Mechanics of contraction and relaxation of the ventricle in experimental heart failure produced by rapid ventricular pacing in the conscious dog

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KEY WORDS: Heart failure, model, contraction, relaxation.

A model of heart failure produced by rapid ventricular pacing in the conscious dog instrumented with a conductance catheter to monitor instantaneous left ventricular volume has been developed. This experimental model is capable of analysis of the left ventricular pressure-volume relationship on a beat-to-beat basis, and has been used to assess ventricular function serially in the progress of heart failure and effects of pharmacological intervention. In seven dogs the magnitude of cardiotoxic effects were significantly attenuated after development of heart failure. These findings support the concept that in the failing heart there is subsensitivy to beta-adrenergic stimulation in proportion to the severity. The failing heart was characterized by incomplete left ventricular relaxation. Dobutamine improved left ventricular early relaxation but did not affect chamber distensibility. In contrast new phosphodiesterase inhibitor, E-1020, improved ventricular distensibility with less marked changes in active relaxation; improved left ventricular relaxation appeared to be mediated by increased systolic shortening with enhancement of internal restoring forces, and improved distensibility by accelerated function of sarcoplasmic reticulum through increased intracellular cyclic AMP.

Introduction

Most of the cardiotonic agents which have become available clinically act to increase the intracellular concentration of cyclic adenosine monophosphate (AMP). This activates a variety of protein kinases with a resultant increase in the transsarcolemmal influx of Ca²⁺, the rate of its dissociation from troponin C and the rate of its uptake by sarcoplasmic reticulum[11]. Recent studies have demonstrated that in the failing human heart, cyclic AMP may be depressed thus reducing the effectiveness of positive inotropic stimulation[2,3].

In the present study chronic experimental heart failure was produced by rapid cardiac pacing in conscious dogs, instrumented with a left ventricular micromanometer and conductance catheter; this allowed continuous measurement of simultaneous ventricular pressure and volume on a beat-to-beat basis[4-5]. This model was employed to evaluate the physiological abnormalities serially during the progress of heart failure. The effects of a new class of positive inotropic agents were also studied in this experimental model.

Methods

INSTRUMENTATION

Seven mongrel dogs underwent thoracotomy in the left fifth intercostal space under anesthesia with 1% halothane following induction with intravenous pentobarbital sodium (25 mg kg⁻¹). The pericardium was opened widely. The superior and inferior venae cavae were isolated and pneumatic cuffs were placed around them. Their inflation allowed the rapid and reversible partial interruption of venous return. A high-fidelity micromanometer (Kornigsberg P-7) was inserted into the left ventricular chamber through a stab incision at the ventricular apex. The micromanometer was calibrated by comparison with pressures obtained through a fluid-filled catheter connected to a Statham P23DB transducer. The conductance catheter was also advanced from the apex so that its tip was passed out of the aortic valve. Another polyvinyl catheter was placed in the pulmonary artery for infusion of hypertonic saline at the time of the experiment. This was to determine parallel conductance by decreasing resistivity of the fluid in structures extrinsic to the left ventricular chamber blood pool[6,7]. Pacing electrodes were sutured to the left ventricular epicardial surface to pace the ventricle at higher rates to induce heart failure.

The catheter system used in this study consisted of a 4F woven dacron catheter with eight ring electrodes mounted equidistant at its distal end. We used a catheter with the distance between the first and last electrodes of either 5, 6 or 7 cm depending upon the size of the canine.
left ventricle. An alternating current (20 KHz, 0.07 mA) was passed between driving electrodes in the apex and at the base. The five potential differences generated between each sensing electrode spanning the left ventricular cavity were measured continuously. Dividing the current by each of the potential differences gives five conductances. The sum of these five segment conductances (G(t)) was linearly related to the ventricular volume (V(t)) by the following equation\textsuperscript{3,6}.

\[ V(t) = \frac{1}{\alpha} \cdot \left( \frac{L^2}{\alpha} \right) G(t) - V_c \]

where \( \alpha \) is a dimensionless slope constant for the V(t) – G(t) relationship, L is the distance between adjacent electrodes, \( \sigma \) is the conductivity of the fluid in the cavity, and \( V_c \) is a correction term that accounts for the parallel conductance of the surrounding structures. The current was delivered by a signal conditioner-processor (Leycom Model Sigma-5, The Neiderlands).

**STUDY PROTOCOL**

Control recordings of haemodynamic data and conductance volume were performed with the unanesthetized animal lying quietly on its right side; studies were obtained during spontaneous sinus rhythm. Then caval occlusion was applied to interrupt venous return with a subsequent fall in left ventricular systolic pressure by 30 to 50 mmHg (Fig. 1).

Dobutamine at 6 \( \mu \text{g} \text{kg}^{-1} \text{min}^{-1} \) was infused in seven dogs. When a new steady state was established, the pressure and volume data were again recorded in the same manner as in the baseline study. On another day, the second baseline study was performed in four dogs following which a new phosphodiesterase inhibitor, E-1020, was infused at a dose of 3 \( \mu \text{g} \text{kg}^{-1} \text{min}^{-1} \). After 30 min, the same set of measurements were made.

Following the control study, stimulation of the heart via the ventricular electrodes was initiated at a rate of 260 beats min\(^{-1}\) with an external pacemaker (Biotonic EDP20, Germany). After 10 to 20 days (average 14 days) of stimulation, all the animals developed congestive symptoms such as ascites, respiratory distress or anorexia and the third heart sound was audible. Following this, all the haemodynamic and conductance volume measurements, both at baseline and during the administration of dobutamine and E-1020, were repeated.

**DATA ANALYSIS**

Micromanometer pressure and conductance catheter volume were digitized using a computer system with PC-9801 RX (NEC, Japan) and pressure-volume loops were obtained on a beat-to-beat basis. The end-systolic pressure–volume point defined as the maximal ratio of instantaneous pressure to volume, was determined for each cardiac cycle during caval occlusion. The slope of the end-systolic pressure–volume relation (Ees) and volume intercept (Vo) were determined by fitting these points by linear regression. Time constant of pressure decay (T) was calculated from a plot of a negative \( \frac{dP}{dt} \) versus \( P(Td) \)\textsuperscript{9}, where \( P \) is left ventricular pressure.

The differences in haemodynamic and volume variables before and after the development of heart failure and the effects of dobutamine and E-1020 administration were analysed by paired t-test. A probability less than 0.05 was considered significant.

**Results**

**DEVELOPMENT OF HEART FAILURE**

The haemodynamic and conductance volume data before and after development of heart failure are summarized in Table 1. All the measures at heart failure were obtained approximately one hour after a cessation of the pacing. In the failing heart, heart rate increased from 86 ± 7 to 115 ± 13 beats min\(^{-1}\) (\( P < 0.01 \)).

All animals demonstrated significant left ventricular dysfunction after pacing. Peak positive \( \frac{dP}{dt} \) was reduced by 34% (\( P < 0.01 \)), and end-diastolic pressure was elevated from an average of 9 to 30 mmHg. Although left ventricular filling period was reduced by the increase in heart rate, left ventricular end-diastolic...
Table 1: Changes in haemodynamic and conductance volume measures in the control and the post-pacing states, and their modification by cardiotonic agents. All data represent mean (±SD).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Failure</th>
<th>P</th>
<th>Control</th>
<th>Failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (beats min⁻¹)</strong></td>
<td>B  86 ± 7</td>
<td>115 ± 13</td>
<td>&lt;0.01</td>
<td>B  85 ± 8</td>
<td>106 ± 13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>D  111 ± 20*</td>
<td>110 ± 20</td>
<td>(+30 ± 23%)*</td>
<td>E  128 ± 19</td>
<td>95 ± 15</td>
<td>+0.05</td>
</tr>
<tr>
<td><strong>LVSP (mmHg)</strong></td>
<td>B  118 ± 12</td>
<td>109 ± 14</td>
<td>(+3 ± 12%)</td>
<td>D  133 ± 12</td>
<td>117 ± 15</td>
<td>(+13 ± 9%)*</td>
</tr>
<tr>
<td></td>
<td>B  126 ± 25</td>
<td>127 ± 15</td>
<td>(+3 ± 12%)</td>
<td>E  127 ± 15</td>
<td>103 ± 15</td>
<td>(+3 ± 15%)*</td>
</tr>
<tr>
<td><strong>LVEDP (mmHg)</strong></td>
<td>B  9 ± 2</td>
<td>30 ± 3</td>
<td>&lt;0.01</td>
<td>B  12 ± 0</td>
<td>27 ± 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  7 ± 3</td>
<td>32 ± 4</td>
<td>(+13 ± 9%)*</td>
<td>E  3 ± 1</td>
<td>22 ± 5</td>
<td>+0.05</td>
</tr>
<tr>
<td><strong>peak +dP/dt (mmHg s⁻¹)</strong></td>
<td>B  2560 ± 351</td>
<td>1685 ± 190</td>
<td>&lt;0.01</td>
<td>B  2592 ± 464</td>
<td>1559 ± 131</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  3720 ± 551</td>
<td>2139 ± 283</td>
<td>(+49 ± 33%)*</td>
<td>E  3926 ± 525</td>
<td>2083 ± 225</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>peak -dP/dt (mmHg s⁻¹)</strong></td>
<td>B  -2167 ± 306</td>
<td>-1600 ± 203</td>
<td>&lt;0.01</td>
<td>B  -2307 ± 546</td>
<td>-1531 ± 232</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  -2567 ± 214</td>
<td>-1968 ± 251</td>
<td>(+49 ± 33%)*</td>
<td>E  -2497 ± 376</td>
<td>-1733 ± 236</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Tw (ms)</strong></td>
<td>B  20 ± 3</td>
<td>33 ± 8</td>
<td>&lt;0.01</td>
<td>B  22 ± 5</td>
<td>32 ± 8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  14 ± 3</td>
<td>28 ± 6</td>
<td>(+34 ± 17%)*</td>
<td>E  14 ± 3</td>
<td>27 ± 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Td (ms)</strong></td>
<td>B  36 ± 4</td>
<td>47 ± 8</td>
<td>&lt;0.05</td>
<td>B  36 ± 1</td>
<td>45 ± 9</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>D  28 ± 3</td>
<td>35 ± 6</td>
<td>(+22 ± 10%)*</td>
<td>E  27 ± 4</td>
<td>38 ± 4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>EDV (ml)</strong></td>
<td>B  57 ± 12</td>
<td>62 ± 8</td>
<td>&lt;0.01</td>
<td>B  60 ± 10</td>
<td>65 ± 19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  43 ± 9</td>
<td>56 ± 9</td>
<td>(+23 ± 15%)**</td>
<td>E  44 ± 8</td>
<td>64 ± 19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>ESV (ml)</strong></td>
<td>B  33 ± 9</td>
<td>41 ± 7</td>
<td>&lt;0.05</td>
<td>B  35 ± 9</td>
<td>43 ± 13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  33 ± 6</td>
<td>37 ± 10</td>
<td>(+46 ± 20%)*</td>
<td>E  37 ± 10</td>
<td>43 ± 13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>SV (ml)</strong></td>
<td>B  24 ± 5</td>
<td>20 ± 5</td>
<td>&lt;0.05</td>
<td>B  25 ± 4</td>
<td>22 ± 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  26 ± 7</td>
<td>23 ± 9</td>
<td>(+37 ± 18%)*</td>
<td>E  32 ± 6</td>
<td>27 ± 11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>B  43 ± 7</td>
<td>33 ± 7</td>
<td>&lt;0.05</td>
<td>B  43 ± 7</td>
<td>34 ± 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  41 ± 11</td>
<td>41 ± 9</td>
<td>(+43 ± 18%)*</td>
<td>E  71 ± 2</td>
<td>41 ± 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Ecs (mmHg ml⁻¹)</strong></td>
<td>B  4.89 ± 2.05</td>
<td>3.53 ± 1.77</td>
<td>&lt;0.05</td>
<td>B  3.68 ± 1.35</td>
<td>2.72 ± 1.15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  14.01 ± 8.14</td>
<td>7.06 ± 3.29</td>
<td>&lt;0.05</td>
<td>E  10.10 ± 11.41</td>
<td>3.27 ± 1.17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Vo (ml)</strong></td>
<td>B  0 ± 6</td>
<td>4 ± 14</td>
<td>&lt;0.05</td>
<td>B  -6 ± 8</td>
<td>-3 ± 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>D  2 ± 4</td>
<td>5 ± 14</td>
<td>(+10 ± 12%)</td>
<td>E  4 ± 2</td>
<td>0 ± 10</td>
<td>&lt;0.05</td>
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</tbody>
</table>

HR: heart rate; LVSP: left ventricular peak systolic pressure; LVEDP: left ventricular end-diastolic pressure; P: left ventricular pressure; t: time; Tw: time constant of pressure decay calculated from a plot of P vs time; Td: time constant pressure decay calculated from a negative dP/dt v P; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; Ecs: slope of the end-systolic pressure-volume relation; Vo: volume intercept of the end-systolic pressure-volume relation; B: baseline state, D: dobutamine, E: E-1020; P compares control and failing heart; Asterisks indicate P values for the effect (*P < 0.05, **P < 0.01).
and end-systolic volumes tended to be augmented with a significant reduction of ejection fraction. Diastolic function was also impaired, as shown by a 26% decrease in peak negative dP/dt, and prolonged isovolumic pressure decay; the time constant calculated by Weiss's method (Tw) and by the derivative method (Td) were augmented from 20 to 33 ms and from 36 to 47 ms respectively (Table 1).

Figure 1 shows typical analogue tracings obtained during an acute caval occlusion before and after development of heart failure. Slope of the end-systolic pressure-volume relationship (Ees) substantially decreased from 4.89 to 3.53 mmHg ml^-1 (P < 0.01) as the heart failed. Although the diastolic pressure-volume curve shifted upward and to the right along with the single pressure-volume relationship, there was a conspicuous upward shift of the early diastolic portion of the pressure-volume loop, achieving higher diastolic pressure for a given volume at early diastole (Fig. 2).

EFFECTS OF DOBUTAMINE IN THE NORMAL AND FAILING HEART

Dobutamine 6 μg kg^-1 min^-1 in the normal heart resulted in significant increases in heart rate (+30%) and left ventricular systolic pressure (+13%) (P < 0.05) but there were no significant changes in end-diastolic pressure. Peak positive dP/dt was increased (+49%) (P < 0.05), and end-diastolic volumes were significantly reduced by 23% and by 46% respectively, with a resultant rise in ejection fraction by 41% (P < 0.01). These changes were associated with a leftward shift of the end-systolic pressure-volume relation with an increased Ees (from 4.89 to 14.1 mmHg ml^-1, P < 0.01). There was an increase in peak negative dP/dt by 20% and a decrease in time constant of the pressure decay (Tw by 34% and Td by 22%), both suggesting improved left ventricular relaxation.

In the failing heart, the same doses of dobutamine resulted in directionally similar haemodynamic and volumetric responses; however, the magnitude of inotropic effect was significantly less than in the normal control states (Table 1, Fig. 3).

Figure 2  Representative pressure-volume loops obtained in the control state (left) and after pacing (right). In the failing heart, an increase in diastolic volume was accompanied by a comparable rise in diastolic pressure. Therefore, the diagram shifted upward and to the right along with the single diastolic pressure-volume relationship; however, there was a conspicuous upward shift of the early diastolic portion of the loop.

Figure 3  Left ventricular pressure-volume loops from one representative dog at baseline and after administration of dobutamine. Left panel: the response in the normal control state, right panel: the response after development of heart failure.
The diastolic pressure–volume curve also shifted leftward, whereby, the left ventricular relaxation was substantially accelerated, as shown by a downward shift of early diastolic point of pressure–volume curve associated with an increase in peak negative dP/dt and a reduction in Tw and Td. However, in the late diastole, the pressure–volume relationship remained unchanged (Fig. 3).

EFFECTS OF E-1020 IN THE NORMAL AND FAILING HEART

Following an infusion of 3 μg kg⁻¹ min⁻¹ of E-1020 in the normal heart there was an increase in heart rate (+51%), and a reduction in left ventricular end-diastolic pressure (12 to 3 mmHg). Peak negative dP/dt remained unchanged; however, peak positive dP/dt significantly increased by 53%. The time constants of left ventricular relaxation (Tw and Td) showed significant improvement. Both left ventricular end-diastolic and end-systolic volumes decreased with a marked rise in ejection fraction. Ees was augmented approximately three times (Table 1).

In the failing heart, the same doses of E-1020 again induced directionally similar changes. However, the magnitude of the changes were relatively less and only the reduction in end-diastolic pressure and the increase in ejection fraction reached a statistically significant level (Table 1).

In the normal heart, there were concomitant decreases in end-diastolic pressure and volume; therefore the diastolic pressure–volume curve simply shifted to the left on the single pressure–volume relation. While in the failing heart, end-diastolic pressure was reduced, end-diastolic volume remained unchanged. Therefore, the curve shifted downward with the diastolic pressure being lower for any given diastolic volume (Fig. 4). An improvement of relaxation did not reach a statistically significant level.

Discussion

Experimental animal models of chronic heart failure are necessary to study the natural history of heart failure, the pathophysiological accompaniments that characterize the syndrome and the response to pharmacological intervention. Low output heart failure produced by chronic rapid ventricular pacing, mimics, both haemodynamically and neurohumorally, heart failure in man[10]. However, little information has been available so far on pressure and volume changes in the conscious experimental animal. In the present study, continuous on-line recordings of the instantaneous pressure–volume relationship over a range of physiological loading conditions were obtained.

A method for determining instantaneous ventricular volume in vivo throughout the cardiac cycle by a measurement of intraventricular conductance with a specially designed catheter has been introduced by Baan et al.[41]. We modified this original catheter so that it could be implantable in the animal for a long period. In the isolated heart, a linear relationship has been shown between the volume measured by the conductance catheter and the actual balloon volume placed inside the ventricle[6].

The profiles of heart failure in this canine model are similar to those of humans, which are characterized by increased heart rate, elevated filling pressure, increased ventricular volume with reduced ejection fraction, and impaired contractility indexes, such as peak positive dP/dt or Ees. However the mechanism by which rapid
ventricular pacing produces heart failure has not been fully elucidated\textsuperscript{[11,12]}

Left ventricular end-diastolic pressure and volume were increased in the failing heart. Therefore, the entire left ventricular diastolic pressure–volume curve shifted more to the right, along with the single pressure–volume relation, indicating that myocardial distensibility remained unaltered. Left ventricular relaxation, assessed by the time constant of isometric pressure decay and peak negative $dP/dt$, was severely impaired with a conspicuous upward shift of the early diastolic portion of the pressure–volume loop, achieving a higher diastolic pressure for a given diastolic volume. The impaired left ventricular pressure decay resulted in a decrease in early diastolic ventricular filling. The active relaxation of myocardium is heavily influenced by the systolic dynamics, because a substantial amount of elastic energy is stored during the process of systolic shortening, which provides for an elastic recoil, to expand the muscle in early diastole\textsuperscript{[13]}. In the failing heart, the sarcomere length at end-systole would be longer than in the normal heart, and elastic energy available for a release during diastole would not be stored sufficiently during contraction. This impaired elastic recoil reduces mitral valve flow in early diastole from a decreased mitral pressure gradient and leaves the heart more dependent on the contribution of atrial contraction.

Dobutamine exerts an inotropic effect by stimulating beta-1-adrenergic receptors, and phosphodiesterase inhibitors reduce breakdown of cyclic AMP. Both lead to an increase in intracellular concentrations of cyclic AMP, which modulates calcium flux across the sarcolemma and reuptake of calcium into the sarcoplasmic reticulum, thereby augmenting strength of cardiac contraction. In the present study, the magnitude of effects of the cardiotonic agents used were significantly attenuated after development of heart failure. This parallels the clinical finding that the positive inotropic response to dobutamine is inversely related to the severity of heart failure\textsuperscript{[14]}. Studies on human myocardium in vitro have also demonstrated that although muscles from the failing heart are able to generate similar forces of contraction to that generated in the control hearts by calcium, basal cyclic AMP production is diminished. For this reason the effectiveness of cyclic AMP dependent positive inotropic agents is markedly diminished in the failing heart.

It has recently been reported that in this canine model of pacing-induced heart failure there was a selective down-regulation of the beta-1-adrenergic receptors and subsensitivity of adenylate cyclase activity to both beta-1 and beta-2 stimulation\textsuperscript{[15]}. In heart failure, therefore, diminished contractile response to beta stimulation may be in part due to abnormalities in the catalytic component of adenylate cyclase or in the activity of a guanine-nucleotide binding regulatory protein\textsuperscript{[16,17]}

Dobutamine caused a concomitant decrease in end-diastolic pressure and volume resulting in a leftward shift of the diastolic pressure–volume curve both in normal and failing hearts (Fig. 5). The time constant of left ventricular isovolumic relaxation in the failing ventricle was also substantially improved by dobutamine. Since the relaxation velocity is primarily influenced by the level of aortic pressure\textsuperscript{[18]}, the observed increase in peak negative $dP/dt$ appears to reflect a significant increase in the pressure at which it occurred\textsuperscript{[19]}. Catecholamines can exert a substantial myocardial relaxing effect, independent of their inotropic effect, in part by stimulating the calcium uptake by sarcoplasmic reticulum\textsuperscript{[20]}, while the rate of pressure decay is largely dependent on the extent of shortening\textsuperscript{[8,19]}. Therefore, an improvement in ventricular relaxation appears to be largely mediated by increased systolic shortening which enhances a physiologically significant degree of internal restoring forces within the ventricle.

In congestive heart failure, left ventricular distensibility can be improved by a cardiotonic agent by relieving extrinsic compression of the distended left ventricle by the pericardium and right ventricle\textsuperscript{[21,22]}. However, in the present model, the pericardium had been left open and external constraint was less likely. In the cardiomyopathic hamster, dobutamine was shown to increase intracellular calcium at diastole\textsuperscript{[23]}. It is conceivable that the lack of change in the passive diastolic pressure volume relationship was related to such a paradoxical increase in intracellular calcium.

The effect of the phosphodiesterase inhibitor, E-1020, on left ventricular diastolic function in the failing heart contrasts with the effect of a receptor-mediated adenylate cyclase stimulation, in that an improvement of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Schematic representation of changes in the diastolic pressure–volume relation with dobutamine (left) and E-1020 (right) in the failing heart.}
\end{figure}
active relaxation was less marked, while left ventricular distensibility was substantially improved (Fig. 5). Changes in end-systolic volume also failed to achieve a statistically significant level. This supports the concept that elastic energy stored in systole and released in early diastole may play an essential role in the early diastolic active relaxation of the ventricle. Augmented intracellular cyclic AMP, through inhibition of phosphodiesterase, accelerates the function of sarcoplasmic reticulum to uptake, store and release calcium and may be partially responsible for improved ventricular distensibility.

References


