Relationship Between Changes in Left Ventricular Inotropic State and Relaxation in Normal Subjects and in Patients with Coronary Artery Disease

MICHEL F. ROUSSEAU, M.D., HUBERT POULEUR, M.D., JEAN-MARIE R. DETRY, M.D., AND LUCIEN A. BRASSEUR, M.D.

SUMMARY The aim of the study was to examine the changes in left ventricular (LV) relaxation rate induced by variations in inotropic state. Eight normal subjects and 29 patients with coronary artery disease (CAD) were studied. First, we used interventions that increase myocardial calcium influx (atrial pacing or postspacing beat) or decrease it (intracoronary injection of nifedipine). Relaxation rate was estimated from the time constant (T1) of isovolumic LV pressure fall during the first 40 msec after peak negative dP/dt. Under basal conditions, T1 was impaired in CAD patients (58 vs 43 msec; p < 0.01), despite similar heart rate, LV pressures and peak positive dP/dt (1620 vs 1787 mm Hg/sec; NS). During atrial pacing at 135 ± 7 beats/min, peak positive dP/dt increased to 2220 mm Hg/sec in 11 CAD patients and to 2256 mm Hg/sec in 8 normal subjects. T1 decreased more in CAD patients than in normal subjects (17 vs 7 msec; p < 0.01). T1 changes also differed in the postspacing beat between CAD patients and normal subjects (-6 vs 5 msec; p < 0.01) or when nifedipine was injected during the pacing (4 vs 20 msec; p < 0.01). Intravenous calcium injection during atrial pacing in another group of 18 CAD patients further improved peak positive dP/dt and T1 (-3 msec; p < 0.05) and normalized the changes in relaxation during the postspacing beat. Our data indicate that a variable coupling between LV inotropic state and relaxation rate exists in man during changes in calcium influx and that this coupling is abnormal in CAD patients.

MYOCARDIAL RELAXATION, the active process by which ventricular muscle returns to its initial length and tension, has been extensively studied in isolated muscle1-8 and in animal experiments.1,8 Clear evidence of an abnormal left ventricular relaxation in cardiac patients has been reported, particularly in coronary patients (both during angina and at rest) and in patients with hypertrophic or congestive cardiomyopathy.10-21 According to the more recent studies, some clinical manifestations, such as increased ventricular filling pressures, might partially result from these alterations in relaxation.17-19

Several investigators have suggested that specific therapeutic approaches, including nifedipine in hypertrophic cardiomyopathy and salbutamol in congestive cardiomyopathy, might improve these alterations in diastolic properties and contribute to the clinical improvement of the patients.16, 17, 19 However, little is known about the possibility of altering relaxation rate independently of the inotropic state. This problem could be particularly important if relaxation had to be modified in patients with normal or depressed ventricular function.

Therefore, we further analyzed these alterations in left ventricular relaxation observed in coronary artery disease (CAD). To separate the contraction and relaxation events, we used, as previously proposed by Parmley and Sonnenblick, several inotropic interventions, including changes in heart rate, calcium or calcium-antagonist injections, in normal subjects and in CAD patients.

We have observed that the coupling between contraction and relaxation depends on the type of inotropic stimulation. In addition, this coupling in normal subjects was different from that in CAD patients. These results are consistent with the previously proposed hypothesis17, 22-25 that the calcium influx-efflux mechanisms might play a key role in the myocardial relaxation process. They also suggest that the ventricular diastolic properties may be modified with minimal changes in systolic function.

Material and Methods

Thirty-seven patients were included in this study. All were in sinus rhythm, and those with hypertension or valvular disease were excluded. All had typical or atypical angina pectoris and the hemodynamic study was performed for diagnostic purposes. Significant CAD, defined as stenosis of 75% or greater of at least one major coronary vessel, was shown in 29 patients (mean age 51.5 years, range 33-61 years), all of whom had typical angina. Eight patients (mean age 45.4 years, range 40-50 years) with completely normal coronary arteries and left ventriculography were considered as normal subjects. Clinical and angiographic data are presented in table 1. All cardioactive drugs were discontinued at least 72 hours before the procedure. In most cases the delay was 1 week. Each patient gave informed consent and no complication resulted from this study.

Left-heart catheterization was performed using the femoral approach with the patient in the fasting state and without premedication. High-fidelity left ventricular pressures were recorded at low (0-160 mm Hg) and high (0-400 mm Hg) gains with a #5F or #6F micromanometer-tip catheter (Millar Instruments). The micromanometer system was calibrated elec-
tronomically against a mercury manometer before insertion and again after withdrawal. The rate of left ventricular pressure change (dP/dt) was obtained using a differentiating amplifier (Physiocardiopan Philips) that has a linear response up to 60 Hz. Aortic or left main coronary artery pressure was measured by a fluid-filled catheter (left coronary catheter) connected to a Statham P23ID strain gauge. A bipolar electrode

**TABLE 1. Clinical and Angiographic Data**

<table>
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<th>Protocol I</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Previous MI</th>
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<th>EF (%)</th>
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**Abbreviations:** LVEDP = left ventricular end-diastolic pressure (peak R Wave, end-expiration); MI = myocardial infarction; EF = ejection fraction; 1VD = one-vessel disease; 2VD = two-vessel disease; 3VD = three-vessel disease; CAD = coronary artery disease; N = normal; ant. aneur. = anterior aneurysm; ant. akin. = anterior akinesia; ant. hyp. = anterior hypokinesia; inf. akin. = inferior akinesia; inf. hyp. = inferior hypokinesia; diff. hyp. = diffuse hypokinesia.
catheter was introduced in the right atrium for atrial pacing. The study was performed before left ventriculography and coronary arteriography (Judkins technique).

Two experimental protocols were used. In protocol I, we attempted to produce identical changes in peak positive dP/dt in normal subjects and in CAD patients and we compared the changes in relaxation rate induced in both groups. We used interventions that increased calcium influx (atrial pacing below anginal threshold, postpacing beat) or decreased it (intracoronary nifedipine). Protocol II, performed only in CAD patients, was designed to examine the direct role of the calcium ions in producing the changes in relaxation rate observed during the first part of the study. For that purpose, the inotropic stimulations used in protocol I were repeated after i.v. calcium administration.

Experimental Protocol I

This experimental protocol (fig. 1A) was performed in eight normal subjects and in 11 CAD patients (table 1). Hemodynamic data (heart rate, systolic and diastolic aortic pressures, left ventricular systolic and end-diastolic pressures, peak positive and negative dP/dt) were first measured under basal conditions, before and after the introduction of the coronary catheter in the left main coronary artery. These hemodynamic measurements were recorded simultaneously during two or three respiratory cycles on a multichannel recording system (Honeywell 1858) at a paper speed of 200 mm/sec. Then atrial pacing was started following the protocol shown in figure 1A. When a steady state was achieved at an average heart rate of 135 beats/min, a 0.1-mg bolus of nifedipine was injected into the left main coronary artery and the pacing was continued for 3 minutes. The dose of 0.1 mg of nifedipine was used because a previous study had shown that it produced insignificant systemic effects and that its cardiac effects were limited to the first minute after injection.

The data were recorded between the fourth and fifth minutes of pacing and 30 seconds and 3 minutes after nifedipine injection. The first postpacing beat was also analyzed (fig. 1A).

Experimental Protocol II

The second protocol (fig. 1B) was performed in 18 CAD patients. This group underwent left-heart catheterization as described above and a #7F Courand catheter was inserted into the pulmonary artery for drug injection.

Control data were recorded twice under basal conditions 5 minutes apart. Calcium injections (bolus of 2 ml of 10% calcium gluconate, i.e., 0.45 mEq of calcium) were made into the pulmonary artery, first under basal conditions and again after 4 minutes of atrial pacing at 121 beats/min (fig. 1B). This dose of calcium was used after preliminary studies because it produced significant positive inotropic effects with insignificant changes in left ventricular peak systolic pressure, left ventricular end-diastolic pressure (LVEDP) or heart rate and without any other side effects. Pacing was stopped 2 minutes after injection, when the positive inotropic effect of calcium was still demonstrated by an increase in peak positive dP/dt above the preinjection level; the first postpacing beat was also recorded.

No patient experienced angina pectoris or chest discomfort during the protocols. The absence of any major myocardial ischemia during pacing was also confirmed by the lack of changes in LVEDP or peak negative dP/dt after the pacings.10, 11

Measurements and Computations

In each recording, the cardiac cycle with the highest LVEDP (measured at the peak of the R wave) was selected for analysis. This procedure ensured that the beat was selected in expiratory phase and prevented artifactual changes in the time course of left ventricular pressure fall due to variations in intrathoracic pressures. LVEDP values obtained in this fashion are higher than those obtained by averaging LVEDP over the entire respiratory cycle.

Left ventricular pressure was digitized every 3 msec (2113E HP computer) and the time course of its fall

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**Figure 1.** Diagram of the two protocols. The asterisks indicate the time when data presented in tables 2 and 3 were sampled. CAD = coronary artery disease; PPB = first postpacing beat; pacing 120, pacing 140 = atrial pacing around 120 or 140 beats/min; Ca++ control, Ca++ pacing = calcium injection under control conditions or during atrial pacing.
during the first 40 msec after peak negative dP/dt was used as an index of left ventricular relaxation. Accordingly, an exponential relationship was fitted by the method of least squares (r ranging from 0.990–0.999; p < 0.0001) to the pressure vs time data. The time constant (T1) of this relation was used as index of early relaxation. No attempt was made to characterize the rate of tension fall later than 40 msec after end-ejection because the duration of isovolumic relaxation was frequently reduced below 80 msec during the increases in heart rate.

In each experimental protocol, the two sets of control data were averaged and the changes induced by the various maneuvers were compared to these control data using a repeated-measure analysis of variance. Comparisons between groups were performed using a two-tailed Mann-Whitney test.

Results

Protocol I: Effects of Inotropic Interventions on Left Ventricular Relaxation Rate

Hemodynamic data under control conditions, during atrial pacing, after nifedipine and during the postpacing beat are presented in table 2. Atrial pacing at 135 beats/min, significantly increased peak positive dP/dt without altering left ventricular systolic pressure; LVEDP and T1 decreased significantly (table 2).

Thirty seconds after nifedipine, left ventricular systolic pressure significantly decreased in both groups; T1 was markedly prolonged while LVEDP increased to the control levels (table 2). At 2 minutes (not displayed in table 2) and at 3 minutes after nifedipine, all hemodynamic variables returned to the values observed during pacing before nifedipine.

During the postpacing beat (mean RR 952 ± 130 msec), peak positive dP/dt significantly increased in normal subjects (1085 mm Hg/sec; p < 0.01) and in CAD patients (1057 mm Hg/sec; p < 0.01). T1 increased significantly in normal subjects only (5 msec; p < 0.05) and tended to decrease in CAD patients.

Protocol II: Effects of Calcium Injection at Different Inotropic States on Left Ventricular Relaxation Rate of CAD Patients

The hemodynamic data from the 18 CAD patients under control conditions, during atrial pacing and during the calcium injections are summarized in table 3.

Positive inotropic effects of calcium injections were illustrated by the significant increases in peak positive dP/dt observed at constant heart rate, LVEDP and left ventricular systolic pressure both under control conditions (130 mm Hg/sec; p < 0.01) and during pacing (271 mm Hg/sec; p < 0.01); T1 significantly decreased (3 msec; p < 0.05) when calcium was injected during pacing. When pacing was stopped after calcium injection, a marked positive inotropic effect was observed during the postpacing beat (1054 mm Hg/sec in peak positive dP/dt; p < 0.001, despite a small decrease in LVEDP), but in this case, T1 was significantly prolonged (5 msec; p < 0.05).

Comparison of the Left Ventricular Relaxation Rates of Normal Subjects and CAD Patients

Data Under Basal Conditions

Under basal conditions, no significant differences were observed between normal subjects and CAD patients with respect to heart rate, LVEDP, left ven-

### Table 2. Hemodynamic Data of Protocol I

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<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Peak + dP/dt (mm Hg/sec)</th>
<th>T1 (msec)</th>
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All values are mean ± SD. Compared to the control:
* p < 0.05.
† p < 0.01.

Abbreviations: HR = heart rate; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; T1 = time constant of isovolumic pressure fall (see Methods section for definition); CAD = coronary artery disease.
tricular systolic pressure, or peak positive dP/dt (1787 mm Hg/sec) in eight normal subjects; 1620 mm Hg/sec in 11 CAD patients, NS; 1756 mm Hg/sec in other 18 CAD patients, NS). However, T1 values were significantly greater in the two CAD groups (58 msec in 11 CAD; p < 0.01; and 53 msec in 18 other CAD; p < 0.01) than in the normal subjects (43 msec).

Data During Changes in Inotropic State

Figure 2 illustrates the changes in T1 and peak positive dP/dt observed between control and pacing of protocol I. Despite similar increases in peak positive dP/dt, T1 decreased significantly more in CAD (16.8 ± 6.7 msec) than in the normal subjects (6.5 ± 2.9 msec; p < 0.01). Consequently, the significant difference present at rest between T1 in normal subjects and in CAD patients tended to disappear during atrial pacing.

Figure 3 is a summary of the effects of intracoronary nifedipine during pacing. Again, peak positive dP/dt changes were similar in both groups, but T1 increased more in normal subjects than in CAD patients.

The changes in T1 and peak positive dP/dt during the postspacing beat are illustrated in figure 4. In the normal subjects, these values increased the T1 values, while in CAD patients, T1 decreased in all but two patients, and the difference between groups was significant despite identical increases in peak positive dP/dt (1085 vs 1057 mm Hg/sec; NS). In contrast, when the postspacing beat was obtained after calcium injection (protocol II), peak positive dP/dt again increased by 1060 mm Hg/sec, but the T1 values increased as in the normal subjects.

Discussion

The present study showed that, in man, a positive inotropic stimulus can either accelerate or slow down the speed of relaxation. Our data also indicated that the changes in left ventricular relaxation rate induced by several inotropic interventions (such as increased heart rate, postspacing beat or calcium antagonist injection) significantly differed between CAD patients and normal subjects.

Effects of Inotropic Interventions on the Relationship Between Contraction and Relaxation

The aim of the study was to compare the coupling between contraction and relaxation in normal subjects and in CAD patients. The changes in inotropic state were estimated from the changes in peak positive dP/dt. Indeed, maximum dP/dt is very responsive to

\[
\begin{align*}
\text{CAD patients (n = 18)} \\
\text{Control} & \quad 71 \pm 8 & 133 \pm 19 & 12.8 \pm 4.0 & 1756 \pm 384 & 53.3 \pm 8.4 \\
\text{Calcium control} & \quad 71 \pm 9 & 133 \pm 18 & 12.8 \pm 4.2 & 1886 \pm 439 & 52.0 \pm 7.3 \\
p & \quad & & & & p < 0.01 \\
\text{Pacing} & \quad 121 \pm 6 & 127 \pm 17 & 6.3 \pm 3.7 & 2133 \pm 464 & 46.9 \pm 8.0 \\
\text{Calcium pacing} & \quad 121 \pm 6 & 128 \pm 17 & 6.5 \pm 3.7 & 2404 \pm 566 & 43.7 \pm 6.1 \\
p & \quad & & & & p < 0.01 \\
\text{Control} & \quad 71 \pm 8 & 133 \pm 19 & 12.8 \pm 4.0 & 1756 \pm 384 & 53.3 \pm 8.4 \\
\text{Calcium postspacing beat} & \quad 63 \pm 10 & 136 \pm 18 & 10.0 \pm 4.0 & 2810 \pm 642 & 58.8 \pm 11.8 \\
p & \quad & & & & p < 0.05 \\
\text{Values are mean ± SD.} \\
\text{Abbreviations: HR = heart rate; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; T1 = time constant of isovolumic pressure fall (see Methods section for definition); CAD = coronary artery disease.}
\end{align*}
\]
changes in the inotropic state and is relatively insensitive to changes in preload and afterload. However, changes in LVEDP were similar during all maneuvers in both groups. This suggests that our comparisons of the changes in peak positive dP/dt between groups is valid. However, a change in ventricular compliance could result from the changes in relaxation rate, so we cannot assume that the changes in ventricular volume during pacing were exactly the same in both groups despite the comparable changes in LVEDP.

The changes in relaxation were estimated from the T₁ variations. However, relaxation of cardiac muscle is load-dependent, so before making our comparisons we had to eliminate changes in relaxation rate caused by changes in systolic pressure. The maximal rate of pressure fall is altered by these changes, and it is also likely that the whole time course of isovolumic pressure fall is affected by changes in systolic pressure, although this is still controversial. Nevertheless, in our study, such changes in systolic pressure were insignificant except during nifedipine injection (tables 2 and 3). During injection of nifedipine, systolic pressure decreased, which should reduce T₁ instead of increasing it, as we observed. Therefore, the changes in relaxation rate observed during our interventions probably were not primarily caused by changes in the loading conditions.

Using these indexes, peak positive dP/dt and T₁, a variable coupling between the contraction and relaxation phases was observed in three interventions. First, during pacing, inotropic state and relaxation rate increased in both normal subjects and CAD patients (fig. 2). Second, when nifedipine was injected during pacing, the inotropic state reverted to control levels but the relaxation was markedly prolonged (fig. 3). Third, during the postpacing beat, the inotropic state increased but the relaxation rate was prolonged in normal subjects and slightly decreased in CAD patients (fig. 4). This contraction-relaxation coupling was quantitatively different in normal subjects and in CAD patients (figs. 2–4).

A variable coupling was also observed in CAD patients during calcium injections which always increased inotropic state but, at the dose used in this study, accelerated relaxation only when pacing was associated (table 3). Calcium injection also suppressed the slight decrease in T₁ previously observed in CAD patients during the postpacing beat (fig. 4).

Clinical Implications

Clinical manifestations of congestive heart failure might partially result from an alteration in the relaxation process of the ventricle and several therapeutic interventions might improve the impaired relaxation and the patient's functional symptoms. Thus, the clinical relevance of our study is twofold. First, a prolonged relaxation can be observed in man despite a depressed, normal or even enhanced inotropic state. Further, the coupling between contraction and relaxation is abnormal in CAD. Thus, a therapeutic intervention aimed at relaxation should be cautiously adopted in each case. A calcium antagonist might improve relaxation in some types of heart disease but have deleterious

\[ \text{NORMAL SUBJECTS} \quad \text{CAD PATIENTS} \]
\[ \Delta T₁ \, \text{ms} \]
\[ \Delta \text{Peak (x)} \, \text{mmHg/s} \]

* P < 0.05 CAD vs NORMAL SUBJECTS

**Figure 3. Mean (± SEM) changes in the time constant (ΔT₁) and peak positive dP/dt (Δ peak + dP/dt) induced by nifedipine injection during atrial pacing compared with control conditions. Despite similar changes in peak positive dP/dt, T₁ was more prolonged in normal subjects than in patients with coronary artery disease (CAD).**

\[ \text{CONTROL vs CAD PATIENTS} \]
\[ \Delta T₁ \, \text{ms} \]
\[ \Delta \text{Peak (x)} \, \text{mmHg/s} \]

* P < 0.01 vs NORMAL SUBJECTS

**Figure 4. Mean (± SEM) changes in the time constant (ΔT₁) and peak positive dP/dt (Δ peak + dP/dt) observed during the postpacing beat (PPB) compared with the control conditions. Despite identical increases in peak positive dP/dt, T₁ increased in normal subjects but decreased in patients with coronary artery disease (CAD). However, when the PPB closely followed a calcium injection (PPB + Ca++.), T₁ also increased in CAD patients.**
effects in other patients. This implies that further studies are needed to elucidate the contraction-relaxation coupling in other conditions with impaired relaxation, such as hypertrophic or congestive cardiomyopathy.

Second, our data indicate that the impairment of relaxation can be the unique abnormality present in CAD patients at rest, and is probably the earliest sign of functional alteration. Repeated studies of this measurement, for example, after bypass surgery, should therefore provide a very precise means of evaluating the beneficial effects of the therapeutic interventions.

The Role of the Calcium Ion in Regulating Contraction-Relaxation Coupling

Relaxation starts when myoplasmic calcium concentration decreases because of an active calcium reuptake by the sarcoplasmic reticulum and perhaps by mitochondria and because of a calcium efflux out of the cell. The calcium efflux, based on a calcium-sodium exchange mechanism, is necessary to achieve steady-state conditions. Otherwise, calcium would accumulate into the cell.

From our results, on the basis of the changes in peak positive dP/dt (tables 2 and 3), we can assume that the total amount of calcium available for the contractile proteins has been increased above control in all but one intervention, nifedipine during pacing. Therefore, had the rate of myoplasmic calcium decrease been constant, we would have expected the rate of tension fall to become slower in most maneuvers and to be unchanged or faster during nifedipine. However, opposite results were observed except during the postpacing beat in normal subjects. In this situation, we observed a 5-msec T1 increase, a result very similar to the 4-msec increase previously reported in man during postextrasystolic potentiation.

This discrepancy between the inotropic state and the relaxation rate implies that the rate of myoplasmic calcium decrease was not constant during our maneuvers. Parmley and Sonnenblick reported similar conclusions from the changes in relaxation observed in cat papillary muscle during positive inotropic stimulations by catecholamines, paired stimulation or changes in calcium concentration. They proposed that such a discrepancy in contraction-relaxation coupling could be due to changes in the calcium gradient between myofilaments and sarcoplasmic reticulum.

Another hypothesis might be that the rate of myoplasmic calcium decrease would be controlled by the calcium influx, following a relation of sigmoid shape (fig. 5). This hypothesis could also explain the differences observed in CAD patients (figs. 2–4), provided that a slightly depressed calcium influx was postulated under basal conditions in this chronic disease. Indeed, such a small decrease in calcium influx (fig. 5) would depress the relaxation under basal conditions, allow proportionally greater improvement in relaxation rate during pacing in CAD patients than in normal subjects, and allow proportionally smaller prolongation in relaxation by nifedipine. The postulated reduction in calcium influx in CAD patients at rest might be related either to the depletion in myocardial catecholamines demonstrated in these patients or to a change in membrane permeability as recently suggested in atherosclerotic rabbits. A depletion in catecholamines would indeed decrease calcium influx by depressing the gating mechanism which controls calcium entry during the action potential.

In conclusion, the discrepancies between contraction and relaxation described in isolated preparations also exist in man. The study of left ventricular relaxation might provide information regarding the biochemical alterations in chronic CAD or cardiomyopathy.

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