Direct Effects of Colchicine on Myocardial Function
Studies in Hypertrophied and Failing Spontaneously Hypertensive Rats


Abstract—The aging spontaneously hypertensive rat (SHR) is a model in which the transition from chronic stable left ventricular hypertrophy to overt heart failure can be observed. Although the mechanisms for impaired function in hypertrophied and failing cardiac muscle from the SHR have been studied, none accounts fully for the myocardial contractile abnormalities. The cardiac cytoskeleton has been implicated as a possible cause for myocardial dysfunction. If an increase in microtubules contributes to dysfunction, then myocardial microtubule disruption by colchicine should promote an improvement in cardiac performance. We studied the active and passive properties of isolated left ventricular papillary muscles from 18- to 24-month-old SHR with evidence of heart failure (SHR-F, n=6), age-matched SHR without heart failure (SHR-NF, n=6), and age-matched normotensive Wistar-Kyoto rats (WKY, n=5). Mechanical parameters were analyzed before and up to 90 minutes after the addition of colchicine (10^{-5}, 10^{-4}, and 10^{-3} mol/L). In the baseline state, active tension (AT) developed by papillary muscles from the WKY group was greater than for SHR-NF and SHR-F groups (WKY 5.69±1.47 g/mm^2 [mean±SD], SHR-NF 3.41±1.05, SHR-F 2.87±0.26; SHR-NF and SHR-F P<0.05 versus WKY rats). The passive stiffness was greater in SHR-F than in the WKY and SHR-NF groups (central segment exponential stiffness constant, K\_s\_c\_s: SHR-F 70±25, SHR-NF 44±17, WKY 41±13 [mean±SD]; SHR-F P<0.05 versus SHR-NF and WKY rats). AT did not improve after 10, 20, and 30 minutes of exposure to colchicine (10^{-5}, 10^{-4}, and 10^{-3} mol/L) in any group. In the SHR-F group, AT and passive stiffness did not change after 30 to 90 minutes of colchicine exposure (10^{-4} mol/L). In summary, the data in this study fail to demonstrate improvement of intrinsic muscle function in SHR with heart failure after colchicine. Thus, in the SHR there is no evidence that colchicine-induced cardiac microtubular depolymerization affects the active or passive properties of hypertrophied or failing left ventricular myocardium. (Hypertension. 1999;33:60-65.)

Key Words: colchicine ■ function, myocardial ■ rats, inbred SHR ■ hypertrophy, cardiac ■ heart failure ■ muscle, papillary ■ muscle, isolated cardiac

Cardiac hypertrophy is a compensatory response to a sustained mechanical stress of the heart that allows it to meet the demands of an increased workload. Although initially beneficial in terms of maintaining total pump performance, stable hypertrophy may progress to a decompensated state, with cardiac pump dysfunction^1 and myocardial depression.\(^2,3\)

The spontaneously hypertensive rat (SHR) is a well-established model of genetic hypertension that leads to an increase in cardiac mass, which often initially maintains cardiac performance despite the elevation of systemic arterial pressure. Nonetheless, if the pressure overload is sustained for a sufficient period of time, cardiac failure may supervene.\(^4\) Thus, the aging SHR is a model in which one can observe the transition from chronic stable left ventricular (LV) hypertrophy to overt heart failure.

Although the mechanisms for impaired function of failing hypertrophied cardiac muscle have been studied, none accounts fully for the contractile abnormalities of failing hypertrophied myocardium from SHR. The mechanisms that may contribute to the development of heart failure include the following: alterations in excitation-contraction coupling, intrinsic changes in contractile proteins, impaired autonomic modulation during stress, insufficient energy supply, extracellular matrix changes, and myocyte dropout.\(^5\)

The cytoskeleton is a well-organized structure that maintains the various subcellular organelles in their normal spatial arrangement and, thus, represents a scaffolding structure within the cells.\(^6-8\) The cytoskeleton can be classified according to the diameter of the component fibers: microfilaments or actin filaments (6 nm), intermediate filaments (10 nm), and microtubules (25 nm).
Tsutsui et al. tested the hypothesis that in excess the microtubules are responsible for the contractile abnormalities of cardiocytes hypertrophing in response to a pressure overload. They analyzed the effects of colchicine on sarcomere motion in cardiocytes isolated from cats submitted to right ventricle (RV) overloading by pulmonary artery banding. Exposure of hypertrophied RV cardiocytes to colchicine normalized the initially abnormal contractile function (ie, the initially depressed shortening and velocity of shortening in RV cells improved in response to colchicine). The investigators concluded that an excess of microtubules in stress-hypertrophied cells increases the resistive intracellular load on the shortening sarcomere, which impedes sarcomere motion. They suggested that the microtubules are causally involved in the contractile dysfunction of cardiocytes hypertrophying in response to a pressure overload and that the microtubules may have significance during the transition from stable compensated hypertrophy to heart failure. Subsequent studies also demonstrated the role of the cytoskeleton in the cardiomyocyte dysfunction of the pressure-overload hypertrophied RV.10–12 On the other hand, Bailey et al.13 showed that depolymerization of microtubules by colchicine did not cause a significant change in contraction amplitude in either normal or hypertrophied myocytes from feline ventricles. Collins et al.14 failed to show that the level of β-tubulin or its polymerization state affects LV function during the transition from compensated pressure-overload hypertrophy to heart failure in aorta-banded guinea pigs. In addition, our group15 administered colchicine to SHR beginning at 12 to 13 months of age in an effort to prevent the transition to heart failure observed in the SHR.1–3 Chronic colchicine administration failed to prevent myocardial dysfunction or heart failure.

In the current study we investigated the direct relationship between mechanical performance and colchicine administration to myocardium from SHR that had developed myocardial dysfunction and heart failure. We hypothesized that if increased microtubules have an important role in contractile dysfunction of failing hypertrophied muscle, colchicine should promote an improvement in the isolated cardiac papillary muscle performance.

**Methods**

**Animal Model**

Male SHR and normotensive Wistar-Kyoto (WKY) control rats 18 to 23 months of age were studied. It is known that a large number of SHR demonstrate evidence of heart failure beginning at the age of 18 months.1,3–5,15 When SHR developed tachypnea and labored respiration, they were studied within 1 to 2 weeks. Failure was documented at sacrifice by the presence of thoracic effusions, left atrial thrombi and right ventricular hypertrophy.1,3–5,15 Left ventricular papillary muscle preparations were examined from 3 groups of rats: (1) aging SHR with evidence of heart failure (SHR-F), (2) age-matched SHR without evidence of heart failure (SHR-NF), and (3) age-matched normotensive WKY rats.

**Isolated Muscle Performance**

Cardiac intrinsic contractile performance was evaluated by studying isolated papillary muscle from the LV as described in detail previously.5 Briefly, at the time of study, rats were killed, and their hearts were quickly removed and placed in oxygenated Krebs-Henseleit solution at 28°C.15 The LV anterior or posterior papillary muscles were dissected free, mounted between 2 spring clips, and placed vertically in a chamber containing Krebs-Henseleit solution at 28°C and oxygenated with a mixture of 95% O2–5% CO2 (pH 7.38). The muscles were stimulated at a rate of 12 contractions/min at a voltage 10% above threshold. The spring clip on the upper end of the muscle was attached to a low inertia DC pen motor (model G100-PD; General Scanning), and the lower clip to a semiconductor strain-gauge tension transducer (model DSC-3; Kistler-Morse). A digital computer with an analog-to-digital interface allowed control of either tension or length of the preparation. Tension and length data were sampled at a rate of 1 kHz and stored on disk for later analysis.

After the muscles were mounted, they were equilibrated for 30 minutes. After this period, muscles were gradually stretched to the peak of the active tension (AT) versus length curve (Lmax, defined as the muscle length resulting in peak AT) and equilibrated for an additional 15 minutes while performing physiologically sequenced contractions.17 Isometric contraction parameters were determined, which included resting tension (RT, g/mm2), active tension (AT, g/mm2, defined as peak isometric tension minus resting tension), peak rate of isometric tension development (peak-dT/dt, g · mm–2 · s–1), electromechanical delay (EMD, ms; defined as the time from stimulation to the onset of tension development), time to peak tension (TPT, ms, defined as the time from the onset of tension development to the time of peak tension), maximum rate of tension decline (−dT/dt, g · mm–2 · s–1), and time from peak tension to 50% relaxation (RT50%, ms). In addition, maximum velocity of isotonic shortening (Vmax, muscle lengths/s) was determined at Lmax.

**Central Segment Measurements**

After these baseline determinations were made, 2 central segment markers, spaced approximately 1 to 2 mm apart, were applied for central segment length determinations as described previously.18,19 The preparation is scanned longitudinally by a laser beam at a rate of 1000 Hz. Resolution is 1.6 μm and root-mean-square noise on the order of 6.5 μm, or approximately 0.4% of central segment length for a typical 2.0-mm segment.

**Stress-Strain Analysis**

The analysis of myocardial stiffness was based on central segment measurements, to avoid potential errors due to “damaged end” effects. Passive tension-length relationships were determined by applying length ramps to the whole papillary muscle at a rate of 1.0 mm/s, corresponding to a normalized rate of length change on the order of 0.1 muscle length/s. Because of the large deformations involved, eulerian stress (tension/instantaneous area) was used, as opposed to Lagrangian stress (tension/reference area). Central segment stress (σcs) was defined as tension normalized by instantaneous cross-sectional area, calculated from the measured cross-sectional area assuming incompressibility:

\[
\text{CSA}_{\text{ext(inst)}} = \text{CSA}_{\text{ref}} \left[ \frac{L_{\text{cs(ref)}}}{L_{\text{cs(inst)}}} \right]
\]

where CSA_{ext(inst)} is instantaneous central segment cross-sectional area, CSA_{ref} is the cross-sectional area at the reference length, L_{ref} is instantaneous central segment length, and L_{ext} is the reference central segment length. Natural strain (ε) is generally defined as \(\epsilon = \ln (L/L_0)\), where L is length and L0 is length at zero stress (or “slack length”). Because of the exponential nature of the stress-strain relation, and therefore the shallow slope at low loads, the determination of true slack length (as used in the traditional definition of strain) is subject to considerable experimental error. Therefore, a modified natural strain definition was used in the present study:

\[
\epsilon_m = \ln \left( \frac{L_m}{L_{m0}} \right)
\]

where \(L_m\) is instantaneous central segment length and \(L_{m0}\) is central segment length at a load of 0.1 kdyne/mm2. With this definition, \(\epsilon = 0\) at a near-slaack “reference length” at which σ = 0.1 kdyne/mm2. If we assume that passive myocardial stress (σ)-strain (G) relations are exponential in nature,20 the relation can be expressed as...
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\[ \sigma = \sigma(e^{\kappa t}) \]  

With a log transformation, \[ \log(\sigma) = \log(e^{\kappa t}) + \kappa e \]  

Thus whole muscle stiffness, \( \kappa \) can be determined from the slope of the log (\( \sigma \)) versus \( e \) relation. The central segment stiffness constant, \( k_{0w} \), was derived from the slope of the log (\( \sigma_{0w} \)) versus \( e_{0w} \) relation. In the present study it was found that the relations were almost invariably well described by a single exponential.

Isometric and isotonic parameters were recorded from all muscles at the apex of the AT-length relation. Initially, the effects of colchicine \( 10^{-4} \) mol/L were studied; however, no change in papillary muscle function was observed. Therefore, the 3 groups of muscles (SHR-F, SHR-NF, and WKY) were studied at colchicine concentrations of \( 10^{-3}, 10^{-4}, \) and \( 10^{-3} \) mol/L. The contractile function of each muscle was followed over a 30-minute period (at 5, 10, 20, and 30 minutes).

LV and RV wet weight normalized by body weight (BW; LV/BW and RV/BW, respectively) were used as indexes of ventricular hypertrophy. All force data compiled during the protocol were normalized by the cross-sectional area of the muscle and \( V_{cm} \) data by the muscle length.

Tubulin Assays

Four additional SHRs were studied: 1 papillary muscle from each animal was immediately frozen in liquid nitrogen. The other muscle preparation was exposed to colchicine \( 10^{-4} \) mol/L for 60 (n=3) or 90 (n=1) minutes while mechanical activity was recorded, and then tissues were immediately frozen. Subsequently, frozen muscle papillary preparations weighing 5 to 10 mg each were homogenized in microtubule stabilization buffer (50% glycerol, 5% dimethyl sulfoxide, 10 mmol/L sodium phosphate, 0.5 mmol/L MgCl2, 0.5 mmol/L ethylenebis[oxyethylenenitrilo] tetraacetic acid, 0.5 mmol/L GTP, and 100 U/mL aprotinin, pH 6.95), homogenized, and incubated for 1 hour at 4°C to depolymerize the microtubules. After centrifugation, the supernatant was assayed for microtubule-derived tubulin.

Forty to 50 \( \mu \)g protein from each fraction was separated on 12% sodium dodecyl sulfate—polyacrylamide gel electrophoresis. The proteins were transferred to nitrocellulose membranes (Schleicher and Schuell), and the membranes were stained with antibodies to Ponceau S to confirm equal loading of the samples. After destaining, the membrane was incubated for 1 hour in blocking buffer (0.25 mol/L sucrose, 0.5 mmol/L GTP, 0.5 mmol/L MgCl2, 10 mmol/L sodium phosphate, and 100 U/mL aprotinin, pH 6.95), homogenized, and incubated for 1 hour at 4°C to depolymerize the microtubules. After centrifugation, the supernatant was assayed for microtubule-derived tubulin.

pericardial effusions, and RV hypertrophy.1,3–5,15 Animals in the SHR-F group were studied when they exhibited tachy- 

permea and labeled respiration, left atrial thrombi, pleural and
depolymerized buffer (0.25 mol/L sucrose, 50% glycerol, 5% dimethyl sulfoxide, 10 mmol/L sodium phosphate, 0.5 mmol/L MgCl2, 0.5 mmol/L ethylenebis[oxyethylenenitrilo] tetraacetic acid, 0.5 mmol/L GTP, and 100 U/mL aprotinin (pH 6.95)) and centrifuged at 10000g for 15 minutes in a bench-top Beckman ultracentrifuge. The supernatant was removed and saved to analyze free tubulin. The pellet was dissolved in depolymerization buffer (0.25 mol/L sucrose, 0.5 mmol/L GTP, 0.5 mmol/L MgCl2, 10 mmol/L sodium phosphate, and 100 U/mL aprotinin, pH 6.95), homogenized, and incubated for 1 hour at 4°C to depolymerize the microtubules. After centrifugation, the supernatant was assayed for microtubule-derived tubulin.

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TABLE 1. Age, Heart Weight, Body Weight, and Tissue Wet-to-Dry Weight Ratios

<table>
<thead>
<tr>
<th></th>
<th>WKY (n=5)</th>
<th>SHR-NF (n=6)</th>
<th>SHR-F (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>21.6±2.1</td>
<td>19.2±1.0</td>
<td>20.7±1.5</td>
</tr>
<tr>
<td>BW, g</td>
<td>668±84</td>
<td>401±35*</td>
<td>407±21*</td>
</tr>
<tr>
<td>LHW, g</td>
<td>1.35±0.13</td>
<td>1.49±0.10</td>
<td>1.57±0.13*</td>
</tr>
<tr>
<td>RWW, g</td>
<td>0.33±0.04</td>
<td>0.25±0.02*</td>
<td>0.46±0.06†</td>
</tr>
<tr>
<td>AW, g</td>
<td>0.19±0.04</td>
<td>0.16±0.02</td>
<td>0.30±0.08†</td>
</tr>
<tr>
<td>LW/BW, mg/g</td>
<td>2.03±0.17</td>
<td>3.72±0.22*</td>
<td>3.85±0.32*</td>
</tr>
<tr>
<td>RV/BW, mg/g</td>
<td>0.50±0.11</td>
<td>0.62±0.09</td>
<td>1.12±0.09†</td>
</tr>
<tr>
<td>AW/BW, mg/g</td>
<td>0.28±0.05</td>
<td>0.40±0.07</td>
<td>0.73±0.19†</td>
</tr>
<tr>
<td>LW W/D, g/g</td>
<td>3.62±0.07</td>
<td>3.74±0.10</td>
<td>3.90±0.15†</td>
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<tr>
<td>RV W/D, g/g</td>
<td>3.91±0.11</td>
<td>3.86±0.16</td>
<td>3.98±1.00</td>
</tr>
<tr>
<td>Lung W/D, g/g</td>
<td>4.12±0.23</td>
<td>4.46±0.38</td>
<td>4.28±0.15</td>
</tr>
<tr>
<td>Liver W/D, g/g</td>
<td>2.09±0.06</td>
<td>2.13±0.10</td>
<td>2.64±0.12†</td>
</tr>
</tbody>
</table>

AW, atria wet weight; and W/D, wet weight–to–dry weight ratios. Values are mean±SD; n indicates number of rats.

*P<0.05 vs WKY; †P<0.05 vs SHR-NF.

Statistical Methods

Data were expressed as mean±SD. Data from SHR-F were compared with those from age-matched SHR-NF and from WKY using a 1-way ANOVA with replications, and the Newman-Keuls multiple sample comparison test21 was used to localize differences where appropriate. The comparisons of AT values obtained at each dose of colchicine (\( 10^{-3}, 10^{-4}, \) and \( 10^{-3} \) mol/L) were made by repeated measures analysis (multivariate analysis—mean profile). The comparisons in each group (baseline versus colchicine) were performed using Student’s paired \( t \) test. Differences were considered to be significant when \( P<0.05 \).

Results

Clinical and Pathological Data

Criteria for heart failure were based on previous findings, in which animals with evidence of heart failure had findings that included labored respiration, left atrial thrombi, pleural and

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**TABLE 2. Baseline Data from Isolated Muscle Preparations**

<table>
<thead>
<tr>
<th>AT, g/mm²</th>
<th>WKY (n=5)</th>
<th>SHR-NF (n=6)</th>
<th>SHR-F (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.69±0.14</td>
<td>3.41±0.105</td>
<td>2.87±0.26*</td>
<td></td>
</tr>
<tr>
<td>RT, g/mm²</td>
<td>0.83±0.24</td>
<td>0.75±0.13</td>
<td>0.96±0.16</td>
</tr>
<tr>
<td>EMD, ms</td>
<td>27±7</td>
<td>30±7</td>
<td>35±2</td>
</tr>
<tr>
<td>+dT/dt, g·mm⁻²·s⁻¹</td>
<td>63±18</td>
<td>32±10*</td>
<td>25±3*</td>
</tr>
<tr>
<td>−dT/dt, g·mm⁻²·s⁻¹</td>
<td>21±5</td>
<td>16±3*</td>
<td>15±1*</td>
</tr>
<tr>
<td>TPT, ms</td>
<td>161±11</td>
<td>173±11</td>
<td>196±11*</td>
</tr>
<tr>
<td>RT₁/₂, ms</td>
<td>206±21</td>
<td>171±24*</td>
<td>155±13*</td>
</tr>
<tr>
<td>Kcs</td>
<td>41±13</td>
<td>44±17</td>
<td>70±25†</td>
</tr>
<tr>
<td>Kwm</td>
<td>61±6</td>
<td>69±6</td>
<td>90±15†</td>
</tr>
<tr>
<td>Vmax, ML/s</td>
<td>1.17±0.21</td>
<td>0.77±0.16*</td>
<td>0.50±0.06*</td>
</tr>
<tr>
<td>CSA, mm²</td>
<td>1.31±0.54</td>
<td>1.90±0.37</td>
<td>1.61±0.32</td>
</tr>
</tbody>
</table>

TPT indicates time to peak tension; RT₁/₂, time from peak tension to 50% relaxation; Kcs, central segment exponential stiffness constant; Kwm, whole muscle exponential stiffness constant; Vmax, maximum velocity of isotonic shortening; ML, muscle length; and CSA, cross-sectional area. Values are mean±SD; n indicates number of rats.

*P<0.05 vs WKY, †P<0.05 vs SHR-NF.

whole muscle exponential stiffness constant (Kwm) were greater in SHR-F group than in SHR-NF and WKY groups.

The sequential response of AT at different colchicine concentrations (10⁻⁵, 10⁻⁴, and 10⁻³ mol/L) is shown in Table 3. There was no increase in AT in the 3 groups at any concentration, and there was no trend for function to increase with time. In the SHR-F at colchicine 10⁻⁵ mol/L, AT decreased slightly but significantly (P<0.05) with time. The effects of 30 minutes of 10⁻⁴ mol/L colchicine treatment on parameters obtained from isometric contraction, maximum velocity of isotonic shortening, and myocardial stiffness are shown in Table 4. The drug did not significantly alter any parameter of myocardial function in the 3 groups studied.

**β-Tubulin Assays**

Papillary muscle preparations (3 controls, 3 colchicine-treated for 60 minutes) demonstrated an increase in soluble β-tubulin in 2 of the 3 colchicine-treated samples. In none of these papillary muscles was an increase in contractile activity observed at any time after the addition of colchicine to the muscle bath. There was no increase in soluble tubulin in the third colchicine-treated muscle. Analysis of 1 control and 1 90-minute colchicine-treated muscle also showed no increase in soluble β-tubulin.

Ponceau S staining of the western blot prepared from depolymerized microtubules showed no staining, indicating the failure to extract protein in the depolymerization buffer. The lack of staining was not due to a problem with protein transfer because the protein standards are seen. The reason for the discrepancies between the present data and those of Tagawa et al is unclear but may relate to the amount of the tissue used for the assay. Tagawa and colleagues used 250 mg tissue, which was not possible in the present studies in which each papillary muscle weighed 5 to 10 mg. The increase in soluble tubulin in preparations from 2 hearts in which no improvement in contractile function was found provides some biochemical support to the concept that microtubular depolymerization does not improve contractile dysfunction in failing SHR myocardium.

**Discussion**

Prior studies have demonstrated a transition from compensated hypertrophy to heart failure in the SHR, with development of impaired muscle function in failing hearts as demonstrated by studies of isolated papillary muscles. The present study investigated the role of colchicine in hypertrophied and failing myocardium from SHR. We examined the hypothesis that microtubular polymerization may participate in the process responsible for myocardial dysfunction in rats with pressure overload and heart failure. If this were the case, myocardial microtubule disruption by colchicine should promote an improvement in the isolated cardiac papillary muscle performance from SHR-F.

The major finding of this study is that there was no improvement in papillary muscle function in SHR-F at any
Effects of Colchicine on Myocardial Function

TABLE 4. Effect of 30 Minutes’ Colchicine (at $10^{-4}$ mol/L) on Papillary Muscle

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>SHR-NF (n=6)</th>
<th>SHR-F (n=6)</th>
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<tbody>
<tr>
<td>AT, g/mm²</td>
<td>5.69±1.47</td>
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<td>2.87±0.26</td>
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<tr>
<td>RT, g/mm²</td>
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<td>32±10</td>
<td>25±3</td>
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<td>15±1</td>
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<td>70±25</td>
</tr>
<tr>
<td>$K_w$</td>
<td>61±6</td>
<td>69±6</td>
<td>90±15</td>
</tr>
<tr>
<td>$V_{max}$, ML/s</td>
<td>1.17±0.21</td>
<td>0.77±0.16</td>
<td>0.50±0.06</td>
</tr>
</tbody>
</table>

Base indicates baseline; Colch, colchicine; $K_s$, central segment exponential stiffness constant; $K_w$, whole muscle exponential stiffness constant; $V_{max}$, maximum velocity of isotonic shortening (muscle length/s). Values are mean±SD; n indicates number of rats.

cytos demonstrated a complete absence of microtubules in the cells. Our initial studies revealed no effect of colchicine $10^{-6}$ mol/L; therefore concentrations of colchicine used in the present study were $10^{-5}$, $10^{-4}$, and $10^{-3}$ mol/L. The possibility that the toxic effects of colchicine at higher concentrations may have offset the improvement of myocardial function appears unlikely because the cardiac muscle response was similar at all concentrations of colchicine studied.

The data in this present study also fail to demonstrate that colchicine results in improved intrinsic muscle function in SHR without heart failure. The data show that hypertrophied nonfailing hearts demonstrate depression of contractile function without an increase in muscle stiffness in the baseline state; neither of these parameters are significantly altered by colchicine.

In a prior study, chronic colchicine (1 mg/kg drinking water) was administered in an attempt to prevent contractile depression and heart failure. In that study daily colchicine intake was 60 g/kg, which was 4 times that used in humans. It is difficult to estimate tissue concentration; however, in human myocardium, colchicine may be concentrated from 2 to 20 times more than levels in plasma. At the doses used, it was found that colchicine did not prevent failure.

In contrast to the prior prevention study, colchicine was administered in the present investigation in an attempt to reverse contractile depression, in vitro, in failing myocardium. No evidence of cardiac muscle function improvement was found in SHR-F or SHR-NF after direct exposure to colchicine. Overall, these data fail to suggest that colchicine either prevents or improves contractile dysfunction of hypertrophied myocardium during the transition to heart failure in SHR.

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