(2\pi b\) of the work-producing step in HS-12 strips, as well as the reduced frequency range over which the HS-12 strips produced work and power, suggests that depressed cross-bridge kinetics and alteration of the intrinsic viscoelastic properties of the myofilament may also contribute to FFR depression.

The substantial decrease in F\(_{\text{min}}\) after the transition to failure in our study is consistent with similar results in human heart failure studies (9, 24). Whereas F\(_{\text{min}}\) reflects the mean cycling rate of the cross bridges (1, 14, 23, 27), it more precisely indicates the frequency where there is maximal resonance between the imposed length change and the frequency-dependent oscillatory force produced by the cross bridges. A reduction in mean cross-bridge cycling rate or rate of maximal work output is consistent with our previous report of decreased myofibrillar ATPase and increased V3 isomyosin (13). It is intriguing that in the compensated state there was no difference in F\(_{\text{min}}\) despite a 24% reduction in ATPase in association with an increase in V3 to about 45% of total myosin. F\(_{\text{min}}\) may thus be a more sensitive indicator of the complex alterations in contractile proteins and thin filament composition accompanying the transition to myocardial failure. Moreover, changes in ATPase rate may not necessarily result in closely correlated changes in contractile performance. In in vitro motility assay studies (10), pure populations of V1 or V3 myosin produced velocities proportional to their actin-activated ATPase rates. However, mixtures of myosin species resulted in velocities that reflected complex mechanical interactions and did not yield a linear relationship.

We documented an increased calcium sensitivity of isometric tension in HS-12 strips. The increased sensitivity is consistent with previous reports in both human (19, 25, 29) and canine (30) failing myocardium. The observed decrease in characteristic frequency \(b\) (apparent rate constant of force production \(2\pi b\)) re-

### Table 2. Parameter values at pCa 5.0

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<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>k</th>
<th>b</th>
<th>c</th>
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<tr>
<td>HS-6</td>
<td>229</td>
<td>388</td>
<td>821</td>
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<tr>
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<td>188</td>
<td>298</td>
<td>696</td>
<td>0.146</td>
<td>2.40</td>
<td>26</td>
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</table>

Data are means ± SD. Coefficients A, B, and C (in kN/m\(^2\)) define the magnitude of the complex stiffness for processes A, B, and C. Kinetic parameters \(b\) and \(c\) (in Hz) define characteristic frequencies of processes B and C. \(* P < 0.01\) vs. age-matched LS control. \(P < 0.05\) vs. LS-6.

### Table 3. Echocardiographic variables

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<th>4 wk</th>
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<th>9 wk</th>
<th>12 wk</th>
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<td>LVEDd, mm</td>
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<td>HS</td>
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<td>6.68</td>
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<td>LS</td>
<td>3.83</td>
<td>3.62</td>
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<tr>
<td>LVSDs, mm</td>
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<tr>
<td>PWT, mm</td>
<td>1.51</td>
<td>2.17</td>
<td>2.25</td>
<td>1.96</td>
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<td>%FS</td>
<td>42.0</td>
<td>46.7</td>
<td>38.3</td>
<td>32.1</td>
</tr>
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</table>

Data are means ± SD. LVEDd, LV end-diastolic dimension; LVSDs, LV end-systolic dimension; PWT, posterior wall thickness; %FS, fractional shortening. \(* P < 0.05\) vs. previous time point; \(† P < 0.05\) vs. LS group at same time point.
ported here suggests a mechanism responsible for this result. We postulate that a reduction of 2 nb leads to an increase in the number of cross bridges in a preforce, weakly bound state that promotes cooperative activation of myosin S1 binding to the thin filament (2, 17). The effect of cross bridges accumulating in this state would be most evident in the submaximal range of calcium activation, where the amplitude of force development depends considerably on the cooperative activation of the thin filament by S1 binding.

In summary, isometric tension generation and sinusoidal analysis of papillary muscle strips from DS rats revealed no differences in the mechanical response at the compensated hypertrophy stage of adaptation but major alterations with the transition to failure. The latter are associated with multiple changes in contractile protein composition and appear to be an important mechanism for the transition to depressed contractile function in this model.

REFERENCES