Distinction Between Metabolic and Myogenic Mechanisms of Coronary Hyperemic Response to Brief Diastolic Occlusion

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We monitored an index of coronary vascular resistance (mean aortic pressure/mean coronary flow) in 19 heart-blocked conscious dogs paced at 60 beats/min and instrumented with an aortic pressure catheter, left circumflex artery electromagnetic flow probe, and a coronary occluder. Cessation of pacing for a single beat resulted in a long diastole control (LDC) intervention beat of 2-second duration characterized by a progressive rise in diastolic coronary vascular resistance index. A 400-msec coronary artery occlusion early in a long diastole (LD4) dramatically inhibited the rate of rise in resistance index during the first 600 msec (phase 1) after occlusion. Partial recovery of the resistance index rise rate was evident during the remaining 400 msec (phase 2) of the long diastole. In nine dogs, LDC and LD4 intervention beats were instituted during two conditions of myocardial metabolic activity in which the myogenic stimuli associated with coronary occlusion would be similar: 1) paired pacing and 2) normal pacing plus intravenous adenosine and phenylephrine infusions (AP) to maintain mean aortic pressure and coronary flow at paired pacing levels. During paired pacing, the LD4—LDC differences in phase 1 and 2 resistance index rise rates (−69±18 and −48±31 mm Hg/ml/sec², respectively) were greater than during normal pacing plus AP (−32±14 and −1±32 mm Hg/ml/sec², phase 1 and 2, respectively) (p<0.05). These differences are consistent with operation of a metabolic mechanism in response to occlusion. Depression of the LD4 phase 1 resistance index rise rate during normal pacing plus AP, when myocardial metabolic supply and demand were uncoupled, suggests that a myogenic mechanism may also have operated in response to occlusion. Full recovery of the phase 2 resistance index rise rate occurred during normal pacing plus AP, but not during paired pacing, suggesting that operation of the putative myogenic mechanism was limited to the first 600 msec after occlusion and that the metabolic mechanism operated for at least 1,000 msec after occlusion. (Circulation Research 1991;68:1313–1321)

Coronary blood flow is tightly coupled to myocardial metabolic activity.1,2 Accordingly, the coronary circulation is highly sensitive to transient reductions in blood flow, responding with reactive hyperemia ranging from ~100% to 600% of occlusion debt. This response pattern is maintained for coronary occlusions as brief as 200–1,000 msec.3–6 It is generally accepted that metabolically based mechanisms, such as a reduction in tissue Po2 or pH or local release of one or more metabolites, play an important role in mediating the observed reactive hyperemic response to coronary occlusions several seconds or more in duration.1,2,7 However, temporary vascular occlusion is associated with a transient reduction in perfusion pressure distal to the occlusion, thereby raising the possibility that the resulting reactive hyperemic response is in part myogenically mediated.8,9 Although the existence of a myogenic mechanism has been convincingly demonstrated in systemic vasculature,9–11 and in isolated coronary arterioles,12 there is a paucity of data to support such a mechanism in the coronary circulation in vivo.2,13 The beating heart poses significant physiological and mechanical limitations to developing experimental interventions that can be distinguished as either myogenic or metabolic stimuli.

We previously reported a hyperemic response during long diastole cardiac cycles after a 400-msec...
coronary artery occlusion early in the same diastole (LD4). In the present study, we report additional in vivo studies designed to identify the mechanism(s) responsible for this response. We used two levels of myocardial metabolic activity during which the myogenic stimuli associated with LD4 were similar. This strategy allowed us to differentiate between metabolic and myogenic mechanisms of coronary vasodilation in response to brief coronary occlusion in conscious dogs.

Materials and Methods

Surgical Preparation

All studies were carried out under protocols approved by the Duke Medical Center and Durham Veterans Administration Medical Center Committees on animal welfare. Nineteen adult mongrel dogs, weighing 25–34 kg, were anesthetized with 25–30 mg/kg i.v. sodium thiamylal (Parke-Davis, Morris Plains, N.J.) followed by supplemental administration as needed to maintain surgical anesthesia. After endotracheal intubation, respiration was maintained with a Harvard respirator (model 613, Harvard Apparatus, South Natick, Mass.). A left thoracotomy was performed through the fourth left intercostal space, and the pericardium was opened. A bipolar epicardial pacing electrode was sutured to the free wall of the right ventricle. Complete heart block was produced by injection of <1 ml of 37% formaldehyde in the atrioventricular node and His bundle according to the method of Steiner and Kovalik.16 Heart rate was maintained subsequently at 100 beats/min by right ventricular pacing using a Cordis Multicor gamma implantable pacemaker and a unipolar lead (model 336A, Cordis Corp., Miami). An electromagnetic flow probe (model HST, Howell Instruments, Camarillo, Calif.) of appropriate size was positioned around the proximal circumflex branch of the left coronary artery. Throughout this report, the term “coronary flow” will denote the measurement of blood flow through the circumflex branch of the left coronary artery. A pneumatic occluder, constructed in our laboratory of polyvinyl chloride tubing with an outside diameter of 2.7 mm, was placed around the coronary artery distal to the flow probe. A heparin-filled polyvinyl chloride catheter (3.0 mm o.d.) was introduced into the arch of the aorta via the left internal mammary artery; another such catheter was inserted through a small incision in the left ventricular apex and into the left ventricular cavity. The flowmeter leads, pacing electrode leads, catheters, and pneumatic occluder were tunneled dorsally into a subcutaneous pouch. The unipolar pacing lead was tunneled to a second subcutaneous pouch containing the pacemaker. The chest was closed, the pneumothorax was evacuated, and the dog was extubated.

Experimental Protocol

Studies were carried out 7–10 days after the initial surgery. All dogs were active and afebrile and had hematocrits ranging from 37% to 45%. The dogs rested quietly on their right sides during the study period. The laboratory was kept dimly illuminated and free of noise. The instrument leads and catheters were exteriorized from the subcutaneous pouch under 2% lidocaine local anesthesia 1 to several days before the day of study. On the day of study, morphine sulfate (10–20 mg) was administered intramuscularly. The coronary sinus was catheterized by advancing a 7F coronary catheter (USCI, Billerica, Mass.) catheter into the left external jugular vein under 2% lidocaine local anesthesia and fluoroscopic control. The catheter position was confirmed by injecting 5 ml of a 75% solution of sodium diatrizoate through the catheter at the beginning and end of each study. The pulse rate of the implanted pacemaker was reset to 30 beats/min by a rate controller (model 255A, Cordis) and the ventricular rate was controlled with a programmable stimulator (model S88, Grass Instrument Co., Quincy, Mass.) connected to the bipolar pacing lead. The stimulator was set to deliver 4-msec square-wave pulses 25% above threshold voltage through an isolation unit at a rate of 60 beats/min. Lead II of the standard electrocardiogram was recorded. The coronary flowprobe was connected to a Howell flowmeter (model HMS 1000). Pressure catheters were connected to Statham pressure transducers (model P23Db, Gould, Cleveland, Ohio).

The pneumatic occluder was connected to an automatic solenoid-activated valve that connected the occluder either to a source of compressed helium to effect inflation or to a vacuum to ensure rapid deflation. The occluder could be inflated either manually (for 10-second occlusions) or by a Kantowitz phase-shift balloon pump (L.VAD Technology, Detroit) triggered by the R wave of the electrocardiogram (for 400-msec diastolic occlusions). The pump produced complete coronary artery occlusion in approximately 10 msec; deflation occurred in approximately 20 msec. A 10-second coronary artery occlusion was performed at the beginning of each study to assess reactive hyperemic capacity. This intervention yielded a flow debt repayment of 433±35% (range 244–766%) for 19 dogs. This response is comparable to those reported previously17,18 and indicates a normal degree of vascular reactivity for dogs used in these experiments.

All dogs were studied under three sets of myocardial metabolic conditions. Each dog was initially studied during the control metabolic condition of normal ventricular pacing at 60 beats/min. Two types of interventions were used. The long diastole control (LDC) intervention was instituted by interrupting the basic paced heart rate of 60 beats/min for a single cycle, yielding a beat of 2,000-msec duration. In the second intervention, the balloon pump was set to initiate LD4, which was delayed to begin 20 msec after peak diastolic coronary flow and to maintain the occlusion for a duration of 400 msec. All dogs received the LD4 intervention, and a subset of nine dogs also received the LDC intervention. During
each of the three metabolic states, at least eight replicates of the intervention(s) (LDC and/or LD4) appropriate for the particular group of dogs were instituted. LDC and/or LD4 interventions were separated by at least 40 seconds.

After the control pacing period, the ventricle of each dog was paced by delivering pairs of electrical stimuli (separated by 200 msec) to the right ventricle. This pacing protocol resulted in two discrete ventricular depolarizations and increased myocardial metabolic activity. However, the short coupling interval prevented extramechanical contraction of the ventricles.19 Thus, the ventricular contraction rate was maintained at 60 beats/min. Paired pacing was continued for at least 5 minutes to ensure that a steady state had been achieved before LDC and/or LD4 interventions were instituted. Paired pacing was then discontinued, and normal ventricular pacing at 60 beats/min was resumed. Although aortic pressure and coronary flow usually returned to baseline within 1 minute of cessation of paired pacing, at least 20 minutes was allowed before initiating the third metabolic condition.

The final metabolic condition was achieved by infusing adenosine (free base, 8 mg/ml of normal saline, Sigma Chemical Co., St. Louis) and phenylephrine (hydrochloride salt, 20 μg/ml of normal saline, Winthrop-Breon Laboratories, New York) simultaneously with independent infusion pumps into separate cephalic veins during normal ventricular pacing. The drug infusion rates were adjusted to maintain mean coronary blood flow and mean aortic pressure at paired pacing levels. LDC and/or LD4 interventions were then introduced as previously described.

Blood samples were obtained from aortic and coronary sinus catheters simultaneously to estimate myocardial VO₂ of the left circumflex coronary bed. Blood specimens were drawn during each steady-state metabolic condition before performing LDC and/or LD4 interventions. Hemoglobin content and oxygen saturations were determined in duplicate on an IL 282 Co-oximeter (Instrumentation Laboratory, Lexington, Mass.). Hemodynamic and electrocardiographic data were recorded with a magnetic tape recorder (model 3966-D, Hewlett-Packard Co., Palo Alto, Calif.) and an eight-channel direct-writing thermal recorder (model 7700, Hewlett-Packard).

Four additional dogs were studied in an anesthetized state (150 mg/kg i.v. α-chloralose [Sigma Chemical] in normal saline followed by supplemental administration as needed to maintain surgical anesthesia) as acute thoracotomy preparations for the purpose of recording coronary artery pressure distal to the pneumatic occluder. The surgical procedure used in preparing these dogs was similar to the procedure used in preparation of the chronically instrumented dogs. However, in the acute preparations, a 20-gauge, 1.5-in. Teflon angiocatheter was inserted through the wall of the coronary artery approximately 1 cm distal to the pneumatic occluder and connected to a Statham P23Db pressure transducer (Gould). LDC and/or LD4 interventions were produced during normal pacing, paired pacing, and normal pacing plus adenosine and phenylephrine infusions (AP) as previously described.

Data Analysis

Analog signals of aortic pressure, left ventricular pressure, and left circumflex coronary flow were digitized at 200 samples/sec using a Hewlett-Packard 1000 computer system, and the data were smoothed once with a three-point moving-average digital filter. Data were analyzed in 10-second segments, each consisting of at least five control beats followed by the intervention beat. The digitized coronary flow data were displayed on a videoscreen, and periods of systole and diastole were defined on the coronary flow waveform for computer analysis.

Aortic blood pressure was taken as coronary perfusion pressure for the calculation of coronary vascular resistance indexes. In the present study and in a study using a similar animal model,3 the pressure gradient between aortic pressure and coronary pressure measured distal to the coronary occluder in a nonoccluded left circumflex artery was 2 or 3 mm Hg. On release of a 400-msec occlusion, distal coronary pressure returned within 50 msec to the levels occurring in nonoccluded control beats. Therefore, no appreciable error should result from the use of aortic pressure in determining the diastolic coronary vascular resistance index (DCVRI).

DCVRIs for the total cardiac cycles of the five preintervention control beats were averaged across intervention replicates to provide a single mean value for each dog. The use of DCVRI obviates the need to know the true back pressure in the coronary circulation, which at this time remains an unobtainable quantity because of the complex collection of factors thought to be possible contributors to back pressure.20,21

Our analysis of the response to brief coronary occlusion focused on the interval of the LD4 coronary flow tracing between the end of the postocclusion overshoot spike and the end of diastole. The limits of this interval, defined for LD4, were used to identify the corresponding interval in the LDC intervention for those dogs that received LDC interventions. These corresponding diastolic intervals will be referred to as the “postspike period” in this study (Figure 1). The postspike period was 1,000 msec in length. We used a computer program to divide the postspike period into ten 100-msec intervals and to compute DCVRI for each 100-msec interval by dividing the mean aortic pressure during the 100-msec interval by the mean coronary flow during that interval.

Subsequent analysis of DCVRI during the postspike period was divided into three parts. In the first part of this analysis, we wanted to identify an appropriate statistical model of the data that could be used to compare results of different experimental interventions. A visual inspection of the LD4 data suggested a linear spline model, which is two straight
lines with a common join point.22 We determined whether the linear spline model was at least as predictive of our animal model as a smooth curvilinear model with curvature described by a polynomial of increasing order (e.g., quadratic, cubic, quartic). In fitting the data to a linear spline model, we allowed the parameters in these statistical models (including the join point, which must be estimated by an iterative nonlinear analysis, NLIN, SAS Institute Inc., Cary, N.C.) to vary from dog to dog to take into account normal interanimal variability. As a test case, we fit the LD4 data for the 19 dogs in the normal pacing condition. The linear spline model provided a significantly better fit of the data (mean square error was significantly smaller, \( p<0.05 \)) than did the quadratic and cubic models but was not significantly improved over the quartic model. Because the quartic model requires five parameters per dog (intercept, linear, quadratic, cubic, and quartic) and the linear spline requires only four parameters per dog (slope line 1, slope line 2, location of the join point on the x axis, and the y value at the join point), the linear spline is a more parsimonious model.

We made the assumption that validity of the linear spline model as a descriptor of the 19-dog group would extend to the nine-dog subset described in this study. We also assumed that the linear spline model would be a statistically appropriate descriptor of LD4 data during paired pacing since the underlying physiological mechanisms of the LD4 response are similar under normal pacing and paired pacing conditions, both conditions being characterized by tight myocardial metabolic coupling. To test the null hypothesis that no differences exist between experimental conditions (normal pacing versus paired pacing versus normal pacing plus AP), it was appropriate and necessary to analyze the data generated during these conditions according to the tenants of the same statistical (linear spline) model.

In the second part of the data analysis, we established a fixed join point as a common reference to allow comparison of the LD4 data between experimental conditions and between the LDC and LD4 data within each metabolic condition for the nine-dog subset. By applying NLIN to the mean DCVRI data of the fixed eligible time values (from 100 to 900 msec in 100-msec increments), the time value of 600 msec provided the best overall fit of the data using the linear spline model.

In the third part of the analysis, the time value of 600 msec established in the second part of the analysis was used to split the data. For each dog, DCVRI during the two phases comprising the postspike response period (phase 1, 0–600 msec; phase 2, 600–1,000 msec) were fit to separate linear regressions, and the resulting slopes were compared among different treatment interventions. Although fitting separate regression lines does not require the lines to intersect at the join point, linear regressions provided a good approximation to the linear spline model and facilitated the comparisons made in the data. Slope values resulting from linear regression analysis describe the rate of change of DCVRI. In this report “slope” will refer to the DCVRI rise rate during the postspike period of an LDC or LD4 intervention.

In each dog, data segments obtained during eight to 10 repetitions of an LDC or LD4 intervention were analyzed, and a single average value for each of the parameters described above was obtained. Thus, each dog was weighted equally in the final data summary, regardless of the number of data segments that were available for analysis. All statistical comparisons were made using Student’s \( t \) test for either paired or independent data, depending on the particular comparison. Multiple comparisons were adjusted appropriately to maintain the alpha error rate at \( p<0.05 \).23 All results are expressed as mean±SEM.

Results

Conscious Dog Studies

Phasic hemodynamic data from a representative dog are shown for LDC and LD4 interventions during three myocardial metabolic conditions in Figure 2. At the same coronary perfusion pressures, coronary flow was lower during LDC (top panels) than during LD4 (bottom panels).

Total cardiac cycle DCVRI of control beats preceding the LDC and LD4 beats were similar (\( p\geq0.2 \)) within each metabolic state and between paired pacing and normal pacing plus AP conditions (Figures 3 and 4).

The LD4 intervention was examined in 19 dogs. Mean aortic pressure, mean left circumflex coronary blood flow, and myocardial VO\(_2\) for this group of dogs appear in Table 1. Mean DCVRI responses to LD4 interventions, instituted during normal pacing,
Figure 2. Phasic hemodynamic data and electrocardiogram (EKG) from a representative dog. LDC, long diastole control intervention beat; LD4, 400-msec coronary artery occlusion early in a long diastole; NP, normal pacing; PP, paired pacing; NP+AP, normal pacing plus adenosine and phenylephrine infusion to maintain mean aortic pressure and mean coronary flow at PP levels. LDC and LD4 interventions during NP, PP, and NP+AP are shown. A control beat precedes each intervention beat.
paired pacing, and normal pacing plus AP, are shown for this group of dogs in Figure 3. The LD4 DCVRI time courses during all myocardial metabolic conditions in this group of dogs were biphasic (phase 1 slopes less than phase 2 slopes, p<0.05, Table 1). LD4 phase 1 and phase 2 slopes during paired pacing were depressed below the corresponding LD4 slopes during normal pacing plus AP (p<0.05, Table 1).

In a nine-dog subset of the 19 dogs, LDC interventions were instituted to determine effects of the different metabolic conditions on the DCVRI time courses in the absence of coronary occlusion and to provide a reference for the purpose of determining the extent of LD4 slope depression within each metabolic condition. During normal ventricular pacing, slopes of LDC phase 1 and phase 2 were similar (p=0.61). By contrast, DCVRI in the LD4 intervention increased slowly during the first 600 msec after occlusion but increased at a rate ~14-fold greater (p=0.05) during the remaining 400 msec of the long diastole (Figure 4). The mean LD4 phase 1 slope was depressed relative to the LDC phase 1 slope (p<0.05). LD4 phase 2 slopes tended to be lower than LDC phase 2 slopes (p=0.14, Figure 4).

During paired pacing, while maintaining heart rate at 60 beats/min, myocardial VO2 and mean coronary blood flow in the left circumflex coronary bed in-

Figure 3. Graph comparing diastolic coronary vascular resistance index (DCVRI) time courses of long diastoles with a 400-msec coronary occlusion during normal pacing (NP, ■), paired pacing (PP, ▲) and normal pacing plus adenosine and phenylephrine infusion (NP+AP, ○). Mean coronary resistance indexes for preintervention cardiac cycles are shown above control (C on the abscissa). The relation between time and mean DCVRI during the postspike period was linearized in two phases by weighted linear regression analysis. Points represent mean±SEM of 19 dogs.

Figure 4. Graph comparing diastolic coronary vascular resistance index (DCVRI) time courses of long diastole control beats (○) and long diastoles with a 400-msec coronary occlusion (●) during normal pacing (NP), paired pacing (PP), and normal pacing plus adenosine and phenylephrine infusion (NP+AP). Mean coronary resistance indexes for preintervention cardiac cycles are shown above control (C on the abscissa). The relation between time and mean DCVRI during the postspike period was linearized in two phases by weighted linear regression analysis. Points represent mean±SEM of nine dogs.

Table 1. Relation Between Hemodynamics, Myocardial VO2, and Diastolic Coronary Vascular Resistance Index Slopes During Long Diastole With 400-msec Coronary Occlusion for All Dogs

<table>
<thead>
<tr>
<th>Metabolic condition</th>
<th>LD4 DCVRI slopes (mm Hg/ml/sec²)</th>
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<tbody>
<tr>
<td></td>
<td>Phase 1</td>
</tr>
<tr>
<td>NP</td>
<td>21±9</td>
</tr>
<tr>
<td>PP</td>
<td>1±8</td>
</tr>
<tr>
<td>NP+AP</td>
<td>34±10</td>
</tr>
</tbody>
</table>

Values represent mean±SEM of 19 dogs. MVO2, oxygen consumption of the left circumflex coronary bed; MAP, mean aortic pressure; MCF, mean left circumflex coronary flow; LD4, long diastole with a 400-msec coronary occlusion; DCVRI, diastolic coronary vascular resistance index; NP, normal pacing; PP, paired pacing; NP+AP, normal pacing plus adenosine and phenylephrine infusion.

*p<0.05 compared with phase 1; †p<0.05 compared with NP; ‡p<0.05 compared with PP.
The LD4 DCVRI time course during paired pacing was biphasic, as evidenced by a slope smaller before than after the 600-msec join point (p<0.05).

During the third myocardial metabolic state, achieved with normal ventricular pacing plus AP, myocardial VO₂ was not different from myocardial VO₂ during normal pacing alone (p=0.59, Table 2). During normal pacing plus AP infusion, the LDC phase 1 slope was similar to the LDC phase 2 slope (p=0.64), and these slopes were also similar to the corresponding LDC slopes during paired pacing (p≥0.59, Figure 4). As during paired pacing, the LD4 phase 1 slope during normal pacing plus AP was depressed relative to the LDC phase 1 slope (p<0.05, Figure 4). However, the difference between LD4 and LDC phase 1 slopes during normal pacing plus AP was less than the LD4−LDC difference between phase 1 slopes during paired pacing (p<0.05, Table 2). LDC and LD4 phase 2 slopes (80±20 and 80±35 mm Hg/ml/sec², respectively) were parallel during normal pacing plus AP in contrast to the nonparallel relation between LDC and LD4 phase 2 slopes during paired pacing. The LD4−LDC phase 2 slope difference during normal pacing plus AP was smaller than the LD4−LDC phase 2 slope difference during paired pacing (p<0.05, Table 2).

**Anesthetized Dog Studies**

Left circumflex coronary artery pressure was measured distal to the coronary pneumatic occluder in four anesthetized open-chest dogs. Under conditions of paired pacing and normal pacing plus AP, coronary perfusion pressures were virtually identical (p≥0.54) throughout the LD4 time course (Figure 5). During both paired pacing and normal pacing plus AP, LDC and LD4 coronary perfusion pressures were similar at the onset of occlusion, at 50 msec after occlusion release, and for the remainder of diastole (not shown). The difference between mean aortic pressure and distal coronary pressure was approximately 2 mm Hg in each of four anesthetized dogs.

**Discussion**

The key finding in this study is that a 400-msec diastolic coronary artery occlusion induced a biphasic coronary resistance response during a long diastole. This response (under conditions of constant coronary myogenic stimuli) was quantitatively modulated by different myocardial metabolic conditions in a manner consistent with operation of both myogenic and metabolic vasoactive mechanisms.

Divergence of the LDC and LD4 DCVRI rise rates appeared to begin within 200 msec after the end of coronary occlusion during all myocardial metabolic conditions, suggestive of vasoactive mechanism(s) having a rapid response time. Few studies have...
determined the latency of myogenic responses with the temporal resolution used in our study. Furthermore, the latency period and magnitude of a myogenically mediated change in vascular resistance is dependent in part on the magnitude and duration of the myogenic stimulus and the rate at which the stimulus is applied.23 In isolated and in situ preparations, myogenic responses follow the myogenic stimulus with a latency of 2–10 seconds.24 However, the latency period as well as other properties of myogenically mediated responses in isolated or in situ vascular preparations may not serve as reliable indicators of the potential in vivo response.24,25 A latent period as short as 200 msec has been observed in nonvascular smooth muscle.26 A transient (330-msec) increase in coronary perfusion pressure evoked a myogenic vasoconstrictor response in the next cardiac cycle,13 consistent with the rapidity of the hyperemic responses of the present study.

Several studies suggest a basis for rapid and exquisite metabolic regulation of coronary flow including beat-to-beat changes in myocardial ATP, creatine phosphate, inorganic phosphate,27 adenosine and degradative products of adenosine, and glycogen phosphorylase activity.28 Coronal vasodilation that is at least in part metabolically mediated can occur with short latency to onset (~250 msec) after a brief coronary occlusion in conscious dogs.29 These studies indicate that cyclic variation of certain myocardial metabolic parameters and metabolic responses to brief perturbations of the myocardial supply/demand ratio can occur with a rapidity consistent with the responses of the present work.

A major difficulty in distinguishing between myogenic and metabolic vascular responses to perturbations in vivo stems from the practical limitations imposed by simultaneous changes in blood flow and perfusion pressure in the same direction.30 We circumvented the limitations of this obligatory pressure–flow relation during brief coronary occlusion by using two conditions of myocardial metabolic supply and demand in which the myogenic stimuli (transient changes in coronary perfusion pressure) associated with coronary occlusion were similar. Consequently, the observation of a depression of the postocclusion DCVRI rise rate that is greater during paired pacing than during normal pacing plus AP indicates that a metabolic mechanism is at least in part responsible for alteration of the DCVRI time course during paired pacing.

Involvement of a metabolic mechanism, however, does not deny the possibility that a myogenic mechanism was also operating in the response. Myocardial VO$_2$ during normal pacing plus AP was similar to VO$_2$ during normal pacing alone. Yet, blood supply was pharmacologically elevated 46% above the blood delivery rate dictated by myocardial demand, resulting in cardiac metabolic uncoupling. Therefore, it is unlikely that a 400-msec occlusion during normal pacing plus AP produced transient ischemia. If, in fact, there was no metabolic stimulus secondary to the 400-msec occlusion, depression of the phase 1 LD4 slope during normal pacing plus AP was likely mediated primarily and possibly exclusively by a vascular myogenic mechanism. If, in fact, the LD4 phase 1 response was myogenically mediated, it is apparent that vascular myogenic mechanisms can begin operating almost immediately after (or perhaps during) the myogenic stimulus. As during normal pacing plus AP, a myogenic mechanism is believed to have also operated in the phase 1 response period during paired pacing. Thus, the data are consistent with a mechanistic model involving simultaneous operation of metabolic and myogenic vasodilatory mechanisms during phase 1 of the coronary response under conditions of coupled myocardial supply and demand.

During normal pacing plus AP, the LD4 DCVRI phase 2 slope was parallel with the LDC DCVRI phase 2 slope. This suggests that the active, putatively myogenic, vasodilatory mechanism operating during phase 1 had terminated after ~600 msec. Other observations are consistent with continued operation of a metabolic mechanism through phase 2 under conditions of cardiac metabolic coupling. Although the LD4 phase 2 slope during paired pacing was not significantly depressed relative to the LDC phase 2 slope, the difference between these slopes suggests that some mechanism (probably metabolic) continued to operate for the remainder of the 1,000-msec postspike period during paired pacing. This tendency for continued depression of the LD4 phase 2 slope during paired pacing, if in fact due to a metabolic mechanism, would be consistent with the observed complete recovery of the LD4 phase 2 slope during normal pacing plus AP when myocardial metabolic uncoupling is believed to have precluded operation of a metabolic mechanism.

The LD4–LDC phase 1 slope difference during paired pacing exceeded the LD4–LDC phase 1 slope difference during normal pacing plus AP. This observation is consistent with our theory that two independent vasodilatory mechanisms were operating during paired pacing, LD4 phase 1, and that one vasodilatory mechanism was operating during normal pacing plus AP, LDC phase 1. An LD4–LDC phase 2 slope difference greater during paired pacing than during normal pacing plus AP supports our contention that a single vasodilatory mechanism continued to operate during paired pacing, phase 2, and that no vasodilatory mechanism operated during phase 2 of normal pacing plus AP. Also consistent with operation of two vasodilatory mechanisms during phase 1 and one vasodilatory mechanism during phase 2 under paired-pacing conditions are the comparative LD4 slopes during paired pacing and normal pacing plus AP in the group of 19 dogs.

Our data clearly indicate that, when myocardial metabolic supply and demand are closely coupled, a metabolic mechanism is operative in the diastolic reactive hyperemic response to brief coronary occlusion earlier in the same diastole. This conclusion
extends earlier findings that noted decreased vascular resistance after a brief coronary occlusion in the absence of an intervening systole but failed to verify a vasoactive mechanism.

It is important to consider the possibility that, despite myocardial metabolic uncoupling during normal pacing plus AP, the myocardium may have perceived a 400-msec occlusion as a metabolic stimulus. In this event, some component of the coronary LD4 response during the postspike period could be attributable to a metabolic mechanism. However, it is still difficult to explain the LD4 responses observed during normal pacing or paired pacing without invoking a myogenic or other second mechanism, since it is unclear how a single metabolic mechanism could yield two distinct, apparently linear phases of DCVRI depression.

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References


KEY WORDS • metabolic hyperemic mechanism • myogenic hyperemic mechanism • coronary blood flow • coronary vascular resistance index • coronary occlusion
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