EXPERIMENTAL STUDIES

Comparative Echocardiographic Study of Recovery of Diastolic Versus Systolic Function After Brief Periods of Coronary Occlusion: Differential Effects of Intravenous Nifedipine Administered Before and During Occlusion

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The effect of intravenous nifedipine (5 μg/kg) on the recovery of myocardial function after occlusion of the left anterior descending coronary artery was studied in 18 closed chest dogs. Using computer-aided analysis of two-dimensional echocardiograms, systolic and diastolic function of ischemic segments in low papillary left ventricular cross sections were characterized, respectively, as holosystolic fractional area change and early diastolic velocity of luminal area change. The time required for systolic function to return to preocclusion values after a 1 minute untreated control occlusion (n = 12) was 5 to 10 minutes, and after a 2 minute occlusion (n = 6) it was 20 to 30 minutes. When nifedipine was administered during the occlusion, recovery after a 2 minute occlusion was accelerated slightly to 10 to 15 minutes.

Recovery times of early diastolic function were substantially longer, and nifedipine effects were more pronounced. After a 1 or 2 minute control coronary occlusion, 60 to 75 minutes or 90 to 105 minutes were needed to return early diastolic function to normal levels. Nifedipine administered during a 1 or 2 minute coronary occlusion improved these recovery times to 10 to 15 minutes. When the dogs were treated with intravenous nifedipine before coronary occlusion, recovery after 1 or 2 minutes of acute ischemia was apparent as early as 2 minutes after reperfusion. Thus, intravenous nifedipine accelerates the recovery of myocardial function after brief periods of ischemia, and when administered before coronary occlusion, it assures very prompt recovery of function.

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With mounting interest in the early spontaneous progression of ischemic dysfunction and treatment of acute obstruction of coronary arteries, numerous investigations (1,2) have been aimed at improved detection and diagnostic evaluation of regional cardiac abnormalities. Whereas most studies concentrated on systolic function, more recent investigations (1–5) found that diastolic function is a more sensitive descriptor of cardiac abnormalities occurring in the early stages of ischemic heart disease, particularly when it is associated with hypertension or metabolic diseases such as diabetes mellitus. Recently, Uchiyama et al. (6) employed mechanocardiology to study angina pectoris in the presence of normal coronary arteries and reported that even small abnormalities in cardiac function could be detected by the noninvasive method in early diastole, while systolic function appeared unaltered. Similarly, Smalling et al. (3) demonstrated with myocardial sonomicrometers in regionally ischemic dogs that early diastolic function was a more sensitive indicator of contractile derangements than were the usual systolic indexes of function.

In view of these previously published reports, we undertook a two-dimensional echocardiographic study of early diastolic as well as systolic left ventricular function during and after brief periods of coronary artery occlusion in dogs. The short duration of acute regional ischemia assured min-
imal permanent damage to the myocardial muscle, a condition that may be representative of coronary spasm or brief intracoronary balloon occlusions during percutaneous transluminal coronary angioplasty. Nifedipine, a calcium channel antagonist, was also administered at different times relative to the coronary occlusion and reperfusion to evaluate its effects, primarily with respect to reperfusion recovery of function.

**Methods**

**Experimental preparation.** Eighteen healthy mongrel dogs, weighing 19.5 to 34.0 kg (mean 26.0), were anesthetized intravenously with sodium pentobarbital (30 mg/kg body weight) 20 minutes after premedication with intramuscular morphine sulfate (1.2 mg/kg). Heparin (10,000 IU) was given intravenously before instrumentation, and supplemented with 3,000 IU every 2 hours. Pentobarbital (3 mg/kg intravenously) was added whenever necessary.

Catheters were introduced through the femoral arteries and connected to Statham P23Db transducers for measurement of aortic root and left ventricular pressures. A Swan-Ganz 7 French thermodilution catheter was placed in the pulmonary artery for cardiac output measurement (American Edwards Laboratories). Under fluoroscopic control in the closed chest, a 2 French balloon catheter was introduced into the left main coronary artery by way of the left carotid artery. After coronary angiography, the catheter balloon was positioned immediately distal to the first diagonal branch of the left anterior descending coronary artery.

**Hemodynamic measurements.** Hemodynamic data recorded included heart rate, systolic and diastolic mean blood pressures, peak first derivative of left ventricular pressure (max dP/dt) and left ventricular end-diastolic pressure. Stroke volume was derived from thermodilution cardiac output and heart rate. Total peripheral resistance was calculated from mean blood pressure and cardiac output. All pressure tracings were recorded on an Electronics for Medicine V-12 recorder at a paper speed of 100 mm/s.

**Two-dimensional echocardiographic measurements.** Two-dimensional echocardiography (Advanced Technology Laboratories, model MK300LX ultrasound system) was used for sequential measurements of global and regional left ventricular function. Short-axis cross sections at a low papillary level were obtained in each dog using a 3.0 MHz transducer (Advanced Technology Laboratories model 722A). Images were recorded with a Panasonic NV8200 videocassette recorder for subsequent measurements.

Sectional and segmental intraluminal systolic fractional area change (FAC%) as well as mean velocity of early diastolic luminal area change (VLAC) were calculated as follows (Fig. 1):

$$\text{FAC\%} = \frac{\text{EDA} - \text{ESA}}{\text{EDA}} \times 100,$$

where EDA (cm$^2$) = end-diastolic area (largest luminal area), ESA (cm$^2$) = end-systolic area (smallest luminal area), FAC% = systolic fractional area change, and:

$$\text{VLAC (cm}^2/\text{s}) = \frac{\text{RFA} - \text{ESA}}{\text{EDP}},$$

where RFA (cm$^2$) = luminal area at the peak of rapid filling (based on left ventricular pressure tracing) and EDP (seconds) = early diastolic period (between ESA and RFA points).

Wall thinning (WTh%) was also calculated as:

$$\text{WTh\%} = \frac{\text{WThx} - \text{WThes}}{\text{WThes}},$$

where WThx = wall thickness at the peak of rapid filling or at end-diastole and WThes = end-systolic wall thickness.

A left ventricular pressure tracing was always recorded simultaneously with the two-dimensional echocardiographic image. The ratio of the RR interval on the electrocardiogram to the period from the onset of the QRS complex to the subsequent peak rapid filling wave on the left ventricular pressure tracing was calculated. The number of videotape frames per cardiac cycle was established, and timing in relation to this ratio was used to obtain the particular videotape frame corresponding to the rapid filling point. While two-dimensional echocardiographic imaging was carried out at a rate of 30 frames/s, frames on the tape were spaced 33.3 ms apart, and the maximal error encountered in this timing sequence would be expected to be less than 33.3 ms.

**For detailed segmental mapping,** a low papillary left ventricular cross section was subdivided counterclockwise into eight segments using standardized indexing and a fixed
interobserver reproducibility of the echocardiographic measurements was studied in terms of short-axis cross-sectional and segmental luminal areas, as well as wall thickness, at end-systole and end-diastole derived from videoscreen stop frames. Additionally, it was examined with respect to designation of the early diastolic peak rapid filling point taken from left ventricular pressure tracings. The number of videotape frames between the end-systolic or end-diastolic luminal areas in the echocardiographic images and the onset of the QRS complex on the electrocardiogram was counted by two independent observers to examine the reproducibility of designating end-systolic or end-diastolic frames.

Experimental protocol. The proximal left anterior descending coronary artery was briefly occluded in 18 dogs. The duration of intracoronary balloon occlusion was 1 minute in 12 dogs and 2 minutes in 6 dogs. Each of the 18 dogs had a preocclusion control measurement followed by two successive coronary occlusions, randomized into one with and one without nifedipine administration. Occlusion was always followed by reperfusion through deflation of the occlusive balloon, and the recovery of left ventricular function was studied during the postreperfusion period. The studies were subdivided as follows:

Dogs with a 1 minute occlusion (n = 12) had 12 untreated occlusion studies (series A), 6 studies with intravenous nifedipine during occlusion (series B) and 6 studies with intravenous nifedipine before the occlusion (series C).

Dogs with a 2 minute occlusion (n = 6) had 6 untreated occlusion studies (series X) and 6 studies with intravenous nifedipine during occlusion (series Y).

Nifedipine (5 μg/kg bolus) was administered intravenously during the occlusion 10 seconds before reperfusion (series B and Y) or just before coronary occlusion (series C). To assure that the sequential occlusions would be at the same level of the left anterior descending coronary artery, the catheter balloon was not withdrawn until the second reperfusion was completed.

Sequential hemodynamics and two-dimensional echocardiographic measurements were obtained in all dogs before occlusion, during occlusion before reperfusion, and at 2, 5, 10, 15, 20, 30, 40, 50, 60, 75 and 90 minutes after reperfusion. For the 2 minute coronary occlusion (series X and Y), an additional two measurements (at 105 and 120 minutes postreperfusion) were obtained. Cardiac output was measured before occlusion and at 2, 10, 20, 30, 40, 60 and 90 minutes after reperfusion, and also at 120 minutes in the 2 minute occlusion (series X and Y).

Statistical analysis. The effects of untreated or treated coronary artery occlusion and reperfusion on hemodynamic variables and two-dimensional echocardiographic measurements were compared among the groups using Student's unpaired t test (series A versus B and C, or series X versus Y). The sequential alterations in an individual series were also compared with the control level using Student's paired t test. Analysis of variance was also performed within each group when appropriate for confirmation. All data are expressed as mean values ± standard error of the mean.

Results

Hemodynamic changes (Table 1). There were no significant differences in preocclusion hemodynamic variables between treated and untreated dogs with either 1 or 2 minutes of occlusion. Positive and negative max dP/dt decreased in all the series during 1 or 2 minutes of occlusion. Mean blood pressure also decreased during the 1 minute occlusion preceded by nifedipine administration, but this pressure returned to normal as early as 2 minutes postreperfusion.

In all treated series, total peripheral resistance was found to be reduced 2 minutes after reperfusion, but returned to normal levels at the 10 minute reperfusion measurement. Similarly, nifedipine given during a 1 minute occlusion was found to temporarily increase heart rate and decrease left ventricular stroke volume at 2 minutes after reperfusion, with these measurements returning to normal, respectively, at 5 and 10 minutes after reperfusion. Apart from such transient variations, none of the hemodynamic factors exhibited significant permanent alteration until the final experimental measurement. Duration of early diastole did not change significantly throughout the experiment (Table 1), ranging from 0.37 to 0.50 second.

Reproducibility of echocardiographic measurements and timing of rapid filling. All interobserver echocardiographic measurement correlations showed high values (r = 0.94 to 0.98), except for myocardial wall thickness measurements which had an observer to observer correlation of 0.84.

Two-dimensional echocardiographic study of segmental function. Figure 2 illustrates the time course of early diastolic function before and during coronary occlusion as well as after reperfusion for eight individual segments of the low papillary short-axis cross section. The most ischemic segment was judged to be the one that exhibited the most prolonged reperfusion recovery. The most pronounced ischemic derangement was noted in segment 2, the low papillary short-axis cross section. The most ischemic segment was judged to be the one that exhibited the most prolonged reperfusion recovery. The most pronounced ischemic derangement was noted in segment 2, the low papillary anterolateral aspect of the left ventricle.

Functional recovery time after a 1 or 2 minute coronary occlusion. Table 2 lists data on reperfusion recovery to preocclusion levels. After a 1 minute control occlusion (series A), recovery time of ischemic segment mean velocity of early diastolic luminal area change was 60 to 75 minutes,
Table 1. Hemodynamic Data in 18 Dogs

<table>
<thead>
<tr>
<th></th>
<th>1 Minute LAD Occlusion</th>
<th>2 Minute LAD Occlusion</th>
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<tbody>
<tr>
<td></td>
<td>Before Occlusion</td>
<td>During Occlusion</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>83.3 ± 7.1</td>
<td>93.6 ± 6.1</td>
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<tr>
<td>N during occ</td>
<td>83.5 ± 9.1</td>
<td>114.1 ± 7.2</td>
</tr>
<tr>
<td>N before occ</td>
<td>90.5 ± 6.4</td>
<td>120.0 ± 7.9*</td>
</tr>
<tr>
<td>Early D duration</td>
<td></td>
<td></td>
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<tr>
<td>(second)</td>
<td></td>
<td></td>
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<tr>
<td>Control untreated occ</td>
<td>0.46 ± 0.03</td>
<td>0.48 ± 0.03</td>
</tr>
<tr>
<td>N during occ</td>
<td>0.45 ± 0.04</td>
<td>0.45 ± 0.02</td>
</tr>
<tr>
<td>N before occ</td>
<td>0.44 ± 0.06</td>
<td>0.48 ± 0.04</td>
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<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
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<tr>
<td>Control untreated occ</td>
<td>88.1 ± 4.4</td>
<td>79.0 ± 4.3</td>
</tr>
<tr>
<td>N during occ</td>
<td>96.6 ± 7.7</td>
<td>91.1 ± 9.8</td>
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<tr>
<td>N before occ</td>
<td>80.8 ± 3.1</td>
<td>59.3 ± 6.1*</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td></td>
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<tr>
<td>Control untreated occ</td>
<td>4.2 ± 1.9</td>
<td>4.4 ± 0.8</td>
</tr>
<tr>
<td>N during occ</td>
<td>3.9 ± 1.1</td>
<td>3.3 ± 0.7</td>
</tr>
<tr>
<td>N before occ</td>
<td>2.7 ± 0.4</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>+dP/dt x 10³ (mm Hg)</td>
<td>1.76 ± 0.10</td>
<td>1.39 ± 0.10*</td>
</tr>
<tr>
<td>N during occ</td>
<td>1.83 ± 0.17</td>
<td>1.45 ± 0.22*</td>
</tr>
<tr>
<td>N before occ</td>
<td>1.70 ± 0.11</td>
<td>1.28 ± 0.14*</td>
</tr>
<tr>
<td>−dP/dt x 10³ (mm Hg)</td>
<td>1.61 ± 0.08</td>
<td>1.40 ± 0.24*</td>
</tr>
<tr>
<td>N during occ</td>
<td>1.71 ± 0.15</td>
<td>1.45 ± 0.16*</td>
</tr>
<tr>
<td>N before occ</td>
<td>1.76 ± 0.26</td>
<td>1.17 ± 0.17*</td>
</tr>
<tr>
<td>Stroke volume</td>
<td></td>
<td>10 Min</td>
</tr>
<tr>
<td>Control untreated occ</td>
<td>30.0 ± 0.1</td>
<td>30.7 ± 2.8</td>
</tr>
<tr>
<td>N during occ</td>
<td>29.8 ± 4.2</td>
<td>19.1 ± 2.3*</td>
</tr>
<tr>
<td>N before occ</td>
<td>23.7 ± 3.0</td>
<td>24.5 ± 2.1</td>
</tr>
<tr>
<td>TPR (dynes*s/cm⁻⁵)</td>
<td>2.7 ± 0.1</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>N during occ</td>
<td>3.1 ± 0.4</td>
<td>2.5 ± 0.4†</td>
</tr>
<tr>
<td>N before occ</td>
<td>3.1 ± 0.2</td>
<td>2.1 ± 0.2*</td>
</tr>
</tbody>
</table>

*p < 0.01, †p < 0.02 relative to preocclusion level. Values are mean ± standard error of mean. D = diastolic; LAD = left anterior descending coronary artery; LVEDP = left ventricular end-diastolic pressure; N = nifedipine; occ = occlusion; TPR = total peripheral resistance.

Figure 2. Illustration in a particular dog of the time course of early diastolic function (mean velocity of luminal area change [VLAC]) in each of the eight segments of a left-ventricular short-axis cross section. In this case, segment 2 was judged to be the most ischemic because it exhibited the most profound ischemic dysfunction and the most prolonged recovery after reperfusion. C = control (preocclusion) level; O = during occlusion.
and after a 2 minute occlusion (series X) it was 90 to 105 minutes. In contrast, corresponding ischemic segment systolic function (fractional area change) appeared to recover fully within 5 to 10 minutes (n = 12) after a 1 minute occlusion and within 20 to 30 minutes (n = 6) after a 2 minute occlusion. Differences between early diastolic and systolic function recovery were statistically significant (p < 0.05 by paired t test), and the significance was also confirmed by analysis of variance. Percent wall thinning during early diastole after both a 1 (n = 6) and a 2 minute (n = 6) occlusion showed almost the same reperfusion recovery time of 40 to 50 minutes. With intravenous nifedipine administration during coronary occlusion, reperfusion return of ischemic segment early diastolic velocity of luminal area change, fractional area change and percent wall thinning (n = 6) was generally accelerated, except for ischemic segment fractional area change in the case of a 1 minute occlusion.

In terms of the whole cross section, early diastolic function recovery times after untreated brief coronary occlusions were shorter than those for the ischemic segment alone, that is, 5 to 10 minutes after a 1 minute occlusion and 15 to 20 minutes after a 2 minute occlusion. This could be the result of a temporary increase in remote nonischemic segment early diastolic function during the postreperfusion period. Yet, sectional fractional area change exhibited a similar recovery to that for the ischemic segment after untreated occlusions, presumably because of no change in the nonischemic zone (Fig. 4b). Comparing holodiastolic and early diastolic ischemic segment wall thinning, the former exhibited a shorter recovery time after 1 and 2 minute coronary occlusions.

**Recovery of early diastolic function with nifedipine administration (Fig. 3).** Figure 3A compares the time course of ischemic segment velocity of early diastolic luminal area change recovery after a 1 minute occlusion in untreated control occlusions and for intravenous nifedipine administration during or before occlusion. Before occlusion, the velocity of luminal area change levels in the three series (series A, B and C) was, respectively, 2.05 ± 0.15, 2.21 ± 0.32 and 1.66 ± 0.12 cm²/s. This early diastolic index of function of the ischemic segment decreased maximally to −0.30 ± 0.17, −0.92 ± 0.36 and −0.66 ± 0.37 cm²/s either during the occlusion or after reperfusion. Recovery times to preocclusion levels in these series were found to be 60 to 75, 10 to 15 and 2 minutes, respectively.

For the whole section, velocity of luminal area change (Fig. 3B) decreased maximally from 18.75 ± 1.53 to 10.54 ± 1.22 cm²/s in series A, from 19.48 ± 2.96 to 6.63 ± 2.31 cm²/s in series B and from 15.95 ± 1.25 to 6.66 ± 2.43 cm²/s in series C. Corresponding recovery times to preocclusion levels were 5 to 10, 2 to 5 and 2 minutes, respectively.

**Recovery of systolic function with nifedipine administration (Fig. 4).** Figure 4A shows the time course of ischemic segment fractional area change recovery for the three series. Preocclusion measurements were 36.2 ± 2.0, 38.1 ± 3.5 and 36.1 ± 2.1% in series A, B and C, respectively. These values decreased maximally to 5.9 ± 3.7, 6.0 ± 5.7 and 1.5 ± 3.8%, respectively, during occlusion or reperfusion. The respective recovery times to preocclusion levels were 5 to 10, 5 to 10 and 2 minutes.

Figure 4B shows the time course of recovery for the whole section fractional area change in the three groups. Systolic function decreased maximally from 38.1 ± 0.9 to 23.4 ± 1.3, 38.8 ± 2.4 to 18.3 ± 4.5 and 38.5 ± 1.8 to 22.4 ± 2.8%, respectively. Recovery times were 5 to 10, 2 to 5 and 2 minutes, respectively.

**Recovery of diastolic wall thinning.** After a 1 minute occlusion, ischemic segment early diastolic percent wall thinning in series A, B and C decreased maximally from 30.1 ± 2.6 to 8.4 ± 1.9, from 30.4 ± 4.6 to 8.4 ± 3.3 and from 33.8 ± 4.1 to 5.6 ± 3.1%, respectively. Recovery times to preocclusion levels were 40 to 50, 2 to 5 and 2 minutes, respectively. Ischemic segment holodiastolic percent wall thinning before occlusion was 39.7 ± 2.3.
39.8 ± 2.7 and 30.4 ± 3.3% in series A, B and C and decreased maximally to 17.8 ± 3.8, 11.7 ± 4.7 and 4.5 ± 5.0%, respectively, during a 1 minute coronary occlusion or reperfusion. Recovery times to preocclusion levels were 10 to 15, 2 to 5 and 2 minutes, respectively.

Changes and recovery of function in regions remote from the ischemic segment. The remote segment was defined as the one that exhibited the most hyperkinetic state after reperfusion, based on measurements of velocity of early diastolic luminal area change. Changes in the latter as well as in fractional area change exhibited no differences among series A, B and C. Fractional area change failed to indicate a hyperkinetic state in any of the series, yet mean velocity of early diastolic luminal area change showed hyperkinetic values of 120 to 160% in all the series. These results for the remote segment were in accord with the lack of difference in the recovery times between the ischemic segment and whole section fractional area change, whereas mean velocity of early diastolic luminal area change did exhibit differences in recovery between the ischemic segment and the whole section.

Discussion

To examine the effects of a calcium channel antagonist on the time course of recovery of regional left ventricular function after brief coronary artery occlusion, nifedipine was administered intravenously in a closed chest dog model either before or during a 1 or 2 minute occlusion of the left anterior descending coronary artery. Systolic and diastolic function was evaluated by means of two-dimensional echocardiography low left ventricular short-axis cross section, which was further subdivided into eight segments by a stan-
standardized computer-assisted method. Both systolic and diastolic indexes of segmental and whole sectional cardiac function were used to analyze posts ischemic restoration of function and the effects of different times of nifedipine administration on the course of coronary occlusion and reperfusion.

**How rapidly does function normalize after brief coronary occlusion?** It has been widely assumed that after a brief temporary coronary artery occlusion (up to 10 minutes), ischemic segment function recovers significantly and rapidly toward normal preocclusion levels (8–10). Nevertheless, questions have been raised as to the appropriate analysis of the true course of reperfusion recovery of ischemic regional function.

Our study of ischemic segments during untreated brief left anterior descending coronary artery occlusion showed that early diastolic function decreased after a 1 minute occlusion from $2.05 \pm 0.15$ to $-0.30 \pm 0.17 \text{ cm}^2/\text{s}$, and after a 2 minute occlusion from $2.14 \pm 0.41$ to $-0.14 \pm 0.45 \text{ cm}^2/\text{s}$. Thereafter, it took 60 to 75 minutes and 90 to 105 minutes of reperfusion, respectively, to return function to preocclusion levels. In contrast, the more commonly employed systolic index of ischemic segment function recovered more rapidly. After a 1 or 2 minute occlusion, fractional area change decreased from $36.2 \pm 2.0$ to $5.9 \pm 3.7\%$ or from $36.9 \pm 4.0$ to $14.5 \pm 3.3\%$, respectively. Reperfusion recovery periods varied but were significantly shorter for systolic than for diastolic function.

Heyndrickx et al. (11) studied the recovery of ischemic segment systolic velocity of shortening after a 5 minute left anterior descending coronary artery occlusion and reported a reperfusion recovery time exceeding 3 hours. Lange et al. (12) demonstrated no cumulative effects after repeated 5 minute occlusions with 30 minute interim reperusions. We
did not study such cumulative effects in terms of early diastolic function, although we would expect substantially longer recovery times than are found with simultaneously measured systolic function.

Abnormalities in early diastolic rapid filling phase. The peak rapid filling wave during early diastole is readily seen in left ventricular pressure tracings, and was used to indicate the end of rapid filling. Some investigators (13–15) concluded that this point on the left ventricular pressure curve corresponds to the point of inflection of the cyclic changes in left ventricular diameter or volume caused by the relaxation phase of the cardiac cycle. Although heart rate affects the length of diastole and can decrease stroke volume, our data show that the duration of early diastole (rapid filling), ranging from 0.37 to 0.50 second, was almost consistent throughout the course of the experiments. This was confirmed by Sheehan et al. (16), who showed that the ventricular volume increase measured in early diastole remained essentially identical at both a high and a low heart rate. Oldershaw et al. (15) studied the relation between heart rate and rapid filling phase and found that heart rate affected the late diastolic phase, but has very little effect on rapid filling. Smalling et al. (3) evaluated early diastolic function in terms of the first one-third of diastole, but any fixed fraction of diastole would, of course, depend on the prevailing heart rate, which in turn influences the left ventricular stroke volume. In contrast, both the duration of the rapid filling phase and its volume changes are found to be relatively constant, so that the mean velocity of luminal area change throughout the course of the experiments. This was confirmed by Sheehan et al. (16), who showed that the ventricular volume increase measured in early diastole remained essentially identical at both a high and a low heart rate. Oldershaw et al. (15) studied the relation between heart rate and rapid filling phase and found that heart rate affected the late diastolic phase, but has very little effect on rapid filling. Smalling et al. (3) evaluated early diastolic function in terms of the first one-third of diastole, but any fixed fraction of diastole would, of course, depend on the prevailing heart rate, which in turn influences the left ventricular stroke volume. In contrast, both the duration of the rapid filling phase and its volume changes are found to be relatively constant, so that the mean velocity of luminal area change is minimally influenced by heart rate and can be satisfactorily applied as an index of early diastolic function of the left ventricle.

Nifedipine administration before versus during coronary occlusion. After the early extensive studies of Fleckenstein et al. (17), calcium channel antagonists have been applied in numerous settings, including coronary heart disease (18), pulmonary hypertension (19), essential hypertension (20) and hypertrophic cardiomyopathy (21). Myocardial effects of a calcium channel antagonist during coronary artery occlusion and reperfusion are complex and not yet fully defined. A number of investigations (22–24) showed calcium deposition in myocardial cells after a 30 minute coronary occlusion followed by reperfusion; however, no data exist about any possible myocardial calcium deposits after very short coronary occlusions and subsequent reperfusion.

In our study with a 1 or 2 minute occlusion, nifedipine significantly accelerated the reperfusion recovery of both systolic and early diastolic regional function. The reasons that we observed a more accelerated recovery with preocclusion than with postocclusion nifedipine administration remain unclear. The time difference for administration of nifedipine was only 1 minute, yet the difference in recovery times was consistently significant (3 to 8 minutes for ischemic segment systolic function and 8 to 13 minutes for ischemic segment early diastolic function). In our study, the first full set of postreperfusion measurements was obtained 2 minutes after reperfusion, but we also recorded two-dimensional echocardiographic images continuously during the coronary occlusion and the first 5 minutes of reperfusion. Visually, recovery of systolic and diastolic function with nifedipine given before the coronary occlusion occurred 20 or 30 seconds after reperfusion. Thus, differences in recovery time between nifedipine administration before and during occlusion may be even larger than just indicated.

One of the well known effects of nifedipine on the myocardial cell is its blocking of slow inward currents, which results in smooth muscle relaxation. Nifedipine also causes vasodilation and hypotension, and this produces a hyper-sympathetic activity by way of the baroreceptor reflex. Furthermore, it has been observed that the level of plasma catecholamines and plasma renin activity increases after nifedipine administration (20) and that beta-adrenergic stimulation could easily prevent this sympathetic nifedipine-induced hyperactivity (25). Another effect of nifedipine relates to myocardial blood flow. In ischemia with a 25 mm Hg residual diastolic perfusion pressure distal to a complete coronary artery occlusion, Weintraub et al. (26) reported that intravenous or intracoronary nifedipine administration did not affect myocardial blood flow in the center of the ischemic zone, in either the subendocardial or the subepicardial layer. This would tend to exclude increased collateral blood flow as a cause of the nifedipine-induced accelerated recovery. Other investigators (27,28) attributed the protective effect of nifedipine during ischemia and subsequent reperfusion to a reductant of calcium (Ca2+) accumulation in mitochondria and a reserve oxidative phosphorylating activity. Reibel et al. observed a slow decrease in adenosine triphosphate (ATP) and a slow increase in adenosine diphosphate (ADP) after a coronary occlusion, yet a prompt decrease in creatine phosphate, reaching the lowest level 3 minutes after occlusion (29). These results would also preclude the possibility that prolonged recovery is due to insufficient adenosine triphosphate. Hess et al. (30), using ultrasound crystals, demonstrated an increased ischemic myocardial wall stiffness after a 1 or 2 minute coronary artery occlusion. This might be another possible reason for persisting dysfunction after reperfusion after even brief (1 or 2 minutes) coronary occlusion.

Limitations of current study methods. One of the limitations of our methods is that we performed echocardiographic measurements in only one cross section at the low papillary level of the left ventricle. The degree of ischemia after a specific site coronary artery occlusion depends on preexisting collateral vessels and will vary for differing levels of the left ventricle, presumably also resulting in differing reperfusion recovery times.
Implications and proposed studies. Noninvasive detection of ischemic regional function abnormalities as an index of local myocardial damage is clearly important and has been increasingly applied. In this study, early diastolic ischemic segment function exhibited a distinctly longer reperfusion recovery time (60 to 75 minutes after a 1 minute occlusion and 90 to 105 minutes after a 2 minute occlusion) than did systolic segmental fractional area change (5 to 10 minutes for a 1 minute occlusion and 20 to 30 minutes for a 2 minute occlusion). Thus, early diastolic function of the ischemic myocardial segment appears to be a better indicator of abnormalities caused by brief coronary artery obstructions and also provides a better description of the sequential spontaneous or treated reperfusion recovery. It remains to be established whether the accelerated recovery of both systolic and diastolic function that we observed with nifedipine is associated with improvements in myocardial salvage. Although the effects of repeated brief coronary occlusions also remain unclear, treatment for each of the occlusive episodes may be necessary if early diastolic dysfunction is encountered, preferably a treatment that does not depress myocardial reserve.

Conclusions. Ischemic segment early diastolic function (mean velocity of luminal area change) and systolic function (systolic fractional area change) were evaluated with two-dimensional echocardiography during a 1 or 2 minute occlusion of the left anterior descending coronary artery, and also after reperfusion. After reperfusion, early diastolic dysfunction persisted up to 105 minutes as compared with much shorter systolic functional abnormalities. Nifedipine was administered either before or during the occlusion for treatment of the postreperfusion dysfunction. We concluded that: 1) early diastolic function is better than systolic function as an index for the study of ischemic regional function during the postreperfusion recovery period, 2) nifedipine generally accelerated the functional recovery time of the ischemic segment, and 3) nifedipine administration before occlusion led to the most rapid reperfusion recovery of regional function to preocclusion levels.

References


