Altered Left Ventricular Diastolic Properties During Pacing-Induced Ischemia in Dogs with Coronary Stenoses

Potentiation by Caffeine

WALTER J. PAULUS, TAKASHI SERIZAWA, AND WILLIAM GROSSMAN

SUMMARY An upward shift of the left ventricular (LV) diastolic pressure-volume relation has been observed during angina in humans and has recently been induced by pacing tachycardia in dogs with coronary stenoses. To assess the mechanism of this phenomenon, we studied the effects of caffeine (an agent known to prolong intracellular calcium availability) on the upward shift of the LV diastolic pressure-volume relation induced by pacing tachycardia in dogs with coronary stenoses. Severe (90%) coronary artery stenoses were produced on both the left anterior descending and circumflex coronary arteries in 14 chloralose-anesthetized, β-blocked dogs with chest and pericardium open. In six dogs, two pairs of ultrasonic crystals were implanted subendocardially in the ischemic areas. The left atrium was paced at a rate of 1.5 times the resting heart rate for 3 minutes. In the immediate post-pacing period there was a rise of the left ventricular end-diastolic pressure (LVEDP) from 9 ± 1 to 15 ± 1 mm Hg (P < 0.005) at comparable peak-systolic pressures and slightly increased end-diastolic segment lengths (16.8 ± 0.9 mm to 17.5 ± 0.9 mm) (P < 0.005). After the return of LV hemodynamics to baseline values, atrial pacing was repeated at a rate and blood pressure comparable to the first pacing run but with the administration of caffeine (20 ± 4 mg/kg, intravenously) in the last 30 seconds of pacing. In the post-pacing period, the LVEDP rose from 9 ± 1 to 27 ± 2 mm Hg (P < 0.005) at comparable peak systolic pressures and slightly increased end-diastolic segment lengths (16.8 ± 0.9 mm to 17.3 ± 1.0 mm) (P < 0.05). The increased LV filling pressure persisted three times longer than in the control pacing run and was associated with a marked upward shift of the LV diastolic pressure-segment length and pressure-volume relation. The same dose of caffeine, when given in the non-ischemic (control) setting, produced a transient (<1 minute) fall in LV peak systolic pressure (112 ± 6 to 97 ± 3 mm Hg, P < 0.005), LVEDP (9 ± 1 to 7 ± 1 mm Hg, P < 0.01) and end-systolic segment length (14.8 ± 0.9 to 14.3 ± 0.9 mm, P < 0.005) consistent with a peripheral vasodilatory effect of caffeine. It is concluded that caffeine potentiates the ischemia-induced changes in LV diastolic stiffness. These findings could be explained by sustained intracellular calcium availability with persistent contractile element interaction in diastole.


ACUTE alterations in left ventricular (LV) diastolic properties associated with an upward shift in the LV diastolic pressure-volume relation have been repeatedly observed in patients with angina pectoris (Dwyer, 1970; McLaurin et al., 1973; Barry et al., 1974; Mann et al., 1977, 1979; Flessas et al., 1977; Rickards and Seabra-Gomes, 1978). Recently, similar alterations have been induced by pacing tachycardia in dogs with coronary stenoses (Serizawa et al., 1980). The underlying mechanism for these observations remains uncertain, and has been the subject of controversy (Glantz and Parmley, 1978; Ross, 1979). Since the shifts in LV diastolic pressure-volume relations were reproduced in dogs with coronary stenoses in the absence of the pericardium and at comparable right ventricular filling pressures, a major role for either pericardium or right ventricle in causing these shifts seemed unlikely.

Possible mechanisms responsible for this phenomenon include: (1) regional LV dyssynchrony (Waters et al., 1977; Kumada et al., 1979) and the different muscle strengths in ischemic and non-ischemic portions of the left ventricle (Wieger et al., 1978); and (2) persistent interaction of some contractile elements in the ischemic myocardium throughout diastole (Grossman and Barry, 1980). Such persistent interaction could result from a hypoxia-induced (Serizawa et al., 1981) incomplete inactivation (partial relaxation) associated with impaired calcium sequestration by an ATP-deficient sarcoplasmic reticulum (Nayler and Williams, 1978; Nayler et al., 1979) and/or increased net calcium influx (Henry et al., 1977). Recent experiments on isolated papillary muscles...
(Chuck et al., 1981) and on isovolumic rabbit hearts (Serizawa et al., 1981) further illustrate the profound influence of hypoxia on cardiac muscle relaxation and resting tension. Muscle hypoxia appears to impair calcium sequestration and prolong intracellular calcium availability, which leads to a loss of load-dependent muscle relaxation (Brutsaert et al., 1980) and an increase in resting tension (Naylor et al., 1979). The administration of caffeine (Chuck et al., 1981) markedly facilitates the hypoxia-induced changes in muscle relaxation. Caffeine is known to prolong intracellular calcium availability through both impaired calcium sequestration by the sarcoplasmic reticulum and increased calcium influx through the sarcolemma (Weber and Herz, 1968; Blinks et al., 1972). Caffeine thereby prolongs muscle relaxation (Blinks et al., 1972) and abolishes load-dependent muscle relaxation (Lecarpentier et al., 1979) in isolated oxygenated mammalian muscle. In well-oxygenated rat papillary muscles, no increase in resting tension was observed for a caffeine dose ranging from 2.5 to 25 mmol/liter (Henderson et al., 1974; Lewis et al., 1979). However, when hypoxic contracture developed in this preparation, caffeine 2.5 mmol/liter increased resting tension (Lewis et al., 1979). In the present experiments, the administration of caffeine (20 mg/kg) to anesthetized, β-blocked dogs with coronary stenoses was found to potentiate the pacing-induced upward shift of the LV diastolic pressure-volume and pressure-segment length relation. A prolonged cytosolic calcium availability due to the combined effects of pacing-induced ischemia and caffeine could explain this greater upward shift in the LV diastolic pressure-volume relation.

Methods

Experimental Preparation

The preparation and operative techniques have been previously described (Serizawa et al., 1980). Fourteen mongrel dogs were anesthetized with intravenous a-chloralose (100 mg/kg), after having been premedicated with a subcutaneous injection of ketamine (10 mg/kg). A left thoracotomy was performed and the pericardium was opened wide. Both proximal circumflex coronary artery and left anterior descending coronary artery were freed from adipose tissue. Pacing electrodes were sutured to the left atrial appendage. A high-fidelity 7F pressure micromanometer catheter (Millar Instruments) was inserted via the right carotid artery into the left ventricle. The high-fidelity recording of the LV pressure was matched with the pressure recording through the catheter lumen before and after each record. The catheter lumen was connected to a Statham P23Db pressure transducer. In six dogs, two pairs of ultrasonic crystals were implanted in the left ventricular wall close to the endocardium in a circumferential plane for continuous measurement of two myocardial segment lengths. One pair of crystals was implanted in an area perfused by the left circumflex coronary artery and the other pair was implanted in an area perfused by the anterior descending coronary artery. Both areas were distal to the coronary stenosis. The transit times of acoustic impulses travelling between the members of each pair of 3-MHz piezoelectric crystals (2 mm in diameter) was measured and calibrated against signals of known duration from a calibrated pulse generator. Instrument drift is less than 0.01 mm in 6 hours and the frequency response is flat to 100 Hz. All signals were recorded on an Electronics for Medicine DR 8 recorder. LV cineangiograms were performed in two experiments using Renografin 76 as contrast agent, as in our previous study (Serizawa et al., 1980). The contrast was injected at a rate of 5 ml/sec for 2–3 seconds. The ventriculogram was recorded with a Siemens 16-mm cineangiography system at 50 frames/sec.

Experimental Procedure

Placement of Coronary Stenoses

Propranolol (0.5 mg/kg) was injected intravenously at the beginning of the experiment to prevent ventricular fibrillation during pacing (Reynolds et al., 1978) and to antagonize the myocardial effects of a catecholamine release induced by the CNS-stimulating action of caffeine (Robertson et al., 1978). Electromagnetic flow probes (Biotronex BL 610) were placed around both left circumflex and left anterior descending coronary arteries. Small metal clips were placed proximally on both arteries so as to reduce antegrade coronary blood flow in the control (unpaced) state in each vessel by 50%. This reduction corresponds to a decrease in coronary diameter of approximately 90% (Gould and Lipscomb, 1974). Baseline LV pressure, LV dp/dt, and LV segment lengths were recorded and a control LV angiogram was performed (n = 2). No segmental myocardial dysfunction was caused by the placement of the coronary stenoses.

(2) Control Pacing Run

The left atrium was paced at a rate of 1.5 times the resting heart rate for 3 minutes (pacing heart rate: 190 ± 7 beats/min; peak LV pressure during pacing; 93 ± 7 mm Hg). LV pressure, LV dp/dt, and LV segment lengths were recorded in the immediate post-pacing period and a LV angiogram was performed. LV hemodynamics returned to control levels within 1 minute after the pacing run.

(3) Caffeine Administration in the Resting State

Diazepam, 0.1 mg/kg, was injected to prevent convulsions during the caffeine infusion. Caffeine sodium benzoate was infused intravenously over a 30-second period at a dose sufficient to lower systolic blood pressure by 20% of its baseline value. A further drop in blood pressure was avoided, since this would compromise myocardial perfusion with
the high grade coronary artery stenoses and might lead to ventricular fibrillation or myocardial infarction. The effective dose of caffeine administered ranged from 12.5 to 50 mg/kg (mean: 20 ± 4 mg/kg). LV hemodynamics were again recorded. LV hemodynamics returned to baseline values within 20 seconds after cessation of the caffeine infusion.

(4) Caffeine Administration during Pacing

Ten minutes later, atrial pacing was repeated at a rate of 1.5 times the resting heart rate ( pacing heart rate: 189 ± 7 beats/min; peak LV systolic pressure during pacing: 93 ± 7 mm Hg). A dose of caffeine equal to that previously used was then infused intravenously in the last 30 seconds of pacing. LV pressure, LV dp/dt, and LV segment lengths were recorded at the time of maximal increase in left ventricular filling pressures. In two experiments, a repeat LV angiogram was performed at the time of maximal increase in LV pressure during pacing: 93 ± 7 mm Hg). A dose of caffeine equal to that previously used was then infused intravenously in the last 30 seconds of pacing. LV hemodynamics returned to control values within 5 minutes after the pacing run.

Data Analysis

LV pressure and segment-length recordings were digitized every 5 msec by means of a Tektronix 4051 computer system. LV angiograms were analyzed frame by frame from end-systole to end-diastole by the area-length method (Sandler and Dodge, 1968), as modified by us in previous studies (Serizawa et al., 1980). Left ventricular pressure vs. segment length plots were constructed by computer analysis using corresponding points of the digitized pressure and segment length data. Segmental stroke work was calculated as the surface enclosed by the pressure-segment length plot. End-systolic segment length and end-diastolic segment length were identified by left ventricular peak negative dp/dt and left ventricular end-diastolic pressure, respectively. Left ventricular diastolic pressure-volume curves were constructed using corresponding pressure and volume points at 20-msec intervals. The time constant (T) of LV pressure fall was calculated by the method of Weiss et al., (1976). Single comparison data were analyzed by Student's t-test for paired data. Multiple values were compared by the Bonferroni method (Wallenstein et al., 1980). Values were considered to be statistically significant at P < 0.05. All values were expressed as mean ± standard error of mean.

Results

Effects of Caffeine on Resting LV Hemodynamics in dogs with Coronary Stenoses

LV hemodynamics before and after an intravenous infusion (30 seconds) of caffeine (average dose 20 ± 4 mg/kg) are summarized in Table 1. Decreases in LV peak systolic pressure (from 112 ± 6 to 97 ± 3 mm Hg, P < 0.005), LVEDP (from 9 ± 1 to 7 ± 1 mm Hg, P < 0.01), peak LV (−) dp/dt (from 1948 ± 115 to 1518 ± 115 mm Hg/sec, P < 0.005), end-diastolic segment length (EDSL) (from 16.9 ± 0.9 mm to 16.6 ± 0.9 mm, p < 0.05), and end-systolic segment length (ESSL) (from 14.8 ± 0.9 to 14.3 ± 0.9 mm, P < 0.005) were recorded. These hemodynamic findings are consistent with a decrease in arterial resistance due to the direct vascular smooth muscle relaxant effect of caffeine (Somlyo and Somlyo, 1968; Ritchie, 1970). This effect was transient, and hemodynamics returned to control by 20 seconds after the infusion was stopped. A repeat infusion of an equal dose caused similar transient changes in hemodynamics.

Effects of Caffeine on Pacing-induced Ischemia

Table 2 compares control LV hemodynamics to LV hemodynamics after 3 minutes of rapid atrial pacing, and to LV hemodynamics after 3 minutes of rapid atrial pacing with an intravenous infusion of caffeine (20 ± 4 mg/kg) in the last 30 seconds of pacing. Measurements were made at the time of maximal increase in left ventricular filling pressures, which occurred within 5 seconds after the

| TABLE 1 Effects of Intravenous Administration of Caffeine on Resting LV Hemodynamics in Dogs with Coronary Stenoses |
|---------------------------------|--------|--------|--------|
|                                | Control| Caffeine| n     |
| HR (beats/min)                 | 120 ± 6 | <0.05  | 124 ± 10 | 14 |
| LVSP (mm Hg)                   | 112 ± 6 | <0.005 | 97 ± 3  | 14 |
| LVEDP (mm Hg)                  | 9 ± 1   | <0.01  | 7 ± 1   | 14 |
| LVMDP (mm Hg)                  | 5 ± 1   | <0.01  | 4 ± 1   | 14 |
| Peak (+) dp/dt (mm Hg/sec)     | 1848 ± 122 | NS     | 1924 ± 137 | 14 |
| Peak (−) dp/dt (mm Hg/sec)     | 1948 ± 115 | <0.005 | 1518 ± 115 | 14 |
| T (msec)                       | 40 ± 3  | NS     | 42 ± 4  | 14 |
| EDSL (mm)                      | 16.8 ± 0.9 | <0.05 | 16.6 ± 0.9 | 6 |
| ESSL (mm)                      | 14.8 ± 0.9 | <0.005 | 14.3 ± 0.9 | 6 |
| % ΔL                           | 12.4 ± 1.2 | NS   | 13.7 ± 1.6 | 6 |

Values expressed as mean ± SE. HR: heart rate; LVSP, LVEDP, and LVMDP: left ventricular peak systolic, end-diastolic, and minimum diastolic pressures; T: time constant of left ventricular relaxation; EDSL, ESSL, and % ΔL: end-diastolic segment length, end-systolic segment length, and percent shortening. EDSL, ESSL, and % ΔL are the averages of the data obtained from both regions in which pairs of ultrasonic crystals were implanted.
TABLE 2  Effects of Intravenous Administration of Caffeine (20 ± 4 mg/kg) on Post-Pacing LV Hemodynamics in Dogs with Coronary Stenoses

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Post-pacing</th>
<th>Post-pacing and caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>121 ± 6</td>
<td>122 ± 6</td>
</tr>
<tr>
<td></td>
<td>LVPSP (mm Hg)</td>
<td>113 ± 4</td>
<td>112 ± 6</td>
</tr>
<tr>
<td></td>
<td>LVEDP (mm Hg)</td>
<td>9 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td></td>
<td>LVMDP (mm Hg)</td>
<td>5 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td></td>
<td>Peak (+) dP/dt</td>
<td>1887 ± 88</td>
<td>1683 ± 103</td>
</tr>
<tr>
<td></td>
<td>(mm Hg/sec)</td>
<td>2066 ± 108</td>
<td>1574 ± 131</td>
</tr>
<tr>
<td></td>
<td>T (msec)</td>
<td>38 ± 2</td>
<td>52 ± 4</td>
</tr>
<tr>
<td></td>
<td>EDSL (mm)</td>
<td>16.8 ± 0.9</td>
<td>17.5 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>ESSL (mm)</td>
<td>14.8 ± 0.9</td>
<td>15.7 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>% AL</td>
<td>11.8 ± 1.2</td>
<td>9.9 ± 1.2</td>
</tr>
</tbody>
</table>

Values expressed as mean ± se. Abbreviations as in Table 1. EDSL, ESSL, and %AL are the averages of the data obtained from both regions in which pairs of ultrasonic crystals were implanted.

cessation of pacing in the control pacing run, and 45 ± 12 seconds after the cessation of pacing in the pacing run with caffeine administration. No significant difference in HR and LV peak systolic pressure was observed. LVEDP showed a stepwise increase from 9 ± 1 to 15 ± 1 mm Hg post-pacing, to 27 ± 2 mm Hg post-pacing plus caffeine.

LVMDP showed similar changes. Peak (-) dP/dt decreased from 2066 ± 108 mm Hg/sec (control) to 1574 ± 131 mm Hg/sec (post-pacing) (P < 0.05). No significant further change was seen after pacing with caffeine. Time constant T increased from 38 ± 2 msec (control) to 52 ± 4 msec (post-pacing) (P < 0.01) and showed no further significant increase when caffeine was infused during the pacing run. EDSL increased from 16.8 ± 0.9 mm (control) to 17.5 ± 0.9 mm (post-pacing) (P < 0.005). After administration of caffeine, there was a small non-significant decrease in EDSL to 17.3 ± 1.0 mm despite the marked increase in LVEDP. ESSL increased from 14.8 ± 0.9 mm (control) to 15.7 ± 0.9 mm (post-pacing) (P < 0.005) and 15.1 ± 0.9 mm (post-pacing and caffeine). Percent systolic shortening (% AL) decreased after pacing (from 11.8 ± 1.2% to 9.9 ± 1.2%, P < 0.05) but returned almost to its control value after the administration of caffeine (11.7 ± 1.4%).

On the last beat of the control pacing run and on the last beat of the pacing run with caffeine administration, we determined ESSL, end-systolic LV pressure (LVESP), and myocardial segmental stroke work (area enclosed by the pressure-segment length loop). No significant differences in myocardial segmental stroke work (from 1.41 ± 0.31 dynes cm/stroke to 1.46 ± 0.41 dynes cm/stroke, NS), ESSL (from 15.0 ± 0.9 mm to 14.9 ± 0.9 mm, NS) and in LVESP (from 56 ± 5 mm Hg to 58 ± 5 mm Hg, NS) were detected. Prior to the administration
of caffeine, percent systolic shortening (% ΔL) was equally reduced in both pacing runs (6.8 ± 2.0% and 7.1 ± 2.5%; NS). In some experiments, a repeat pacing run with the administration of an equal dose of caffeine was performed after removal of the coronary stenoses. Under these conditions no changes in left ventricular filling pressures were observed in the post-pacing period.

Figure 1 shows the time course of the LV pressure changes in the control pacing run (upper row) and in the pacing run with caffeine administration (lower row) in a representative experiment. The upper row shows the EKG, LV pressure, and LV dP/dt before, 10 seconds after rapid atrial pacing, and 60 seconds after rapid atrial pacing, by which time LV filling pressures had returned to baseline. On the lower row, the same recordings are shown before and at several intervals after rapid atrial pacing with an intravenous infusion of caffeine in the last 30 seconds of pacing. As can be seen, the magnitude and duration of the increased LV filling pressure was greater after the administration of caffeine. Figure 2 shows LV pressure, LV dP/dt, and two segment length recordings before rapid atrial pacing, after pacing, and after pacing with the administration of caffeine in a typical experiment. As can be seen, EDSL is smaller on both segment length tracings after caffeine, despite a marked further increase in LVEDP. The left ventricular diastolic pressure-volume relations in the two experiments where repeated LV angiograms were done are shown in Figure 3. In the panel on the left, the diastolic pressure-volume relation after pacing tachycardia with caffeine infusion shows an upward shift when compared to the control diastolic pressure-volume relation. In the panel on the right, the diastolic pressure-volume relation after pacing tachycardia with caffeine infusion is shifted upward with respect to the diastolic pressure-volume relation after pacing tachycardia, which is itself shifted upward with respect to the control diastolic pressure-volume relation. Figure 4 shows the LV diastolic pressure-myocardial segment length plots obtained from the digitized data of one representative segment length tracing and the LV pressure trace for each of the six experiments in which ultrasonic crystals were implanted. The diastolic pressure-segment length curves before rapid atrial pacing, after pacing, and after pacing with caffeine administration are, respectively, the bottom, middle, and top tracings of each set of three curves.

**Discussion**

The mechanism of the upward shift in the diastolic LV pressure-volume relation in angina has been the subject of considerable controversy (Glantz et al., 1978; Ross, 1979; Grossman et al., 1980; Grossman and Barry, 1980). Recently, this
upward shift was demonstrated in our laboratory in open-chest, anesthetized dogs with open pericardium and high-grade (90%) stenoses on both left anterior descending and circumflex coronary arteries following pacing-induced ischemia (Serizawa et al., 1980), arguing against a predominant role for either pericardial restriction or ventricular interaction as determinants of the upward shift seen in myocardial ischemia of the increased-demand type. However, the precise mechanism by which pacing-induced ischemia affects the LV diastolic pressure-volume relation is still unclear. Is this change in ventricular chamber distensibility a manifestation of a "reversible" ischemic contracture? Does it reflect a delay and/or an incompleteness in the process of ventricular relaxation? Or does it reflect the regional and temporal dyssynchrony between ischemic and normal cardiac muscle (Waters et al., 1977; Wiegner et al., 1978)?

Hypoxic cardiac muscle contracture has received renewed attention in recent years both in isolated myocardial preparations (Greene and Weisfeldt, 1977; Lewis et al., 1979, 1980) and in isolated perfused hearts (Apstein et al., 1978; Nayler et al., 1979). The complete (Greene and Weisfeldt, 1977) or partial recovery (Lewis et al., 1979) of papillary muscle function after a period of hypoxic contracture stresses the dynamic state, rather than the irreversible injury aspect of hypoxic contracture. The dynamic state and reversible nature of hypoxic contracture are further illustrated by the reduction and the prevention of hypoxic contracture through mechanical systolic stretches (Brutsaert et al., 1970; Lewis et al., 1980; Apstein and Ogilby, 1980). The development of myocardial contracture and a leftward shift of the diastolic pressure-volume curve have been observed after prolonged (60-minute) ischemic arrest in isolated blood perfused dog hearts (Gaasch et al., 1978). In similar experiments using isolated rat hearts, Apstein and co-workers (1977) described complete recovery of contractile function and a reversion of ischemic contracture after moderate ischemia. Myocardial contractures induced by Ba** are completely reversed upon removal of the Ba** and addition of Ca** to the bathing fluid (Munch et al., 1980).

An increased cytosolic calcium ion concentration and a low energy availability may induce hypoxic cardiac muscle contracture, which is associated with an increased muscle stiffness (Lewis et al.,
1979, 1980). The prompt rise in resting tension may not simply be related to influx of extracellular calcium, since it is not prevented by the removal of extracellular calcium or the addition of verapamil (Nayler et al., 1979). Only alterations in myocardial energy supply-demand balance, changes in pH (Bing et al., 1973), and the addition of caffeine are capable of modulating the development of such a myocardial contracture. Caffeine increases myocardial resting tension in hypoxic contracture presumably through impaired internal calcium sequestration (Lewis et al., 1979), although other mechanisms may contribute. In the present experiments, caffeine augmented LV diastolic pressure relative to volume in pacing-induced ischemia. The similar response to caffeine in both hypoxic contracture and pacing-induced ischemia points toward a common pathophysiological mechanism. A reversible form of hypoxic cardiac muscle "contracture" as a mechanism for an upward shift in the diastolic pressure-volume relationship in pacing-induced ischemia could explain both the decreased ventricular distensibility and the observed pharmacological modulation by caffeine.

Peak (-) dP/dt decreased and time constant T increased after pacing-induced ischemia. Caffeine caused no further increase in time constant T in pacing-induced ischemia despite a doubling of the LV filling pressures and a further upward shift of the diastolic pressure-volume relation. This finding suggests a dissociation between the rate and extent of myocardial relaxation, possibly related to saturation of calcium-binding capacity of sarcoplasmic reticulum. A similar dissociation between resting tension and rate of tension decay has been observed in reoxygenation "contracture" (Greene and Weisfeldt, 1977). A complete transition from a load-dependent relaxation to an activation-dependent relaxation is probably already achieved in post-pacing ischemia, and the addition of caffeine therefore does not cause any further change in the rate of tension decay (Brutsaert et al., 1980), but does affect the final resting tension level, possibly by further impairing sarcoplasmic reticular capacity for binding of systolic calcium. Thus, incomplete relaxation (partial inactivation) results in persistent interaction of contractile elements throughout diastole, and superimposes an "active" stiffness on the passive elasticity of the ventricular myocardium. As a working hypothesis, we suggest that a reversible form of hypoxic cardiac muscle "contracture," due to incomplete diastolic relaxation (partial inactivation) of the contractile elements following each systolic contraction, could explain the observations of this study, as well as previous observations of decreased chamber distensibility in patients with pacing-induced angina pectoris.

The administration of caffeine in the resting state
ALTERED LV DIASTOLIC PROPERTIES DURING ISCHEMIA/Paulus et al.

provoked a transient drop in arterial resistance and a concomitant decline in blood pressure. Both the myocardial and peripheral actions of caffeine were manifest because pretreatment with β-blockers counteracted the CNS stimulation and increased levels of catecholamines induced by the administration of caffeine in conscious subjects (Robertson et al., 1978).

The decreased LV filling pressures after caffeine infusion in the resting state and the increased LV filling pressures after caffeine infusion in the post-pacing ischemia state point toward a direct action of caffeine on ischemic muscle compliance, rather than on right ventricular filling or venous return, as the cause of an increased upward shift of the diastolic pressure-volume relation after pacing tachycardia.

A worsening of myocardial ischemia or an increase in myocardial oxygen demand related to the positive inotropic action of caffeine also warrants consideration as a possible mechanism for the observed hemodynamic changes induced by caffeine during pacing ischemia. The administration of caffeine at the end of the pacing run was followed by improved shortening of the ischemic segment, compared to shortening of the same segment during the control pacing run. The absence of segmental deterioration does not exclude a worsening of regional ischemia. Previous studies on the influence of positive inotropic agents such as isoproterenol on myocardial function of ischemic segments distal to a coronary occlusion documented transient improvement of systolic shortening despite worsened myocardial ischemia (Theroux et al., 1974). However, in that study, improvement of systolic function resulted in lower left ventricular filling pressures, whereas in the present study caffeine administration during pacing ischemia increased left ventricular filling pressures despite improved systolic shortening. The observed combination of an increase in LV filling pressures and improved systolic function in the ischemic segment possibly reflects the unique cellular mechanism of caffeine. Since both the positive inotropic and vasodilatory actions of caffeine could interfere with myocardial oxygen demands during pacing, we elected to administer the caffeine during the last 30 seconds of rapid atrial pacing rather than continuously during the entire 3 minutes of pacing or in the prepacing period. Using this approach, 85% of the pacing run

**FIGURE 4** Left ventricular diastolic pressure-segment length plots obtained from segment length tracing and the simultaneous left ventricular pressure signal for each of the six experiments in which ultrasonic crystals were implanted. The left ventricular diastolic pressure-segment length plots shown were constructed by computer analysis using corresponding points of the digitized pressure and segment length data up to end diastole. The diastolic pressure-segment length curve before pacing, after pacing, and after pacing plus caffeine are the bottom, middle, and top curves (respectively) of each set of three curves.
occurred at comparable blood pressure to the initial pacing run. Moreover, at the end of both pacing runs, the determinants of myocardial oxygen consumption (mechanical stroke work and end-systolic elastic potential energy) were comparable. In recent work, Suga et al. (1981a, 1981b) demonstrated a high correlation between myocardial oxygen consumption and the simple sum of external mechanical work and end-systolic elastic potential energy. From the present data, mechanical stroke work and the determinants of end-systolic elastic potential energy (end-systolic pressure and end-systolic length) were comparable at the end of both pacing runs. Although the determinants of myocardial oxygen consumption are comparable at the end of both pacing runs, caffeine administration resulted in improved systolic shortening at the time of maximal elevation of left ventricular filling pressures (45 ± 12 seconds after the cessation of pacing). At this moment, myocardial ischemia could have been increased by the positive inotropic action of caffeine. Therefore, we cannot exclude a nonspecific worsening of myocardial ischemia related to the positive inotropic action of caffeine as contributing to the observed left ventricular hemodynamics.

It must be emphasized that myocardial ischemia in our model is due to increased demand superimposed on restricted, fixed supply. As we have pointed out (Serizawa et al., 1980; Grossman et al., 1981), this type of increased-demand myocardial ischemia differs substantially from models involving a primary reduction in coronary blood flow (e.g., coronary ligation or low coronary perfusion global ischemia). In the latter "supply side" types of ischemia, decreased coronary vascular pressure and turgor combined with accumulation of local metabolites and acidosis tend to mask and/or attenuate the increased myocardial stiffness (Serizawa et al., 1981). However, even in such "supply side" models of myocardial ischemia, increased myocardial stiffness appears very rapidly (within 30 seconds) under appropriate experimental conditions (Apstein et al., 1978). The increased myocardial stiffness during pacing-induced ischemia in dogs with coronary stenoses is thus most relevant to the clinical phenomenon of exertion or stress-induced angina pectoris, rather than to the "supply side" ischemia of acute myocardial infarction.

Although these experiments and the potentiating effect of caffeine support the concept of increased myocardial stiffness related to incomplete muscle inactivation, other possibilities need to be considered. Dysynchronous contraction of normal and ischemic myocardium in series (Waters et al., 1977; Wiegner et al., 1978; Kumada et al., 1979) has been suggested as an explanation for the fall in peak negative dp/dt and possibly could account to some extent for the upward shift in diastolic pressure-volume relations. Although none of our current or previous studies (Mann et al., 1977; Grossman and Mann, 1978; Serizawa et al., 1980) have shown any obvious angiographic evidence of systolic bulging of previously contracting muscle during post-pacing ischemia, further studies will be needed before a definite conclusion can be reached concerning a possible role for such dysynchrony.

Finally, it must be acknowledged that, since caffeine has additional and as yet incompletely understood effects on myocardial cells, the potentiation of the upward shift seen in our studies with caffeine could be due in part to cellular mechanisms (e.g., sensitization of myofilaments to calcium, change in slow inward calcium current) other than incomplete myocardial inactivation. Also, the effects of caffeine before pacing cannot strictly be compared with those during pacing. This is because the second injection of caffeine, while of the same size as the first, is superimposed on an unknown basal level of the drug established by redistribution of the first injection. Nevertheless, the potentiation of the upward shift in diastolic pressure relative to ischemic segment length following caffeine is striking (Fig. 4), and occurred at a time when systolic function of the ischemic segment was unchanged or improved.

In summary, an infusion of caffeine markedly potentiated the increased ventricular filling pressure and upward shift of the LV diastolic pressure-volume and pressure myocardial segment length relations resulting from pacing-induced ischemia. This pharmacological modulation by caffeine favors a reversible form of "contracture" due to incomplete myocardial relaxation (partial inactivation) as an underlying pathophysiological mechanism.

Acknowledgments

We gratefully acknowledge the helpful comments of Dr. William H. Barry and Dr. Beverly H. Lorell, and the skilled technical assistance of Abby Henneman.

References


Brutsaert DL, Housmans PR, Goethals MA (1980) Dual control
ALTERED LV DIASTOLIC PROPERTIES DURING ISCHEMIA/


Waters DD, Da Luz P, Wyatt HL, Swan HJC, Forrester JS (1977) Early changes in regional and global left ventricular function induced by graded reductions in regional coronary perfusion. Am J Cardiol 39: 537-543


of relaxation: Its role in the ventricular function in the mammalian heart. Circ Res 47: 637-652


McLaurin LP, Roellet EL, Grossman, W (1973) Impaired left ventricular relaxation during pacing-induced ischemia. Am J. Cardiol 32: 751-757

Downloaded from http://circ.ahajournals.org/ by guest on October 19, 2017
Altered left ventricular diastolic properties during pacing-induced ischemia in dogs with coronary stenoses. Potentiation by caffeine.

W J Paulus, T Serizawa and W Grossman

_Circ Res._ 1982;50:218-227
doi: 10.1161/01.RES.50.2.218

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/50/2/218.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/