Comparative Effects of Pacing-Induced and Flow-Limited Ischemia on Left Ventricular Function

Robert J. Applegate, MD, Richard A. Walsh, MD, and Robert A. O'Rourke, MD

We compared left ventricular (LV) myocardial blood flow and function accompanying severe demand ischemia (rapid atrial pacing in the presence of critical bilateral coronary stenoses) and supply ischemia (complete bilateral coronary occlusion) of the same ischemic regions in 14 pentobarbital-anesthetized dogs. Pacing-induced ischemia resulted in pronounced reductions in average regional epicardial blood flow (0.8±0.4 vs. control 1.2±0.4 [±SD] ml/g/min, p<0.05) and endocardial blood flow (0.4±0.1 vs. control 1.3±0.3 ml/g/min, p<0.05). More severe reductions in average regional epicardial and endocardial blood flow were seen after bilateral coronary occlusion (BCO) (0.3±0.3 and 0.1±0.1 vs. control 1.3±0.3 ml/g/min, p<0.05, respectively). Hemodynamics of postpacing ischemia (PPI) were consistently characterized by systolic impairment including depressed systolic contractile performance ([(+)]dP/dt$_{max}$ 1.281±442 vs. control 2.173±775 mm Hg/sec, p<0.05), ventricular dilation (left ventricular [LV] end-diastolic dimension [EDD] 47.6±7.8 vs. control 44.7±8.6 mm, p<0.05), and an increase in LV end-diastolic pressure (EDP) (14.4±2.8 vs. control 4.2±2.8 mm Hg, p<0.05). Abnormalities in early and late diastolic function with PPI included increased time constant of isovolumic relaxation (78.0±40.4 vs. control 46.4±20.5 msec, p<0.05) and increased chamber stiffness (1.9±0.77 vs. control 0.81±0.55 mm Hg/mm, p<0.05), respectively. The LV diastolic pressure-dimension relation, however, shifted upward and to the right in eight of nine animals, whereas an upward shift was observed in only one animal. Thus, in this model of postpacing ischemia, we observed contractile failure and passive changes in diastolic function. Alterations in ventricular function occurred consistently earlier and to a greater extent during BCO than PPI, including higher LVEDP (25.3±8.1 vs. 14.9±6.6 mm Hg, p<0.05), greater ventricular dilation (ΔLVEDD 4.9±2.5 vs. 3.5±2.8 mm, p<0.05), and reduced minor-axis dimension shortening (3.3±3.1% vs. 6.5±3.6%, p<0.05). To detect potential qualitative differences in ventricular function between the two types of ischemia, we evaluated hemodynamics at comparable loading conditions (30 seconds to 1 minute of BCO). Impairment in systolic function was similar, and abnormalities in early and late diastolic function were qualitatively similar with PPI and the early phase of BCO, including equivalent prolongation of the time constant of isovolumic relaxation (78.0±40.4 and 72.2±30.6 msec, p=NS), elevation in minimal LV diastolic pressure (5.6±4.4 and 4.6±2.6 mm Hg, p=NS), and shifts in the LV diastolic pressure-dimension relation. Thus, although bilateral coronary occlusion produced quantitatively more extensive ischemia than a comparable duration of pacing-induced ischemia, abnormalities in systolic and diastolic function were qualitatively similar during a severe form of demand ischemia. Therefore, the ventricular response to ischemia does not simply depend on whether supply or demand ischemia is present but on a complex interaction between the duration, extent and severity, and type of ischemia elicited. (Circulation 1990;81:1380–1392)

Myocardial ischemia can result from increased myocardial oxygen demand in the presence of critical narrowing of a coronary artery ("demand ischemia") or by reducing coronary flow ("supply ischemia"). Diastolic dysfunction including impaired isovolumic relaxation and

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decreased left ventricular passive chamber compliance has been considered the primary hemodynamic abnormality during demand ischemia, whereas supply or flow-limited ischemia is typically associated with primary systolic contractile impairment, passive increases in end-diastolic pressure, and increased chamber compliance.1–8 Two recent experimental studies have directly compared the effects of supply and demand ischemia on ventricular function in the anesthetized dog.9,10 They observed an upward shift in the diastolic pressure–segment length relation immediately after cessation of pacing in the presence of bilateral coronary stenoses (demand ischemia) and a rightward shift during complete coronary artery occlusion, indicating that pacing-induced ischemia produced a decrease, whereas coronary occlusion caused an increase in left ventricular (LV) chamber compliance in the same dog. These studies concluded that supply and demand ischemia had intrinsically different effects on myocardial ventricular function and suggested that the basic pathophysiological mechanisms of these types of ischemia differed.

The ventricular response during ischemia depends on a complex relation between the resting contractile state, the rate and extent of substrate limitation, waste product elimination, and interaction with nonischemic areas.1,11 Significant differences in the ventricular response to supply and demand ischemia have been ascribed to basic differences in the type of ischemia in previous studies using the “angina physiology” model of demand ischemia.1,9,10,12 Alternatively, these abnormalities might have been significantly influenced by differences in the severity of the ischemia as well as differences in the interaction between ischemic and nonischemic areas. Momomura et al12 reported that demand ischemia was accompanied by less severe reductions in myocardial blood flow, myocardial pH, and creatine phosphate than a comparable duration of supply ischemia. These metabolic consequences might have been because of less severe ischemia during demand ischemia than supply ischemia. Additionally, regions supplied by both the left anterior descending (LAD) and left circumflex (LCx) coronary arteries were included during demand ischemia; however, only the LAD region was included during supply ischemia creating differences in the extent of myocardial ischemia and relation between ischemic and nonischemic areas during supply and demand ischemia.

To address these points, we developed a reversible model of bilateral coronary flow obstruction in the anesthetized dog to allow hemodynamic comparisons of the same ischemic myocardial regions during both pacing-induced and flow-limited ischemia. We hypothesized that supply and demand ischemia represented progressive imbalances in myocardial oxygen supply relative to demand and that previous differences represented variations in the severity of the ischemia and not intrinsic differences in the type of ischemia. We tested this hypothesis by evaluating pacing-induced ischemia that resulted in a more severe degree of ventricular dysfunction than has been previously reported and comparing it with supply ischemia involving the same ischemic area.

Methods

Animal Preparation

Fourteen healthy mongrel dogs (20–30 kg) were surgically instrumented for physiological monitoring by methods previously described for this laboratory.13,14 After premedication with xylazine and pentobarbital sodium (7–10 mg/kg i.v.), endotracheal intubation was accomplished and anesthesia maintained with pentobarbital sodium (1–2 mg/kg) as needed during instrumentation and throughout the experimental protocol. Respiration was maintained during the study with a Bird respirator (15 cc/kg) (Bird Electronic Corp., Cleveland, Ohio). Oxygen saturation and pH were monitored periodically throughout the study and adjusted to keep values within the physiological range. Instrumentation was performed through a left thoracotomy. Polyvinyl 16-gauge catheters were implanted in the descending aorta, left atrium, right ventricle (RV), and apex of the LV. A solid-state micromanometer pressure transducer (P-18, Konigsberg Instruments, Inc., Pasadena, California) was also implanted in the apex of the LV. Pacing electrodes were sutured to the left atrium to permit rapid atrial pacing. Two 5-MHz piezoelectric crystals (4 mm in diameter) were placed on the endocardium across the LV anteroposterior minor axis in the central ischemic zones of both the LAD and LCx coronary arteries for continuous measurement of LV internal dimension and global percentage of shortening. Miniature 2-mm subendocardial ultrasonic segment gauge pairs for measuring regional segment lengths and shortening were implanted in ischemic areas perfused by the LAD and LCx coronary arteries. The regional ultrasonic crystal pairs were aligned perpendicular to the long axis and parallel to circumferential fibers of the LV wall, close to the endocardium as described previously for this laboratory.13,14

Polyvinyl circumferential hydraulic occluders (5–7 mm wide) were constructed to allow reversible partial or complete occlusion of the coronary artery distal to the occluders. The proximal portions of the LAD distal to the first septal artery and LCx coronary artery were exposed, the occluders placed around the coronary arteries, and secured in place. Obstruction of the coronary arteries in the deflated position was carefully prevented. A diagrammatic representation of the study model is shown in Figure 1. The pericardium was widely incised and left open throughout the study. Three of the nine animals were instrumented 2 weeks before experimentation and were studied under pentobarbital anesthesia but with closed chest and with pericardia unopposed. Results
from these three closed-chest animals were similar to the open-chest preparations, and the data were, therefore, pooled. This protocol received previous approval of our AALAC-approved lab animal research committee.

Data Collection

Studies were performed with the dog lying on the right side in a hammock. To avoid respiratory variation in transmural pressure, hemodynamic data were collected at end expiration in three dogs and during posthyperventilation apnea in the remainder of the dogs. In any single dog, hemodynamics were collected during the same phase of respiration.

The solid-state micromanometers were checked and calibrated before use with a standard mercury manometer. Before the study, the LV, the RV, and the aortic catheters were connected to Statham P23dB external pressure transducers (Gould Inc., Glen Burnie, Maryland) precalibrated with a mercury manometer using the vertebral column at atmospheric pressure as the zero (Z) reference point. Throughout the study, zero drift was repeatedly checked. Zero drift of the micromanometer catheter was corrected by matching the LV end-diastolic pressure (EDP) signal to the LVEDP measured simultaneously through the LV catheter. The first derivative of LV pressure was obtained electronically from the micromanometer signal using a resistance-capacitance circuit with a linear frequency response to 70 Hz and 3 dB down at 100 Hz. Mean aortic pressure was derived electronically. The transit time of the 5-MHz ultrasonic crystals and the 2-mm regional segment crystal pairs was measured with a multichannel sonomicrometer (Schuessler and Associates, San Diego, California) and was converted to distance, assuming a constant velocity of sound in blood of 1.55 m/sec. High-fidelity LV pressure, the first derivative of LV pressure (dp/dt), RV pressure, aortic pressure, the LV minor-axis dimension, apical and basal regional segment lengths, and a surface electrocardiogram were recorded on an eight-channel forced-ink pen oscillograph (Beckman Instruments, Inc., Fullerton, California) at a paper speed of 25 mm/sec with an average of 15–25 consecutive cardiac cycles recorded. The analog signals were also digitized with an on-line analog-to-digital converter system (IBM PC AT) at 5-msec intervals and stored on floppy disks for off-line analysis with software developed in our laboratory.

Data Analysis

Data were analyzed by means of computer algorithm. End-diastolic minor-axis dimension and segment length were defined as the distance between crystal pairs at the Z point of the high-fidelity LV pressure signal, or at the peak of the R wave on the electrocardiographic signal. End-systolic lengths were measured at the minimum intercrystal distance before (−)dp/dtmax. Percentage of shortening of the LV transverse dimension and regional shortening were calculated as the end-diastolic length minus the end-systolic length divided by the end-diastolic length times 100.

Isovolumic relaxation was defined as the time from (−)dp/dtmax to 5 mm Hg more than end-diastolic pressure of the same beat to provide an isovolumic period beginning after aortic valve closure and before mitral valve opening. The decay of LV pressure (P) during this period can be described by a monoexponential function allowing a variable asymptote of the following form: P(t)=Pe^−t/T+Pb, where T represents the time constant of isovolumic relaxation, and Pb equals the pressure axis intercept at zero rate of change of pressure.15 According to the method of Raff and Glantz,15 T was calculated from the linear regression of dp/dt versus P for the points obtained every 5 msec during isovolumic relaxation. The resultant line has a slope of (−1)/T. The correlation of the plots of dp/dt versus P was 0.89±0.17 (±SD).

The LV pressure−minor-axis dimension relation from (−)dp/dtmax to the peak of the A wave was plotted for each study condition. Data from minimal LV diastolic pressure to the peak of the A wave were then used to determine an LV diastolic dynamic elastic chamber stiffness constant (k), according to the following monoexponential function: P=be^−d+C, where P is LV pressure, b is the factor characterizing the position of the pressure-dimension relation, d is the LV minor-axis dimension, and C is the empirically derived constant.16 This analysis integrates the viscous effects of early rapid filling and late atrial contraction with passive chamber properties and might, therefore, not purely reflect passive chamber stiffness.17 Data from this study, however, indicate that pacing-induced and flow-limited ischemia have similar effects on early and late diastolic function, and heart rate and size, suggesting that viscous forces are probably similar during these two forms of ischemia, and this method of computing chamber stiffness should, therefore, adequately reflect significant differences in passive chamber properties. Because a
single minor-axis dimension was used to calculate chamber compliance, it is possible that the results might be influenced by placement of the crystals. The crystals were positioned in the ischemic regions of the LAD and LCx and carefully sutured in place. Because the shifts of both the LV diastolic pressure-dimension relations were similar to the shifts in the LV diastolic pressure-segment length relations in almost all cases, it suggests that the changes in compliance of the ischemic areas are fairly well reproduced by this method. Thus, with this technique, we were able to compare the effects of both types of ischemia on this index of chamber stiffness but could not evaluate differences in chamber stiffness between areas of the LV.

Protocol

Baseline hemodynamic recordings were made at rest, and low-dose propranolol (0.5 mg/kg) was administered to prevent ventricular fibrillation during ischemia similar to that routinely used in previous studies of postpacing ischemia. Simultaneous inflation of the hydraulic occluders on both the LAD and LCx coronary arteries was then performed with a Y-connector and sustained for up to 2–3 minutes. Hemodynamics were assessed when LVEDP had increased to approximately 15 mm Hg and, again, at the end of the coronary occlusion. Bilateral coronary occlusion (BCO), rather than single vessel coronary occlusion, was chosen to provide an ischemic region similar to that used during pacing-induced ischemia and to minimize the effects of asynchronous relaxation on parameters of diastolic function. Brief BCOs by using hydraulic occluders in this manner result in complete cessation of coronary flow as measured by electromagnetic flow probes, are reproducible, and cause mild-to-moderate left ventricular systolic failure within 1 minute but have minimal cumulative effects on left ventricular function. Deflation of the hydraulic occluders results in prompt reperfusion and return of baseline hemodynamics within 2–3 minutes of deflation. Hemodynamics were allowed to return to baseline and at least 20 minutes was allowed after BCO before further experimentation.

After hemodynamics had returned to preclosure levels, rapid atrial pacing was initiated at a rate 1.7–2.0-fold that of control heart rate and sustained for 3 minutes, similar to the protocol used in previous studies of postpacing ischemia. Hemodynamics were recorded immediately after cessation of pacing. After return to baseline, both of the hydraulic occluders were connected to a screw-driven hydraulic pump by a Y-connector, and bilateral stenoses were created by partial inflation of the occluders. During this process, the inflation setting at which regional segment dysfunction first occurred was noted, and then, the occluders were partially deflated so that the bilateral stenoses had no discernible effect on regional or global LV function. Previous work has shown that this degree of narrowing represents a critical stenosis of approximately 90%. Regional function rather than epicardial coronary flow was used to assess the degree of flow limitation because regional dysfunction occurs with as little as 20% reduction in subendocardial flow, and epicardial coronary artery flow might not accurately reflect subendocardial flow during ischemia. Rapid atrial pacing was then initiated and sustained for 3 minutes or until LVEDP was in a range similar to that seen during BCO. Runs were accepted for analysis only if a comparable decrease in regional shortening was observed in both the LAD and LCx regions during pacing-induced ischemia. Hemodynamics were recorded immediately after cessation of pacing. Data from beats 5–15 after cessation of pacing-induced ischemia were analyzed as had been done in previous studies evaluating postpacing ischemia. The partially inflated occluders were then fully deflated, and the dog was allowed to recover.

In three dogs, pacing-induced ischemia was performed before BCO to determine if previous ischemia influenced the outcome of the study. As has been shown by Momomura et al, the mechanical response to ischemia is unaffected by a previous episode of brief ischemia. Therefore, the results from the three dogs with pacing-induced ischemia first and the results from the six dogs with BCO first were combined.

Myocardial Blood Flow

Regional myocardial blood flow was determined in five additional dogs by using gadolinium 153, strontium 85, scandium 46, chromium 51 (15 μm, 3M, St. Paul, Minnesota), and tin 113 radiolabeled microspheres (15 μm, New England Nuclear, Boston, Massachusetts), which allowed up to five separate measurements in each dog. These dogs were instrumented in a manner identical to the other animals and were subjected to the same protocol. Of each different isotope-labeled microsphere, 1.5–2.5×10⁹, were thoroughly mixed and injected into the left atrium over 10–15 seconds. Reference samples were withdrawn from the femoral artery over 3 minutes, and the blood radioactivity was assessed by LKB 1282 computer-linked gamma counter as per standard protocol. Microsphere injection was performed at steady state under resting conditions, in the presence of bilateral critical stenoses, and also, 30 seconds after initiation of rapid atrial pacing and coronary occlusion. At the end of the experiment, both hydraulic occluders were inflated and methylene blue was injected in the aortic root to help outline the ischemic areas (nonstaining). The dogs were then quickly killed with potassium chloride. The heart was excised immediately, and the myocardium was sectioned, 1.0–1.5-g tissue sections were split into epicardial and endocardial portions from the central ischemic areas of the LAD and LCx, and from a nons ischemic area near the base of the heart. Each section was then assessed for radioactivity at each specific isotopic window with a standardized software program. Myocardial blood flow was calculated
TABLE 1. Hemodynamics During Controls, Bilateral Critical Coronary Stenoses, and Postpacing Ischemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>(+)dp/dt (mm Hg/sec)</th>
<th>LVEDD (mm)</th>
<th>AP%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td>105±14</td>
<td>94±12</td>
<td>4.2±2.8</td>
<td>1.9±2.6</td>
<td>2,173±775</td>
<td>44.7±8.6</td>
<td>11.8±3.9</td>
</tr>
<tr>
<td>PPc</td>
<td>108±16</td>
<td>79±16*</td>
<td>3.6±2.8</td>
<td>1.8±2.1</td>
<td>1,796±650*</td>
<td>43.3±8.3</td>
<td>10.1±3.2</td>
</tr>
<tr>
<td>STEN</td>
<td>108±23</td>
<td>89±22</td>
<td>5.8±4.8</td>
<td>2.2±1.9</td>
<td>2,053±491</td>
<td>44.9±8.1</td>
<td>11.1±4.9</td>
</tr>
<tr>
<td>PPI</td>
<td>118±22</td>
<td>61±15††</td>
<td>14.4±2.8††</td>
<td>2.9±1.6</td>
<td>1,281±442††</td>
<td>47.6±7.8††</td>
<td>6.2±3.5††</td>
</tr>
</tbody>
</table>

Values are mean±1 SD; n=9. All data involving pacing (PPc and PPI) were obtained immediately after cessation of rapid atrial pacing (see "Methods").

HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; RVEDP, right ventricular end-diastolic pressure; LVEDD, left ventricular end-diastolic dimension; AP%S, anteroposterior left ventricular percentage of shortening; CONT, control; PPc, pacing control; STEN, bilateral stenoses at rest; PPI, postpacing ischemia.

*p<0.05 vs. control; †p<0.05 vs. STEN; ‡p<0.05 vs. PPc, §p<0.08 vs. PPc.

garding to the following formula: Fm=Fb×Cm/Cb×1/W, where Fm is myocardial blood flow (ml/g/min), Fb is flow rate of withdrawing pump (ml/min), Cm is corrected counts in myocardial sample at each specific isotope window (counts/min), Cb is reference blood sample counts, and W is weight of the tissue in grams.

Statistical Analysis

Data were analyzed by analysis of variance by a standard program (BMDP2V, University of California, Los Angeles, California) and paired t testing where appropriate. The Newman-Keuls multiple range test was used to determine significant group mean differences. The results are presented as the respective group mean±SD. A p value less than or equal to 0.05 was considered significant.

Results

Pacing Alone

Left ventricular performance immediately after rapid atrial pacing (peak-paced heart rate, 204±24 beats/min) in the absence of coronary stenoses was assessed (Tables 1 and 2, and Figure 2, left panel). Mean arterial pressure (MAP) was reduced by rapid atrial pacing (79±16 vs. 94±12 mm Hg), possibly secondary to reduced diastolic filling and anesthetic depression of baroreceptor reflex function. Contractile performance did not appear to be substantially altered because AP dimension shortening (AP%S) was not significantly reduced after rapid atrial pacing. Although peak (-)dp/dt was minimally reduced, the time constant of isovolumic relaxation (T) and minimal LV diastolic pressure (LVPp) were unaffected as compared with normal, suggesting that pacing alone had a negligible effect on early diastolic function. The pressure-dimension relations plotted from isovolumic relaxation to the peak of the A wave for control and after rapid atrial pacing were similar (Figure 2, left panel), indicating that, additionally, passive LV chamber properties were not significantly altered by pacing alone.

Bilateral Coronary Stenoses

After rapid atrial pacing alone, critical stenoses were created simultaneously (see "Methods") by partial inflation of the LAD and LCx hydraulic occluders such that global and regional function remained at baseline levels (Tables 1 and 2, and Figure 2, right panel). Left ventricular end-diastolic dimension (LVEDD) and segment lengths were not significantly different from control, and both dimension and segment length shortening were equivalent to control. Additionally, early diastolic function (Table 3) and the diastolic pressure-dimension relation (Figure 2, right panel) were similar to that seen before partial cuff inflation. Thus, critical stenoses were imposed with unaltered resting myocardial systolic and diastolic function.

Pacing-Induced Ischemia

A representative analog recording depicting hemodynamic, LV dimension, and segment length variables during pacing-induced ischemia is shown in Figure 3. Systolic and diastolic dysfunction occurred simultaneously during pacing-induced ischemia. Hemodynamic results during pacing-induced isch-

TABLE 2. Left Ventricular Minor-Axis Dimension and Regional Segment Lengths During Control, Bilateral Critical Coronary Stenoses, and Postpacing Ischemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>AP minor axis</th>
<th>Base</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDD (mm)</td>
<td>ESD (mm)</td>
<td>%S</td>
</tr>
<tr>
<td>CONT</td>
<td>44.1±8.5</td>
<td>39.2±8.3</td>
<td>11.4±4.1</td>
</tr>
<tr>
<td>STEN</td>
<td>44.9±8.1</td>
<td>40.0±8.0</td>
<td>11.1±4.9</td>
</tr>
<tr>
<td>PPI</td>
<td>47.6±7.8††</td>
<td>44.8±7.8††</td>
<td>6.2±3.5††</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=9. PPI data were obtained immediately after cessation of rapid atrial pacing (see "Methods"). AP, anteroposterior; EDD, end-diastolic dimension; ESD, end-systolic dimension; %S, percentage of shortening; EDL, end-diastolic length; ESL, end-systolic length; CONT, control; STEN, bilateral stenoses at rest; PPI, postpacing ischemia.

*p<0.05 vs. control; †p<0.05 vs. STEN.
A typical response to pacing-induced ischemia is shown in Figure 2 (right panel). Diastolic pressure-dimension relations for control and pacing-induced ischemia were constructed for each of the nine dogs and are displayed in Figure 5. Diastolic pressure-dimension relations during the early phase (30 seconds to 1 minute) of BCO over a similar pressure and dimension range are plotted for comparison. An upward and rightward shift with steepening of the slope throughout diastole was seen in eight of nine dogs during pacing-induced ischemia, whereas a predominantly upward shift was seen in one dog (dog 6). Similar qualitative changes were seen in the diastolic pressure-dimension relation during flow-limited ischemia, including a predominantly upward shift in dog 6. The regional diastolic pressure–segment length relations from the same dog as shown in Figure 4 are depicted in Figure 6. The pressure–segment length relations during both pacing-induced and flow-limited ischemia were shifted upward and to the right, suggesting equivalent changes in passive diastolic behavior despite differences in regional systolic wall motion. Thus, in contrast to previous studies demonstrating an upward shift in the diastolic pressure–segment length relation, we consistently observed a rightward and upward shift of the relation.

Pacing-Induced Versus Flow-Limited Ischemia

We compared ventricular function immediately after pacing-induced ischemia to BCO of similar duration (Table 4). Alterations in ventricular function consistently occurred earlier and to a greater extent during flow-limited ischemia than pacing-induced ischemia. Bilateral coronary occlusion sustained for a comparable duration as pacing-induced ischemia resulted in a higher LVEDP than postpacing ischemia (25.3±8.1 vs. 14.9±6.6 mm Hg, p<0.05). There was also greater cardiac dilation during coronary occlusion (LVEDD, 44.8±6.4 mm) than during postpacing ischemia (LVEDD, 43.4±6.5 mm; p<0.05) and greater depression of systolic contractile function (AP%S, 3.3±3.2%) than pacing-induced ischemia (AP%S, 6.5±3.6%, p<0.05). Thus, in this model and consistent with the findings of previous studies, supply ischemia resulted in greater impairment in systolic function than postpacing ischemia.

Because pacing-induced ischemia resulted in quantitatively less severe alterations in ventricular function than a comparable duration of coronary occlusion, we compared LV function of postpacing ischemia to the early phase of BCO (30 seconds to 1 minute) at a similar LVEDP to detect potential qualitative differences in the ventricular response to

Table 3. Left Ventricular Early Diastolic Function for Controls, Bilateral Critical Coronary Stenoses, and Postpacing Ischemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>(−)dP/dt\text{max} (mm Hg/sec)</th>
<th>T (msec)</th>
<th>LVP\text{min} (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td>2,173±775</td>
<td>46.4±20.5</td>
<td>−2.3±4.2</td>
</tr>
<tr>
<td>PPe</td>
<td>1,796±650*</td>
<td>46.6±15.9</td>
<td>−2.2±4.2</td>
</tr>
<tr>
<td>STEN</td>
<td>2,053±491</td>
<td>43.0±11.4</td>
<td>−2.8±3.7</td>
</tr>
<tr>
<td>PPI</td>
<td>1,281±400†‡</td>
<td>78.0±40.4†‡</td>
<td>5.6±4.4†‡</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=9. All pacing data were obtained immediately after cessation of pacing (see "Methods").

T, time constant of isovolumic relaxation; LVP\text{min}, minimal diastolic left ventricular pressure; CONT, control; PPe, postpacing control; STEN, bilateral stenosis at rest; PPI, postpacing ischemia.

*p<0.05 vs. control; †p<0.05 vs. STEN; ‡p<0.05 vs. PPe.
these two forms of ischemia. At matched increases in LVEDP during ischemia, MAP decreased from control (94±12 mm Hg) after pacing-induced ischemia (61±15 mm Hg) and during flow-limited ischemia (67±16 mm Hg); percentage of LV chamber shortening declined equivalently (6.2±3.5% and 5.8±2.2% vs. control 11.8±3.9%), and (+)dP/dt\text{max} was similarly reduced (1,281±442 and 1,479±363 mm Hg/sec vs. control 2,173±775 mm Hg/sec). Left ventricular end-diastolic minor-axis dimension increased equivalently from control (44.7±8.6 mm) after pacing-induced ischemia (47.6±7.8 mm) and during flow-limited ischemia (46.9±8.0 mm). Right ventricular end-diastolic pressure increased slightly during both pacing-induced and flow-limited ischemia (2.9±1.6 and 3.4±1.8 mm Hg) as compared with control (1.9±2.6 mm Hg) but the differences were not significant. Thus, there was not a significant difference in the effect of these two forms of ischemia on systolic function when the same regions of ischemia were evaluated at a common end-diastolic pressure.

After similar increases in LVEDP, regional segment lengths were similar immediately after pacing-induced ischemia and during coronary occlusion although there was a trend toward a greater reduction in regional shortening during coronary occlusion. Regional shortening tended to be reduced to a greater extent in the apex as compared with the base during pacing-induced ischemia (−40±62% vs. −75±62%, p=NS) but the differences were not significant, and similar changes occurred during bilateral coronary occlusion (−64±27% vs. −99±49%, p=NS). During this brief period of occlusion (30 seconds to 1 minute), regional segment dynamics were characterized by delayed and reduced shortening in most animals and dyskinesis of one segment in three animals. Regional segment shortening was reduced but was not delayed during pacing-induced ischemia in most animals, and dyskinesis was noted in two of the three same segments noted during occlusion.

To minimize the effects of loading on early diastolic events and to provide a common physiological end point, pacing-induced and flow-limited ischemia (30 seconds to 1 minute) were evaluated at similar elevations in LVEDP (14.4±2.8 and 13.7±4.8 mm Hg vs. control 4.2±2.8 mm Hg). Alterations in early and late diastolic function were equivalent immediately after pacing-induced ischemia and during BCO when evaluated under matched loading conditions (Table 5). Similarly, during both types of ischemia, end-diastolic chamber stiffness (k) increased comparably (1.94±0.77 vs. 1.87±0.76 mm Hg/mm, p=NS). Thus, no qualitative differences
in diastolic function were observed between these two forms of ischemia in this study.

**Myocardial Blood Flow**

Microsphere regional myocardial blood flow data were obtained in five additional dogs during pacing-induced and flow-limited ischemia and are presented in Table 6. Myocardial blood flow was determined during rapid atrial pacing in the presence of critical bilateral coronary stenoses and compared with a similar duration of BCO. Resting myocardial blood flow was similar in the LAD and LCx region and was comparable with previously reported values. Bilateral coronary occlusion resulted in pronounced reductions in both average (LAD and LCx) epicardial blood flow (0.3±0.3 vs. control 1.4±0.4 ml/g/min, p<0.05) and average endocardial blood flow (0.1±0.1 vs. control 1.3±0.3 ml/g/min, p<0.05). These blood flows are similar to values reported by Momomura et al during a 3-minute occlusion of the LAD. The introduction of bilateral coronary stenoses did not significantly affect epicardial blood flow. Resting endocardial blood flow in the LAD region was decreased in the presence of the stenoses (0.9±0.6 vs. control 1.2±0.4 ml/g/min, p<0.05) but was not associated with a measurable change in regional function. There was no difference in regional flow in the LCx region after introduction of the coronary stenoses. Rapid atrial pacing in the presence of critical bilateral coronary stenoses resulted in a significant decrease in epicardial blood flow in the LAD region (0.6±0.3 vs. control 1.2±0.4 ml/g/min, p<0.05). Epicardial blood flow also decreased in the LCx region (1.0±0.05 ml/g/min) but the reduction was not statistically significant as compared with control. A significant decrease in endocardial blood flow in the ischemic regions of both the LAD and LCx was also observed (0.2±0.1 and 0.7±0.1 ml/g/min, respectively; both, p<0.05 vs. stenoses). Both epicardial and endocardial blood flow to nonischemic areas increased significantly during pacing-induced ischemia (2.11±0.3 and 1.74±0.1 ml/g/min, respectively; p<0.05 vs. control), indicating that a generalized reduction in myocardial blood flow because of
rapid atrial pacing per se was not responsible for the alteration in myocardial blood flow observed in the ischemic areas. Thus, these data indicate that pacing-induced ischemia in this model resulted in a substantial decrease in transmural myocardial blood flow and represents a more severe form of pacing-induced ischemia than has been previously described.

Discussion

This study evaluated a more severe form of postpacing or demand ischemia than has been previously reported. After 3 minutes of rapid atrial pacing in the presence of critical bilateral coronary stenoses, ventricular function after cessation of pacing was characterized by moderately severe contractile depression, LV dilation, impairment of isovolumic relaxation, an upward and rightward shift in the diastolic pressure-dimension relation, and an increase in passive diastolic chamber stiffness. Although epicardial and endocardial blood flow were similar to control in the presence of bilateral coronary stenoses, both were reduced significantly after pacing-induced ischemia. These findings differ from previous studies that have demonstrated primarily diastolic dysfunction with preservation of contractile function after pacing-induced ischemia in the presence of bilateral coronary stenoses. 

Although the pacing protocols were similar in this and previous studies, we observed a greater reduction in myocardial blood flow than had been seen in previous studies. This suggests that pacing-induced ischemia is a more severe form of coronary artery disease than rapid atrial pacing per se.

Figure 5. Graphs showing left ventricular diastolic pressure-dimension curves plotted from isovolumic relaxation to peak of A wave for control (○), flow-limited ischemia (○), and postpacing ischemia (+) for all nine dogs. In eight of nine dogs, relation shifted upward and to right during both forms of ischemia, whereas shift was predominantly upward (dog 6) for both postpacing and flow-limited ischemia in only one dog.

Figure 6. Graphs showing left ventricular diastolic pressure (LVP)-regional segment length relations from same dog used for Figure 2. Left panel: Basal region (left circumflex artery [LCx]). Right panel: Apical region (left anterior descending artery [LAD]), control (○), flow-limited ischemia (○), and postpacing ischemia (+). Despite differences in regional systolic function, diastolic pressure-segment length relations for both flow-limited and postpacing ischemia are similar in both regions.
studies, consistent with a more severe form of postpacing ischemia. Thus, the results from this and previous studies suggest that alterations in ventricular function during demand ischemia are critically dependent on the severity of ischemia elicited.

We also compared ventricular function obtained with postpacing ischemia with two different durations of BCO. Alterations in myocardial blood flow and systolic function observed in this study during demand ischemia were quantitatively less severe than BCO of comparable duration (3 minutes), similar to results from previous studies. The changes in both systolic and diastolic function observed during postpacing ischemia, however, were qualitatively similar to changes in function obtained during the early phase of flow-limiting ischemia (30 seconds to 1 minute). Thus, in this model of supply and demand ischemia, the major difference in the alterations in ventricular function between these two types of ischemia seemed to be a slower progression of contractile failure during demand ischemia than during coronary occlusion. Unlike previous studies, we did not observe qualitative differences in the ventricular responses to ischemia.

Abnormalities in ventricular function during ischemia have been the subject of considerable interest and controversy since Tennant and Wiggers first described the phenomenon of systolic bulging during coronary artery occlusion in 1935. Since then, the mechanical alterations accompanying various degrees and duration of coronary flow obstruction have been extensively evaluated. Abnormalities in diastolic function, manifested primarily as shifts in the LV diastolic pressure–segment length and pressure-volume relations, and indices of chamber stiffness have been of particular interest. During acute coronary occlusion or supply ischemia, both rightward and upward shifts of the LV diastolic pressure–segment length relation have been observed, as well as increases, decreases, or no change in LV diastolic chamber stiffness. These alterations in diastolic function have been attributed primarily to passive changes in diastolic chamber properties accompanying contractile depression and compensatory ventricular dilation. By contrast, Grossman and colleagues have extensively evaluated diastolic function during acute demand ischemia using an angina physiology model of postpacing ischemia. They observed an upward shift of the LV diastolic pressure–segment length relation and concluded that intrinsic changes in myocardial stiffness were responsible for the altered diastolic properties during demand ischemia.

The hallmark of postpacing ischemia in previous studies has been a substantial impairment in diastolic function in the absence of systolic contractile failure, manifested by an upward shift in the LV diastolic pressure–segment length relation. Serizawa et al developed an angina physiology model of demand ischemia and observed a distinct dissociation between systolic and diastolic function.

### Table 4. Comparison of Hemodynamics During Postpacing Ischemia and Bilateral Coronary Occlusion

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>CONT</th>
<th>PPI</th>
<th>BCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>117±24</td>
<td>139±22</td>
<td>135±17</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>94±23</td>
<td>65±12*</td>
<td>58±13*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>5.3±2.1</td>
<td>14.9±6.6*</td>
<td>25.3±8.1*†</td>
</tr>
<tr>
<td>(+)dP/dtmax (mm Hg/sec)</td>
<td>1,791±540</td>
<td>1,302±417*</td>
<td>1,217±360*</td>
</tr>
<tr>
<td>AP%S</td>
<td>11.8±3.0</td>
<td>6.5±3.6*</td>
<td>3.3±3.2*‡</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>39.9±4.7</td>
<td>43.4±6.5*</td>
<td>44.8±6.4*‡</td>
</tr>
<tr>
<td>Base EDL (mm)</td>
<td>12.2±1.3</td>
<td>13.2±1.8*</td>
<td>13.8±2.0*‡</td>
</tr>
<tr>
<td>Apex EDL (mm)</td>
<td>11.9±0.7</td>
<td>12.5±0.8*</td>
<td>13.3±0.7*</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=6. PPI data were obtained immediately after cessation of rapid atrial pacing (see "Methods"); BCO evaluated at similar duration as PPI; comparisons for paired data.

CONT, control; PPI, postpacing ischemia; BCO, bilateral coronary occlusion; HR, heart rate; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; AP%S, anteroposterior left ventricular percentage of shortening; LVEDD, left ventricular end-diastolic dimension; EDL, end-diastolic length.

*p<0.05 vs. control; †p<0.08 vs. PPI; ‡p<0.05 vs. PPI.”

### Table 5. Comparison of Diastolic Function at Control, Postpacing Ischemia, and Bilateral Coronary Occlusion at Matched Loading Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>LVEDP (mm Hg)</th>
<th>T (msec)</th>
<th>LVPmin (mm Hg)</th>
<th>k (mm Hg/mm)</th>
<th>b (mm Hg)</th>
<th>c (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td>4.2±2.8</td>
<td>46.4±20.5</td>
<td>−2.3±4.2</td>
<td>0.81±0.55</td>
<td>1.97±1.08</td>
<td>−2.75±2.40</td>
</tr>
<tr>
<td>PPI</td>
<td>14.4±2.8*</td>
<td>78.0±40.4*</td>
<td>5.6±4.4*</td>
<td>1.94±0.77*</td>
<td>4.62±2.93*</td>
<td>4.73±3.25*</td>
</tr>
<tr>
<td>BCO (30 sec)</td>
<td>13.4±4.8*</td>
<td>72.2±30.6*</td>
<td>4.6±2.6*</td>
<td>1.87±0.76*</td>
<td>5.24±4.06*</td>
<td>3.70±2.66*</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=9. PPI data were obtained immediately after cessation of rapid atrial pacing (see “Methods”). BCO (30 seconds) was obtained early in course of bilateral coronary occlusion at same LVEDP as PPI.

LVEDP, left ventricular end-diastolic pressure; T, time constant of isovolumic relaxation; LVPmin, minimal left ventricular diastolic pressure; k, left ventricular chamber stiffness; b, left ventricular diastolic pressure intercept; c, constant; CONT, control; PPI, postpacing ischemia; BCO, bilateral coronary occlusion.

*p<0.05 vs. control, PPI vs. BCO (30 seconds); p=NS for all variables.”
TABLE 6. Regional Myocardial Blood Flow During Pacing-Induced Ischemia and Bilateral Coronary Occlusion

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Bilateral stenoses</th>
<th>Pacing ischemia</th>
<th>Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>1.4±0.4</td>
<td>1.2±0.4</td>
<td>0.6±0.3*†</td>
<td>0.3±0.3*‡†</td>
</tr>
<tr>
<td>Endo</td>
<td>1.2±0.3</td>
<td>0.9±0.4*</td>
<td>0.2±0.1*†</td>
<td>0.1±0.2*†</td>
</tr>
<tr>
<td>LCx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>1.3±0.3</td>
<td>1.2±0.3</td>
<td>1.0±0.5</td>
<td>0.2±0.2*‡†</td>
</tr>
<tr>
<td>Endo</td>
<td>1.4±0.3</td>
<td>1.3±0.4</td>
<td>0.6±0.5*†</td>
<td>0.1±0.1*‡‡</td>
</tr>
<tr>
<td>Nonischemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>1.2±0.2</td>
<td>1.2±0.3</td>
<td>1.4±0.4</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>Endo</td>
<td>1.4±0.4</td>
<td>1.4±0.4</td>
<td>1.5±0.8</td>
<td>1.3±0.5</td>
</tr>
</tbody>
</table>

Values are mean±SD; n = 5. Myocardial blood flow (ml/g/min) was determined during rapid atrial pacing in presence of critical bilateral coronary stenoses and during bilateral coronary occlusion of comparable duration.
LAD, left anterior descending coronary artery; Epi, epicardium; Endo, endocardium; LCx, left circumflex artery.
* p<0.05 vs. control, † p<0.05 vs. stenoses, ‡ p<0.05 vs. pacing-induced ischemia.

between systolic and diastolic function during ischemia immediately after the cessation of rapid atrial pacing in the presence of critical bilateral coronary stenoses. Left ventricular systolic pressure and (+)dP/dtmax were only mildly reduced, and LV size appeared unchanged. By contrast, LVEDP rose significantly, isovolumic relaxation was impaired, and LV chamber compliance decreased. They postulated that ischemia produced by myocardial oxygen needs in excess of supply, or "demand-induced ischemia," was intrinsically different than flow-limited, or "supply-limited," ischemia.1 Paulus et al10 compared ischemia after 3 minutes of rapid atrial pacing in the presence of critical stenoses on both the LAD and LCx coronary arteries with 3 minutes of occlusion of the LAD coronary artery alone. They found that regional systolic shortening was maintained, and an upward shift in the diastolic pressure–segment length relation occurred after pacing-induced ischemia in contrast to holosystolic bulging, passive early diastolic lengthening, and a rightward and downward shift of the pressure–segment length relation during coronary occlusion.

In this study, various degrees of contractile impairment were consistently observed during pacing-induced ischemia. Additionally, we did not observe dissociation of systolic and diastolic function during postpacing ischemia in any of the dogs studied. In each dog, a rightward and upward shift in the end-diastolic pressure–dimension and pressure–segment length relation was observed that was qualitatively similar to the change observed during bilateral coronary occlusion. We did not observe a purely upward shift in the LV pressure–dimension or segment length relation in any of the dogs. The major difference between the two forms of ischemia was that, quantitatively, greater impairment of systolic and diastolic function was observed during coronary occlusion as compared with pacing-induced ischemia of a similar duration.

Responses to postpacing ischemia similar to what was found in this study have also been observed in several recent studies. Paulus et al10 noted a predominantly rightward shift in the diastolic pressure–volume relation in two animals with postpacing ischemia that was associated with decreased contractile performance similar to what was observed in this study. Sasayama et al31 noted an upward shift in the LV diastolic pressure–volume relation in four of seven patients with pacing-induced angina but a rightward shift in three of seven patients, similar to the shift observed in the present study. A significant decrease in ejection fraction was noted for all patients during pacing-induced angina. Bronzwaer et al33 examined the effects of both pacing-induced ischemia and coronary occlusion in patients undergoing coronary angioplasty. They found that pacing-induced ischemia resulted in an upward shift of the diastolic pressure–volume relation when systolic function was maintained but resulted in a rightward shift similar to coronary occlusion when systolic performance was depressed. They concluded that systolic shortening determined diastolic distensibility.

The heterogeneous diastolic pressure–dimension shifts from previous studies with pacing-induced ischemia indicate that the diastolic pressure–dimension or segment length relation might depend to a great extent on the severity of the ischemia elicited. The data from this and previous studies9,10 provide experimental evidence that two qualitatively distinct ventricular responses might be observed during demand ischemia, that is, 1) an intrinsic increase in myocardial diastolic stiffness with milder demand ischemia manifested as an upward shift of the LV diastolic pressure–segment length relation, and 2) passive increases in diastolic stiffness resulting from contractile dysfunction and manifested as a rightward and upward shift of the LV diastolic pressure–segment length relation. The precise mechanism for these differences is still to be elucidated but might depend on a critical balance of myocardial oxygen supply relative to demand, with reduction of this ratio below a threshold value causing contractile failure.

There are several potential reasons why the results obtained from postpacing ischemia in this study differ from the findings of previous studies. First, and by
design, it is likely that occluders in this study were placed in a more proximal position on the coronary arteries, resulting in a greater mass of ischemic myocardium than was obtained in previous studies. Second, the methods of producing bilateral critical coronary stenoses differed. Paulus et al. and Momomura et al. tightened metal clips around the coronary arteries until epicardial phasic blood flow was reduced to 50% of baseline. This was chosen based on the assumption that this degree of flow obstruction abolished the hyperemic response and was associated with critical narrowing of the coronary lumen by 85–93%. We chose to monitor regional contractile function as a physiological marker of the adequacy of resting subendocardial blood flow. This degree of flow limitation might result in a reduction of up to 20% in resting blood flow without affecting regional function. Although both of these approaches resulted in critical stenoses at rest with no measurable effect on resting ventricular function, our method might have resulted in greater luminal stenoses at rest than the other method. Imposing comparable increases in myocardial oxygen demand would then result in a greater degree of ischemia because myocardial oxygen supply relative to demand would be reduced to a greater extent. Additionally, there were differences in the responses to rapid atrial pacing before creation of critical stenoses between the studies. In the present study, MAP and diastolic filling pressures were lower immediately after cessation of pacing than at control but were similar in previous studies. This might have been because of lower resting pressures in this study as compared with previous studies (LVEDP, 4±4 vs. 8±6 mm Hg in Momomura et al.) or because of mild contractile depression as a consequence of pentobarbital anesthesia (vs. α-chloralose in previous studies). This might have resulted in a reduction of the compensatory response of nonischemic areas during ischemia with a greater degree of overall contractile failure.

Finally, it is possible that the shifts of the LV diastolic pressure-volume relations obtained from postspacing ischemia observed in these studies might have been affected by differences in tissue turgor. Several investigators have demonstrated that an increase in coronary turgor can influence the LV diastolic pressure-volume relation, acting as an external constraint and causing an upward shift of the relation. Momomura et al. reported that epicardial blood flow actually increased during pacing ischemia in the ischemic areas of the LAD and LCx, whereas endocardial blood flow decreased. Epicardial and endocardial blood flow decreased during pacing-induced ischemia in our study (Table 6), which might have occurred as a result of a coronary steal-type of phenomenon. This increase in epicardial blood flow in previous studies might have resulted in an increase in epicardial tissue turgor and acted as an external constraint. The exact relation of the role of tissue turgor on shifts in the LV diastolic pressure–volume relation during demand ischemia, however, is still to be determined.

Limitations of the Study

There are certain limitations of this study that merit discussion. First, we used regional subendocardial function as a physiological marker of resting coronary blood flow during demand ischemia. The relation of resting blood flow to regional function has been well characterized and was commonly used in previous studies of demand ischemia. Second, LV minor-axis anterior-posterior dimension was used to measure chamber size and to compute LV chamber stiffness. Because this single dimension might not accurately reflect changes in total LV volume, these values represent indices of chamber size and stiffness. Because the crystals were sutured in place, however, we consistently measured the same dimension throughout the study. Additionally, the shifts in the LV diastolic pressure–dimension relation were similar to the shifts in the pressure–segment length relation, indicating that changes in chamber properties were fairly well reproduced by this method. Finally, these were significant differences in myocardial blood flow between these two types of ischemia. This is consistent with different degrees of severity although myocardial oxygen consumption was not measured. Thus, analysis of alterations in ventricular function after similar duration of the two types of ischemia was affected by differences in the severity of the ischemia. To minimize the potential problem of evaluating ventricular function at different levels of ischemic severity, however, we analyzed ventricular function over comparable ranges of pressure and dimension during the two types of ischemia.

Summary

We compared the ventricular response to severe pacing-induced ischemia and coronary occlusion. Pacing-induced ischemia was consistently associated with contractile depression, rightward and upward shifts in the position of the LV diastolic pressure–dimension, and pressure–segment length relations. Changes in systolic and diastolic function occurred earlier and to a greater extent during coronary occlusion but qualitatively similar changes were observed during pacing-induced ischemia. These data extend our understanding of the ventricular response to demand ischemia. The fact that different degrees and types of ventricular dysfunction have been obtained using different models of ischemia suggests that the ventricular response to ischemia should not be classified simply based on whether supply or demand ischemia is present but rather on a complex interaction between the duration, extent and severity, and type of ischemia elicited.

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References

Key Words • myocardial ischemia • left ventricular function • diastolic function
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R J Applegate, R A Walsh and R A O'Rourke

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