Faster Time to Peak Tension and Velocity of Shortening in Right Versus Left Ventricular Trabeculae and Papillary Muscles of Dogs

Jean-Lucien Rouleau, Pierre Paradis, Hossein Shenasa, and Carl Juneau

Some of the mechanical characteristics of papillary muscles and trabeculae (n = 14) isolated from the free wall of the right ventricle of dogs were compared to those obtained from the free wall of the left ventricle (n = 14). Peak total tension (7.2 ± 1.6 versus 7.9 ± 1.7 g/mm², p = NS) and peak velocity of tension development (31 ± 8 vs. 28 ± 4 g/mm²/sec, p = NS) were similar in both groups of muscles. However, right ventricular muscles shortened faster over nearly all loading conditions, and during isotropic contraction, their time to attain peak total tension was shorter (336 ± 26 vs. 401 ± 42 msec, p < 0.005) than that of left ventricular muscles. Varying stimulation rates (6, 12, 24, and 36 stimuli/min), increasing calcium concentration from 2.54 to 6.35 mM or adding norepinephrine 50 µM, did not significantly alter these differences. There were no differences in myosin isozymes (V1, V2, or V3) between ventricles to explain these differences. These results indicate that important mechanical differences exist between right and left ventricular myocardium and that these differences should be considered when extrapolations are made from myocardium of one area of the heart to another. (Circulation Research 1986;59:556–561)

The importance and extent of regional differences in myocardial characteristics has recently been underlined. Non-uniformity of contraction and relaxation as well as regional differences in excitation—contraction coupling have been well documented and appear to be related to the specific role of a specific region of the heart.¹⁻¹⁰ Previous studies have demonstrated biochemical and electrophysiologic differences between myocardium of the right ventricle, that ejects blood against a high pressure system, and myocardium of the left ventricle that ejects blood against a high pressure system.²⁻⁶ One recent study suggests that mechanical differences also exist between rat right and left ventricular papillary muscles and that these differences are related to differences in V1/V3 myosin isozymes ratios.¹⁰ In this study performed on dogs, we compared the ratio of V1/V3 myosin isozymes from the free wall of left and right ventricles and compared some of the in vitro mechanical characteristics of trabeculae and papillary muscles of the left and right ventricles.

Materials and Methods

In Vitro Myocardial Mechanical Studies

Ninety-two mongrel dogs weighing 15–27 kg were anesthetized with 25 mg/kg of nembutal intravenously. The heart was excised and either a right or left ventricular trabecular or papillary muscle located in the basal portion of the free wall was dissected, removed and mounted in an isolated bath. Only muscles free from the ventricular wall for at least 5 mm and only muscles with cross-sectional areas of less than 1.2 mm² were used in this study.¹¹ Fourteen left ventricular and 14 right ventricular muscles met these criteria. Seven left ventricular muscles were trabeculae, and 7 were papillary muscles. Eight right ventricular muscles were trabeculae, and 6 were papillary muscles. No mechanical differences could be found between trabecular and papillary muscles and a maximum of 1 muscle per dog was used.

The base of the muscle was held by a lucite clamp and the other end tied to a lever with an electromagnetic feedback system to allow control of force, length, and velocity.¹² The muscles were bathed in Krebs-Henseleit solution, kept at 29°C, at pH of 7.4, and saturated with 95% O₂ and 5% CO₂. The muscles were stimulated 10% above threshold at 6 stimuli/min with a Grass S-88 stimulator through platinum field electrodes. In all experiments, the preload on the muscle was adjusted so that the initial muscle length was at Lmax. The muscle was then stabilized at Lmax for 3 hours and isometric and isotonic contractions were recorded at a speed of 100 mm/sec on a Brush 200 recorder.

After adjusting the elastic damping of the force—length—velocity lever feedback system to compensate for electro-mechanical transients,¹² the velocity of shortening at 5% of total tension was obtained by abruptly decreasing the load on the muscle at the time of activation (5% load clamp). A series of shortening velocities was then obtained after clamping the load to 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90% of total tension. The muscles were permitted to restabilize while contracting isometrically at Lmax preload for at least 10 stimuli between each load clamp.

The muscles were then stabilized while contracting...
isometrically at \(L_\text{max}^\circ\) preload at 6 stimuli/min, and a contraction was recorded with a paper speed of 100 mm/sec. The muscles were then stimulated at 12, 24, and 36 stimuli/min, and when stable, isometric contractions were recorded with a paper speed of 100 mm/sec at each frequency. Between each frequency of stimulation the muscles were permitted to stabilize at 6 stimuli/min for at least 10 minutes.

Protocol A

The calcium concentration was increased from 2.54 to 6.35 mM by adding calcium from a stock solution. The muscles were permitted to stabilize for at least 45 minutes. The complete tension–velocity relation from 5% total tension to total tension was then repeated.

Norepinephrine (Winthrop Laboratories, Aurora, Ontario), was added to 50 \(\mu\)M concentration. The muscles were permitted to stabilize for at least 45 minutes. The complete tension–velocity relation from 5% total tension to total tension was then repeated. The cross-sectional area of the muscle was obtained by dividing the muscle weight by its length, assuming a general cylindrical shape and a specific gravity of 1.0.

Protocol B

Protocol B was exactly the same as Protocol A, except that the order of the calcium and norepinephrine was reversed. Half the muscles from each ventricle were studied using Protocol A and half were studied using Protocol B. No muscle was studied using both protocols.

The lever system is identical to that described in detail by Brutsaert et al.\(^\text{12}\)

Pyrophosphate Gel Electrophoresis of Myosin Isozymes

At the time of sacrifice of the final 8 dogs of the 28 dogs from which 1 muscle was used for the mechanical study, a sample of myocardium from the base of the left and right ventricular free walls was obtained for myosin isozyme measurements. Cardiac myosin was extracted by homogenization of tissue with a polytron (Brinkman homogenizator) and extracted for 1 hour at \(0^\circ\) C with 4 volumes of slightly modified Guba solution\(^\text{13}\) [300 mM KCl, 100 mM \(K_2HPO_4\), 50 mM \(K_3HPO_4\), 1 mM MgCl\(_2\), 10 mM \(Na_3P_2O_7\), 1% (w/v) azide Na, 1% (w/v) 2-mercaptoethanol]. The homogenate was centrifuged 20 minutes at \(+2^\circ\) C and 30,000g and the supernatant was stored at \(-20^\circ\) C in 50% (v/v) glycerol.

Pyrophosphate gel electrophoresis was carried out essentially according to the method of Hoh et al.\(^\text{14}\) The electrophoresis was performed on a Bio Rad electrophoresis slab cell (Protein Cell, 16-cm slab) that allows many samples to be studied on the same gel and at 30 mA (constant current) for 24 hours at \(-3^\circ\) C. During this time, a solution of 1 mM EDTA, 0.01% v/v 2-mercaptoethanol, 10% glycerol, and 20 mM \(Na_3P_2O_7\), was continuously circulated in the upper and lower chambers by a pump (March, Glenview Ill.). Gels were strained 2 hours for protein in Coomassie Brilliant Blue R solution\(^\text{15}\) then destained overnight in 7% (v/v) acetic acid. The quantification of isomyosins was done by densitometric scan using a Bio Rad densitometer (model 1650). The percent of each isozyme (V1, V2, V3, Litten et al\(^\text{6}\)) was calculated according to the method of Holubarsh.\(^\text{15}\)

Statistical Methods

The values for left and right ventricular muscles were compared using an unpaired \(t\) test. All values are mean ± SD.

Results

In Vitro Myocardial Mechanical Studies

There was no difference in papillary muscle length, (right ventricle = 8.4 ± 1.5 mm, left ventricle = 7.8 ± 2.0 mm) cross-sectional area (right ventricle = 0.75 ± 0.34 mm\(^2\), left ventricle = 0.86 ± 0.34 mm\(^2\)) or preload at \(L_\text{max}^\circ\) (right ventricle = 0.76 ± 0.21 g/mm\(^2\), left ventricle = 0.83 ± 0.24 g/mm\(^2\)).

Using the control calcium concentration (2.54 mM), there was no difference in tension, in \(dT/dt\) or in time to attain one-half tension decline between the left and right ventricular myocardium. There was also no difference in isotonic muscle shortening (right ventricle = 20.6 ± 2.7% \(L_\text{max}^\circ\), left ventricle = 20.4 ± 2.4% \(L_\text{max}^\circ\)). However, time to attain peak total tension was longer in left ventricular muscle (Table 1). These similarities and differences between left and right ventricular muscle were maintained at the four stimulation rates studied (Figure 1), at high calcium concentration (6.32 mM), at high norepinephrine concentration (50 \(\mu\)M), and with the combination of high calcium and high norepinephrine concentrations (Table 1).

In addition to having a shorter time to peak tension, right ventricular muscles shortened faster under nearly all loading conditions (Figure 2). High calcium concentrations and/or high norepinephrine concentrations did not substantially alter these differences (Figure 2).

Myosin Isozymes

The overwhelming majority of myosin isozyme make-up of both left and right ventricular free wall myocardium was of the V3 type indicating that VI and V2 myosin isozymes make up only a very small minority of the myosin isozymes of the free wall of either ventricle (Figure 3).

Discussion

This study 1) adds to the important myocardial regional differences that have already been described and 2) indicates that extrapolations from the results of findings and interventions from one area of the heart to another should be done with caution.

The characteristics of myocardium obtained from the same heart varies depending on the site from which it was obtained and the specific role that this region is called on to perform.\(^\text{16-10}\) In this study, right ventricular papillary muscles had a faster velocity of shortening and a shorter time to attain peak total tension than left ventricular papillary muscles. This could be a physio-
### Table 1. Comparison of Right and Left Ventricular Papillary Muscle Mechanics

<table>
<thead>
<tr>
<th></th>
<th>Control (2.54 mM Ca(^{2+}))</th>
<th>High calcium (6.32 mM Ca(^{2+}))</th>
<th>Norepinephrine (50 µM)</th>
<th>High calcium* norepinephrine (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T (g/mm(^2))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>7.2±1.6</td>
<td>9.8±1.3</td>
<td>11.4±2.1</td>
<td>11.9±1.6</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>7.9±1.7</td>
<td>10.4±1.4</td>
<td>11.0±2.6</td>
<td>11.7±2.4</td>
</tr>
<tr>
<td><strong>dT/dt (mm(^2)/g/s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>31±8</td>
<td>47±8</td>
<td>84±28</td>
<td>88±25†</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>28±4</td>
<td>47±8</td>
<td>65±10</td>
<td>70±16</td>
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<tr>
<td><strong>TTP (ms)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Right ventricle</td>
<td>336±26</td>
<td>317±10</td>
<td>238±35</td>
<td>232±26</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>401±42†</td>
<td>366±27†</td>
<td>318±42†</td>
<td>297±37†</td>
</tr>
<tr>
<td><strong>RT(\frac{1}{2}) (ms)</strong></td>
<td></td>
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<tr>
<td>Right ventricle</td>
<td>269±31</td>
<td>252±32</td>
<td>195±48</td>
<td>204±41</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>292±49</td>
<td>282±40</td>
<td>253±39†</td>
<td>232±34†</td>
</tr>
</tbody>
</table>

Values are mean ± SD, T = total tension, \(dT/dt\) = maximum rate of tension development, TTP = time to attain peak total tension, RT\(\frac{1}{2}\) = time to attain V\(\frac{1}{2}\) tension decline.

* = \(p < 0.1\), † = \(p < 0.05\), and ‡ = \(p < 0.005\) right versus left ventricle.

logic adaptation to the lower pressure system against which the right ventricle must eject blood. In support of this concept are pulmonary artery banding studies by Alpert et al., which showed that when the right ventricle is made to eject against a high pressure system, right ventricular myocardium adapts by decreasing muscle shortening velocity and by increasing time to attain peak total tension, changes that would tend to abolish the mechanical differences that we found between left and right ventricular papillary muscles.

In many physiologic and pathologic conditions, changes in action potential duration have tended to parallel changes in time to attain peak total tension and changes in velocity of muscle shortening suggesting a close relation between changes in these variables. For example, the increase in action potential duration that occurs with aging is accompanied by an increase in time to attain peak total tension and by a decrease in velocity of muscle shortening. As well, the increase in action potential duration that occurs as myocardium hypertrophies in response to an increase in afterload is accompanied by an increase in time to attain peak total tension and by a decrease in velocity of muscle shortening.

In rats, the work of Watanabe et al. and Brooks et al. has shown that in this species, the shorter action potential duration of right ventricular myocardium...
um as compared to left ventricular myocardium is accompanied by a shorter time to attain peak total tension and by a slower velocity of muscle shortening. Our results, coupled with those of Gulch, indicate that the same is true for myocardium from the left and right ventricular free walls of dogs. The exact stimulus that causes changes in these variables to occur in contrast, and the cause and effect relation, if any, that exists between one or another of these variables is difficult to determine because of the close relation between excitation, contraction and loading conditions. However, it appears that in response to an increase in afterload, action potential duration increases, time to attain peak total tension increases, and velocity of muscle shortening decreases. Similarly the differences in action potential duration and velocity of muscle shortening between myocardium of the left and right ventricles may be related to different loading conditions against which each ventricle must work.

Differences in muscle mechanics such as those described in our study have in some species been closely related to differences in myosin isozymes. Indeed, Brooks et al. found that the shorter time to peak total tension and the increase in velocity of muscle shortening in right versus left ventricular myocardium of rats was accompanied by a higher V1/V3 myosin isozyme ratio. However, this relation is more complex and uncertain in larger species where myocardial cells have been found to contain only small amounts (0–15%) of V1 and where changes in myosin isozymes do not appear to be of physiologic significance in either hypertrophy or failure. In this study, we found no

**Figure 2.** Right ventricular papillary muscles shortened faster than left ventricular papillary muscles over most loading conditions. Increasing calcium concentration and/or stimulating the muscles with norepinephrine did not alter these differences. Values as mean ± SD. * = p < 0.05, and ** p < 0.005, left versus right ventricle.

**Figure 3.** Native sodium pyrophosphate polyacrylamide gel electrophoresis and densitometric pattern of myosin isozymes in left ventricular (LV) and right ventricular (RV) free walls. There was no difference in myosin isozyme make-up of the left or right ventricular free walls, the overwhelming majority of both ventricles being of the V3 type.
differences in myosin isoforms between the left and right ventricular free walls of dogs, suggesting that at best, only a weak relation exists between myosin isoforms and the regional differences in myocardial mechanics that we found. However, regional differences in myosin isozyme activation could still explain some of the mechanical differences that we found because, according to Winegrad, rapid changes in cellular regulatory state can occur through activation of fast myosin (VI) from an off to on state, and in some regions of the heart, cells could have variable VI to V3 activation with a constant V1 to V3 content. In this way a higher in vivo activation of V1 in right ventricular myocardium would allow it to contract faster than left ventricular myocardium despite similar V1 + V3 contents.

Some differences in cellular calcium kinetics and some differences in myosin calcium sensitivities between right and left ventricular myocardium have been described, but the importance of these differences remains uncertain. In our study we found that varying stimulation rates and calcium concentrations had no effect on the differences between left and right ventricular myocardial mechanics. However, our results do not rule out regional differences in calcium handling as a cause for the regional differences in myocardial mechanics that we found. Calcium transients could be prolonged in left ventricular myocardium compared to right ventricular myocardium much like calcium transients and isometric contractions are prolonged in experimental pressure overload hypertrophied right ventricular myocardium of ferrets.

No difference in myocardial norepinephrine content and no difference in adrenergic receptor number or affinity have been described between left and right ventricular myocardium although regional differences in adrenergic function have been found within the left ventricle itself. In this study, by maximally stimulating our muscles with norepinephrine, we ruled out a varying response to adrenergic stimulation as a possible explanation for our results. Finally, no difference in cell size or composition between left and right ventricles have been described to explain the differences in muscle mechanics that we found.

We conclude that important mechanical differences exist between papillary muscles from the left and right ventricles. It is possible that these differences are the result of the different role each ventricle is called on to perform.

References


KEY WORDS • ventricular trabeculae shortening • papillary muscle shortening • peak tension • peak velocity • isometric contraction • myosin isozymes
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