Coronary Vasodilation after a Single Ventricular Extra-Activation in the Conscious Dog

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SUMMARY This study was undertaken to determine if coronary blood flow can be regulated in response to a transient increase in cardiac metabolic demand. Eight conscious dogs with experimentally produced complete heart block, a chronically implanted electromagnetic flow probe on the left circumflex coronary artery, and fluid-filled catheters for measurement of left ventricular and aortic pressures were studied. At a paced heart rate of 60 beats/min, a single ventricular extra-stimulus was introduced with a delay of 150–200 msec from the preceding R-wave. The extra-stimulus produced a ventricular extra-activation, but not a discrete mechanical extra-systole. The ensuing beats exhibited systolic potentiation, manifest by a 50 ± 8% increase from control in maximum left ventricular dp/dt in the first potentiated beat, presumably accompanied by increased myocardial oxygen demand. In the diastole immediately following the first potentiated systole, the coronary vascular resistance index (mean aortic pressure/mean coronary flow in that diastole) fell significantly from control by 12 ± 2%. The results indicate that a transient increase in cardiac metabolic demand is followed immediately by a compensatory coronary vasodilation that occurs within the same cardiac cycle. Circ Res 50: 38-46, 1982

A CLOSE coupling exists between coronary blood flow and myocardial energy demand, due to the dependence of the heart on aerobic metabolism and the near-maximal extraction of oxygen from coronary arterial blood under basal conditions. The matching of nutrient flow to cardiac oxygen requirements in the steady state was demonstrated in the early experiments of Eckenhoff et al. (1947) and in subsequent studies (Katz and Feinberg, 1958; Miller et al., 1979; Saito et al., 1980).

To date, it has not been determined whether a similar coupling between coronary blood flow and cardiac metabolic demand exists when the latter quantity is transiently altered. If coronary blood flow is tightly regulated with respect to cardiac metabolism, a transient increase in myocardial oxygen requirements should be accompanied by a simultaneous transient increase in coronary blood flow.

The present investigation tests the hypothesis that beat-to-beat regulation of coronary blood flow can occur in response to a transient augmentation of cardiac metabolic demand. To this end, a brief increase in metabolic demand was produced by the augmentation of contractility which follows a single ventricular extra-activation, and the concomitant coronary vascular responses were observed.

Methods

Surgical Preparation

Eight adult mongrel dogs, weighing 19-32 kg, were anesthetized with sodium thiopental (25–30 mg/kg, iv). After endotracheal intubation, respiration was maintained with an Emerson model 3-PV respirator. A left thoracotomy was performed through the 5th intercostal space and the pericardium was opened. A Medtronic model 6917A, sutureless, unipolar lead and a bipolar pacing electrode constructed in our laboratory were implanted on the free wall of the right ventricle. Complete heart block was produced by injection of less than 1 ml of 40% formaldehyde in the His bundle, using a modification of the method of Steiner and Kovalik (1968). Heart rate was maintained subsequently at 62 beats/min using a Medtronic model 5973 implantable pacemaker and the unipolar pacing electrode constructed in our laboratory were implanted on the free wall of the right ventricle. Complete heart block was produced by injection of less than 1 ml of 40% formaldehyde in the His bundle, using a modification of the method of Steiner and Kovalik (1968). Heart rate was maintained subsequently at 62 beats/min using a Medtronic model 5973 implantable pacemaker and the unipolar pacing lead. The proximal 2 cm of the circumflex branch of the left coronary artery was dissected free, and an electromagnetic flowmeter probe (Howell Instruments model HST) was positioned around the coronary artery. A pneumatic occluder, constructed in our laboratory of polyvinyl...
chloride tubing (2.7 mm, o.d.), was placed around the coronary artery just distal to the flow probe. The occluder site was chosen so that no branch vessels originated between the flow probe and the occluder; this ensured that no blood could flow through the probe when the occluder was inflated. 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 the left ventricular apex into the left ventricular lumen. The flowmeter and bipolar pacing leads, catheters, and pneumatic occluder tubing were tunneled dorsally into a subcutaneous pouch but were not exteriorized until the day of the study to protect them from damage. The unipolar pacing lead was tunneled to a second dorsal subcutaneous pouch in which the pacemaker was placed. The chest was closed, the pneumothorax evacuated, and the animal extubated. The pacemaker was used to maintain heart rate throughout the postoperative period.

Experimental Protocol

Studies were carried out 7–10 days after the initial surgery. All dogs were active and appeared to be in good health, were afebrile, and had hematocrits ranging from 35 to 47%. The dogs were trained to lie quietly on their right sides during the period of study. The laboratory was kept dimly illuminated and free of noise and other activity which might disturb the dogs. The subcutaneous pouches were anesthetized with 2% lidocaine infiltration. The catheters, wires, and tubing were exteriorized through a 1-cm skin incision. A second small incision was made to disconnect the implanted pacemaker; simultaneously, pacing was begun with a programmable stimulator (Devices Instruments Digitimer type 3290) connected to the bipolar pacing lead. The instrument was set to deliver 4-msec square wave pulses 25% above threshold voltage through an isolation unit at a rate of 60/min. This was the basic heart rate maintained through all subsequent interventions. Lead II of a standard electrocardiogram was obtained. Coronary flow was measured with a Howell Instruments model HMS-1000 electromagnetic flowmeter. Flowmeter calibrations, performed by passing a range of measured flows of normal saline through the flowmeter probes, remained linear with a standard deviation of no more than ±8% for all probes used. Aortic and left ventricular pressures were measured with Statham model P23Db pressure transducers. The time derivative of left ventricular pressure (LV dp/dt) was obtained with a Hewlett-Packard model 8814A derivative computer. Data were recorded with a Hewlett-Packard model 3955-D magnetic tape recorder and model 7700 8-channel direct-writing thermal recorder.

A 10-sec complete coronary artery occlusion was performed by abruptly inflating the occluder with an air-filled syringe. This was repeated at least 5 times with an interval of 3–4 minutes between occlusions. The degree of reactive hyperemia was compared to established values for 10-second occlusions (Olsson and Gregg, 1965; Bache et al., 1974) to ensure that the vascular reactivity of the dog was within normal limits. The occlusions also provided a mechanical zero flow baseline that was rechecked before and after each intervention to ensure that no drift had occurred.

To produce a transient increase in cardiac metabolic demand, the stimulator was programmed to deliver a pair of stimuli every 16th beat, followed by 15 single stimuli. The delay between the pair of stimuli was adjusted to achieve the earliest possible second depolarization, and ranged from 150 to 200 msec in this group of dogs. The short delay ensured that the extra-activation did not cause a second ventricular contraction. This 16-beat cycle was repeated 20–40 times in each dog. Figure 1 illustrates a recording of a single ventricular extra-activation of this type.

The passive pressure-resistance characteristics of the intact coronary vasculature were investigated in two dogs. The right femoral artery was exposed under 2% lidocaine anesthesia. An intra-aortic balloon catheter (AVCO-Everett Medical Products, balloon size 12 ml) was introduced into the artery and advanced under fluoroscopic visualization to the arch of the aorta, just distal to the aortic pressure catheter. The balloon was connected to an automatic solenoid-actuated pump (Plastron Medical Devices), designed to inflate and deflate the balloon rapidly at precisely adjustable intervals from the QRS complex of the electrocardiogram.

**Figure 1** A typical phasic recording obtained during the course of a single ventricular extra-activation.
Aortic Pressure (mm Hg)

Left Circumflex Coronary Artery Flow (cc/sec)

FIGURE 2 Phasic data obtained during the course of intra-aortic balloon inflation for one diastole. Arrows denote the interval of inflation.

The pump was set to inflate the balloon for the duration of a single diastole. Balloon distending pressures of 100, 130, and 160 mm Hg were applied. Ten to 15 inflations were performed at each pressure, with successive inflations separated by approximately 30 s. Figure 2 depicts this intervention.

Data Analysis

Analog data from tape were digitized at 200 samples/sec and smoothed once with a three-point moving average digital filter, using an IBM 1130/ System 7 computer. Data were computer analyzed in 10-second segments, two of which were required to describe an extra-activation response. The two segments encompassed 5 control beats preceding the extra-activation and 11–12 beats after the extra-activation. Figure 3 is a schematic representation of a portion of a data segment used to analyze a response to this intervention. The digitized coronary flow data were displayed on an oscilloscope screen for visual identification of specific points in each cardiac cycle. For the purposes of this study, systole corresponds to the ejection phase of the cardiac cycle. Values of peak LV dp/dt were obtained from the original analog recording to avoid errors due to sampling at times other than the peak of that signal.

Several hemodynamic parameters were calculated for each analyzed cardiac cycle. These include mean diastolic and systolic aortic pressures (MDP and MSP, respectively) and mean diastolic and systolic coronary flows (MDF and MSF, respectively). For each beat, the diastolic coronary vascular resistance index was calculated as:

$$DCVRI = \frac{MDP}{MDF}$$

Similarly, the systolic coronary vascular resistance index was calculated as:

$$SCVRI = \frac{MSP}{MSF}$$

A late diastolic coronary vascular resistance index (late DCVRI) was calculated in the same manner as DCVRI, using the second half of each diastolic interval. Values of peak LV dp/dt, left ventricular end-diastolic pressure (EDP), and peak systolic pressure (PSP), were also obtained for each beat. Developed pressure was calculated as

$$DP = PSP - EDP$$

The average value of each hemodynamic parameter for the beats preceding the extra-activation was computed to serve as the control for comparison with the values for each of the individual beats following the intervention. The percentage change from control of these parameters was calculated for each diastole and systole following the intervention, indicated in Figure 3.

In each dog, data segments obtained during 8 to 9 repetitions of the intervention were analyzed, and a single average value for each of the above parameters was obtained. Thus, each dog is weighted equally in the final data summary, regardless of the absolute number of data segments that were available for analysis. The statistical significance ($p < 0.05$) of a change from control in a hemodynamic parameter was determined.
Parameter at a specific post-extra-activation time (e.g., \( S_i \) or \( D_i \)) was assessed with a Sign Test based on the average change in each of the dogs (Snedecor and Cochran, 1967). For each parameter in which a significant change from control occurred, the beat in which the parameter initially departed from control by at least 5% was designated as the onset of the response. The first ensuing beat in which the parameter returned to within 5% of control was designated as the end of the response.

The reactive hyperemic responses to 10-second coronary artery occlusions were assessed by calculating a blood flow debt repayment (%) according to standard methods (Coffman and Gregg, 1960).

**Results**

At a paced heart rate of 60 beats/min, the mean aortic pressure was 93 ± 3 mm Hg (mean ± SEM) and the mean coronary flow was 0.44 ± 0.10 ml/sec. A 10-second coronary artery occlusion resulted in a blood flow debt repayment of 374 ± 47% (range, 166%-623%).

Figure 1 illustrates a typical response to a single ventricular extra-activation. Figure 4 and Table 1 display the pooled results of 67 repetitions of this intervention in eight dogs. In the beat associated with the extra-activation (systole \( S_0 \) and diastole \( D_0 \) in Figures 3 and 4), aortic and left ventricular pressures, peak LV dp/dt, and coronary flow were not different from their control levels. The next systole, designated \( S_i \) in Figures 3 and 4, exhibited the phenomenon commonly referred to as post-extrasystolic potentiation (Hoffman et al., 1956), but more aptly described as "premature activation potentiation" (Koch-Weser, 1966), since the second depolarization in this study was mechanically ineffective. The potentiation, or increased contractility, of \( S_i \) was manifest by a statistically significant 50 ± 8% rise in peak LV dp/dt above control levels, accompanied by a significant 13 ± 2% increase in developed pressure. The ratio of peak LV dp/dt/DP rose 35 ± 1% over control. A 9 ± 1% significant increment in aortic and left ventricular mean systolic pressure occurred, as well. The following diastole, \( D_i \), exhibited a significant 7 ± 1% increase in mean aortic diastolic pressure over control. Diastolic coronary flow rose more than proportionally to the increased perfusion pressure, reflected in

### Table 1  Changes in Hemodynamic Parameters after a Single Ventricular Extra-Activation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( S_0 )</th>
<th>( D_0 )</th>
<th>( S_1 )</th>
<th>( D_1 )</th>
<th>( S_2 )</th>
<th>( D_2 )</th>
<th>( S_3 )</th>
<th>( D_3 )</th>
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<th>( S_5 )</th>
<th>( D_5 )</th>
<th>( S_6 )</th>
<th>( D_6 )</th>
<th>( S_7 )</th>
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<tr>
<td>Maximum LV dp/dt</td>
<td>-2 ± 3</td>
<td>+50 ± 8*</td>
<td>+41 ± 7*</td>
<td>+28 ± 4*</td>
<td>+22 ± 3*</td>
<td>+22 ± 4*</td>
<td>+12 ± 4</td>
<td>+8 ± 3</td>
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<tr>
<td>Mean systolic aortic pressure</td>
<td>+1 ± 1</td>
<td>+9 ± 1*</td>
<td>+10 ± 1*</td>
<td>+9 ± 1*</td>
<td>+8 ± 1*</td>
<td>+7 ± 1*</td>
<td>+6 ± 1</td>
<td>+4 ± 1</td>
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<td>Mean diastolic aortic pressure</td>
<td>+2 ± 1</td>
<td>+7 ± 1*</td>
<td>+8 ± 1*</td>
<td>+8 ± 2*</td>
<td>+8 ± 2*</td>
<td>+7 ± 2*</td>
<td>+6 ± 1</td>
<td>+4 ± 1</td>
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<tr>
<td>DCVRI</td>
<td>-1 ± 2</td>
<td>-12 ± 2*</td>
<td>-11 ± 3*</td>
<td>-9 ± 3</td>
<td>-6 ± 2</td>
<td>-3 ± 2</td>
<td>-1 ± 2</td>
<td>0 ± 2</td>
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<tr>
<td>Late DCVRI</td>
<td>-5 ± 2</td>
<td>-14 ± 2*</td>
<td>-12 ± 2*</td>
<td>-9 ± 3</td>
<td>-7 ± 3</td>
<td>-4 ± 2</td>
<td>-1 ± 2</td>
<td>2 ± 2</td>
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<tr>
<td>SCVRI</td>
<td>-7 ± 3</td>
<td>-2 ± 6</td>
<td>-5 ± 2</td>
<td>-5 ± 5</td>
<td>-6 ± 5</td>
<td>-6 ± 4</td>
<td>-4 ± 5</td>
<td>-3 ± 4</td>
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All results are expressed as percentage change from the average value obtained during control beats (mean change ± SEM). Post-extra-activation time intervals correspond to those indicated in Figure 3.

* Significantly different from control \( (P < 0.05) \), as assessed by a Sign Test.
Statistically significant drops of 12 ± 2% in DCVRI and 14 ± 2% in late DCVRI in D1.

Systolic potentiation was maximal in the first potentiated beat, with peak LV dp/dt returning to its control level in systoles S2-S1. Maximum mean systolic pressure (10 ± 1% over control) was attained in the second potentiated systole, S2, while maximum mean aortic diastolic pressure (8 ± 1% over control) was attained in the ensuing diastole, D2, and maintained through D4. Systolic and diastolic aortic pressures remained significantly above their control levels for a total of seven cardiac cycles. Left ventricular EDP was not affected by this intervention, showing no significant change from its control value of 13 ± 2 mm Hg in any of the beats following the extra-activation. The minimal of DCVRI and late DCVRI occurred in D1; these parameters returned toward control in the following beats, with DCVRI and late DCVRI remaining significantly reduced until diastole D6.

The SCVRI exhibited a variable pattern from dog to dog. In four dogs, SCVRI decreased in the potentiated systoles, in three animals an increase in SCVRI was observed, and in one dog there was no appreciable change. The pooled results failed to demonstrate significant changes in SCVRI in any of the potentiated beats.

Figure 2 is a recording of data obtained during inflation of the intra-aortic balloon for a single diastole. Figure 5 displays the results of nine inflations at each of three levels of pressure in one of the dogs. Inflation of the balloon with 100, 130, and 160 mm Hg pressure caused mean pressure in that diastole to increase by an average of 4, 10 and 13% above control mean diastolic pressure, respectively. Simultaneously, DCVRI fell by an average of 0, 3, and 4%, respectively, below its control value. Figure 5 compares these changes in pressure and resistance with those occurring in the same dog in the D1 intervals following a single ventricular extra-activation. This intervention resulted in an average decrease of 10% in DCVRI from control levels. Similar results were obtained in the other dogs studied in this manner. Thus, comparable increases in mean diastolic pressure were accompanied by much larger decreases in DCVRI following an extra-activation than during inflation of the balloon.

Discussion

The results of the present study indicate that coronary vascular resistance is sensitively and rapidly adjusted in response to transient changes in cardiac metabolic demand. When contractility is increased after a single ventricular extra-activation, a compensatory fall in coronary vascular resistance occurs within the same cardiac cycle as the initial augmentation of cardiac energy demand.

The current findings were obtained in conscious dogs with normal coronary vascular reactivity, as assessed by the reactive hyperemic response to a standard 10-second coronary occlusion. The blood flow debt repayment (averaging 374%) is within the range of values reported by others (Olsson and Gregg, 1965; Bache et al., 1974). The use of an experimental preparation with complete heart block and external ventricular pacing at a constant rate of 60 beats/min has several advantages. The introduction of an early extra-activation results in maximal potentiation of the ensuing beats at this slow but physiological heart rate (Koch-Weser, 1966). In addition, any effects of beat-to-beat changes in heart rate on coronary vascular resistance are eliminated.

The observation that the first contraction after an extrasystole is stronger than the beats of the preceding regular rhythm was first made by Langendorff (1885), using an isolated frog heart preparation. Woodworth (1903) noted in the spontaneously beating apex of dog heart that the degree of post-extrasystolic potentiation increased with the prematurity of the extrasystole. Koch-Weser (1966), using isolated cat papillary muscle, systematically described the degree of potentiation resulting from varying the prematurity of activation at various contraction frequencies. He noted that when a premature stimulus was applied, the necessary and sufficient condition for potentiation was propagation of an action potential, and not the extent to which the contractile elements respond to this extra-activation. Thus, an early extra-activation is capable of producing potentiation without a discrete mechanical extrasystole. Such early extra-activations were employed in this investigation to allow cardiac metabolic demand to be increased by an augmentation of contractility and systolic wall tension without the additional factor of an extra mechanical systole. The additional throttling of
coronary flow resulting from an extra contraction would have caused difficulty in separating the effect of decreased oxygen supply from that of increased oxygen demand on the coronary vasculature.

In this preparation, it was not possible to measure the transient changes in myocardial oxygen consumption (MVO₂) resulting from the experimental intervention. However, other investigators have measured the steady state change in MVO₂ resulting from continuous paired pacing with minimal delay between pairs of stimuli. Chardack et al. (1965), studying open-chest dogs with either right heart or right heart-lung bypass, found that paired pacing at heart rates of 100 to 160 beats/min increased coronary blood flow by an average of 57% and MVO₂ by an average of 70% above the levels obtained by pacing with single stimuli at the same mechanical rate. Bache et al. (1973) performed a similar experiment in conscious dogs at a mechanical rate of 120 beats/min. With paired pacing, the average increases in coronary blood flow and MVO₂ were 35% and 28%, respectively. Although it is impossible to extrapolate these results to the case of a single paired activation, it is reasonable to assume that this intervention also increases MVO₂.

Data are reported here in terms of a coronary vascular resistance index (CVRI), defined as the mean inflow perfusion pressure divided by the mean coronary flow during the time interval in question. Calculation of a true coronary vascular resistance (CVR) requires knowledge of an effective downstream pressure representing the height of the "vascular waterfall" (Permutt and Riley, 1963; Bellamy, 1978). Since this is not a measurable quantity at present and since the purpose of this study was to detect changes in CVR rather than to quantify the absolute value of that variable, the CVRI is a convenient parameter by which to gauge the responses to these interventions. The height of the vascular waterfall is thought to depend on the level of vascular smooth muscle tone and on the intramyocardial tissue pressure. The latter quantity, in turn, is a function of left ventricular pressure. The hypercontractile beats following a ventricular extra-activation probably result in a smaller end-systolic volume; consequently, the early diastolic LV pressure and diameter following these contractions may be slightly lower than in control beats. This, in turn, would increase the effective pressure gradient for coronary flow by lowering early diastolic ventricular wall stress and intramyocardial tissue pressure. Thus, the increased coronary flow in these beats could be due to the combined effects of decreased vascular resistance, increased inflow perfusion pressure, and decreased downstream pressure. The calculation of the DCVRI does not take the last factor into account, and thereby might overestimate the contribution of decreased vascular resistance. To assess the potential magnitude of such an error, the late diastolic CVRI was calculated.

The calculation of coronary vascular resistance in the second half of diastole is based on the assumption that ventricular filling is virtually complete by the end of the first half of diastole. This assumption was verified in two dogs in which a set of circumferentially oriented, ultrasonic segmental dimension crystals had been placed midway through the anterior wall of the left ventricle. In control beats at a rate of 60/min, an average of 90% of the total diastolic segmental elongation occurred within the first half of diastole. In D₁ diastoles following extra-activations, an average of 91% of the total diastolic elongation had occurred. In addition, LV EDP following the hypercontractile beats was not different from control. Consequently, LV diastolic size and diastolic pressure in the second half of diastole following hypercontractile beats should not be appreciably different from control, and the late DCVRI calculated during this interval should not be susceptible to the above-mentioned potential error during early diastole. The results reveal that changes in late DCVRI were not appreciably different from those in DCVRI calculated over all of diastole. Also, the time courses of the changes in these two parameters bear a qualitative resemblance (Table 1). Therefore, any effect of decreased LV diastolic size and pressure on DCVRI is minor, and both the DCVRI and late DCVRI provide valid estimates of the changes in CVR following a ventricular extra-activation.

In the cardiac cycle associated with the extra-activation (systole S₀ and diastole D₀), there were no significant changes from control in peak LV dp/dt, mean diastolic and mean systolic pressures, or DCVRI. No change in contractility or blood pressure is expected, since potentiation begins in the following beat. The lack of change in DCVRI is consistent with the fact that electrical activation in the absence of an accompanying contraction causes a minimal increase in MVO₂ (Klocke et al., 1966) which should not elicit a change in vascular resistance.

The first potentiated systole, S₁, exhibited a significant 50 ± 8% increase in peak LV dp/dt, and a significant 9 ± 1% increase in mean systolic pressure, presumably associated with an increase in MVO₂ above the control level. It is possible that compensatory coronary vasodilation began in this systole; however, the rise in mean systolic pressure may have masked such active vasodilation by increasing systolic extravascular compression. The net change in SCVRI in this and in the following potentiated systoles may reflect which of these two opposing factors was predominant. The dog-to-dog variation in the changes in SCVRI may indicate that the relative importance of active vasodilation and extravascular compression differed among these animals.

The key finding of this experiment is the significant 12 ± 2% fall in DCVRI (14 ± 2% fall in late DCVRI) which occurred in diastole D₁. In this diastole, immediately following the initial period of
increased cardiac metabolic demand (systole S1), a compensatory decrease in coronary vascular resistance occurred. Thus, coronary blood flow was adjusted within a single cardiac cycle to meet a change in cardiac metabolic demand. This is evidence of an extraordinarily sensitive and rapid regulatory mechanism.

While peak LV dp/dt began to return toward control in systole S2, maximum mean systolic pressure did not occur until systole S3, and maximum mean diastolic pressure was not attained until diastoles D2-D4. Most likely, the pressure maxima occurred after that of peak LV dp/dt, because of the cumulative effect of the increased stroke volume ejected into the aorta by successive hypercontractile systoles. It is notable that the shape of the return of DCVRI values to control qualitatively mirrors that of peak LV dp/dt (Fig. 4). This may be indicative of a continued beat-to-beat metering of coronary vascular resistance to cardiac metabolic demand throughout the duration of this response.

An examination of the additional volume of coronary flow after an extra-activation provides another means of describing the response to this intervention. In the 12 beats analyzed after an extra-activation, total coronary flow averaged 5.72 ml. This compares with an average of 5.20 ml of flow during 12 control beats. The difference of 0.52 ml can be attributed to the combined effects of increased perfusion pressure and decreased vascular resistance. It is not possible to determine precisely the relative contributions of these two factors. However, it is possible to calculate the flow which would have occurred if inflow pressure alone had increased while resistance had remained constant at control levels, and if the effect of downstream pressure is ignored. Under these conditions, coronary flow in the 12 beats following an extra-activation would have averaged 5.43 ml. There still remains 0.29 ml of flow (5.72-5.43 ml) which cannot be attributed to increased perfusion pressure and which may reflect the effect of decreased CVR.

The introduction of a single extra-activation results in an increase in coronary perfusion pressure. Any non-rigid tube, such as a blood vessel, will distend when subjected to increased intraluminal pressure. The resulting increase in cross-sectional area decreases the resistance to flow through the conduit in question. A reduction in vascular resistance by this mechanism is a passive phenomenon, related to the elastic properties of the vessel wall, and is independent of changes in active vascular smooth muscle tone.

In these experiments, it was necessary to determine to what extent passive distension of vascular structures contributed to the observed decrease in coronary vascular resistance. Three types of evidence indicate that passive effects had but a minor influence on the results. First, the histogram representing the changes in DCVRI following an extra-activation does not bear a qualitative resemblance to that representing the changes in mean diastolic pressure (Fig. 4). If there were a causal relationship between these two parameters, a strong similarity in the appearance of their histograms would be expected. The second piece of evidence was obtained by pairing the D1 diastole following each extra-activation, when DCVRI changes were maximal, with a control beat with the same mean diastolic pressure. Although, on the average, mean diastolic pressure in D1 was higher than control, there was sufficient variability in pressure in the control beats to permit such a pairing. In the control diastoles, mean diastolic pressure averaged 94 mm Hg and DCVRI averaged 229 mm Hg/ml per sec. In the D1 diastoles, mean diastolic pressure averaged 94 mm Hg but DCVRI averaged 200 mm Hg/ml per sec (P < 0.05 compared to control). If passive factors alone were responsible for the changes in DCVRI, then control and post-intervention beats of identical mean diastolic pressure should have had the same DCVRI. The finding that the D1 beats had significantly lower DCVRI than control beats of the same pressure indicates that passive distension alone cannot account for the data.

To quantify the effect of passive distension on DCVRI, the intra-aortic balloon experiment was performed. The effect of inflation of the balloon was to increase diastolic aortic pressure, and, thus, coronary perfusion pressure, for the length of a single diastole. Previous data from this laboratory (Schwartz et al., 1981) have shown that, following a coronary artery occlusion of duration shorter than one diastole, changes in vascular resistance do not occur until the succeeding systole. Also, Bellamy (1978) has obtained linear coronary pressure-flow relations, indicating constant CVR, during the course of long diastoles. In light of these studies, it is reasonable to assume that when coronary perfusion pressure is increased by inflation of the intra-aortic balloon, changes in active vascular smooth muscle tone do not occur within the same diastole. Thus, any changes in DCVRI during the diastole of inflation can be attributed to passive distension of the vasculature by the increased perfusion pressure. The results shown in Figure 5 indicate that such a passive mechanism could account for only a small fraction of the decrease in DCVRI following an extra-activation. For example, a 10% average increase in mean diastolic pressure due to inflation of the balloon caused an average 3% drop in DCVRI, presumably by a passive mechanism. But the D1 diastoles following an extra-activation showed a 10% average drop in DCVRI with just a 5% average rise in mean diastolic pressure.

Several mechanisms for the regulation of coronary blood flow have been proposed. The myogenic hypothesis, first formulated by Bayliss (1902), postulates that vascular smooth muscle tone is regulated in response to a counteracting force applied by the intravascular distending pressure. According to this theory, a rise in arterial pressure would
increase the passive mechanical stretch of the smooth muscle, causing its active tone and, hence, vascular resistance, to increase. Since the current experiment produced a fall in vascular resistance accompanying a rise in arterial pressure, it is improbable that a myogenic mechanism was involved. One study (Johansson and Mellander, 1975) has indicated that the rate of change of transmural pressure, as well as its absolute value, determines the magnitude of a myogenic response. If the difference of aortic and left ventricular pressures is taken as an index of transmural coronary pressure, then transmural pressure decreases more rapidly in early systole and increases more rapidly in late systole of the hypercontractile beats. This is evident from Figure 1, which demonstrates that both maximum positive and negative dp/dt are increased in the hypercontractile beats. Thus, any potential myogenic effects of these increases in the rates of change of transmural pressure are likely to cancel one another.

The autonomic nervous system is capable of modulating the primary control of the coronary circulation by local mechanisms, but does not alter the basic coupling between coronary blood flow and MVO₂. Gregg et al. (1972) studied the effects of surgical cardiac denervation on the coronary vascular responses to exercise and excitation in conscious dogs. Both at rest and during treadmill exercise at 10° grade and 9 km/hr, coronary blood flow and MVO₂ in the denervated dogs were roughly half their levels in the control dogs. However, denervation did not affect the proportionality of increases in coronary blood flow and MVO₂. Bache et al. (1975) studied the effects of surgical denervation, chemical sympathectomy with 6-hydroxydopamine, and adrenergic blockade with propranolol and phentolamine on reactive hyperemia following 10-second coronary occlusions in conscious dogs. In no instance was the degree of reactive hyperemia significantly different from that obtained in control dogs. These studies indicate that appropriate regulation of coronary blood flow, in response to changes in cardiac oxygen demand or supply, occurs in the absence of autonomic nervous influences. However, experimental activation of coronary vascular α-adrenergic receptors by cardiac sympathetic nerve stimulation or intracoronary norepinephrine infusion has been found to attenuate the vasodilation accompanying an increase in myocardial metabolic activity (Mohrman and Feigl, 1978; Smith et al., 1978).

It is plausible that the observed decline in DCVRI following an extra-activation resulted from a reflex withdrawal of α-adrenergic vasoconstrictor tone or an increase in β-adrenergic or vagal vasodilator tone; however, the potential involvement of such mechanisms was not investigated. Two characteristics of the DCVRI data are difficult to reconcile with any type of nervous reflex. First, if the fall in DCVRI represents the response to a neural reflex stimulated by the extra-activation, there is no apparent reason why this response should consistently be delayed one cardiac cycle, until after the first potentiated systole. Second, if neural factors were responsible for the decrease in DCVRI, the close correspondence between the shapes of the peak LV dp/dt and DCVRI histograms would be purely fortuitous.

Until recently, it was deemed unlikely that coronary blood flow could be regulated in response to myocardial metabolic need within a time span briefer than several seconds (Olsson, 1975; Belloni, 1979). This viewpoint was supported by Olsson's calculation that myocardial myoglobin contains oxygen stores sufficient to sustain myocardial metabolism for 6 seconds (Olsson, 1964), and by the observation that myocardial lactate production, an indicator of anaerobic metabolism, cannot be detected in coronary sinus blood until 6 seconds of coronary occlusion have elapsed.

At present, however, considerable evidence has been amassed to support the hypothesis that myocardial metabolic perturbations can occur on a beat-to-beat basis. Harden et al. (1979), studying isolated isovolumetric contracting rabbit hearts perfused with Krebs-Ringers solution, detected increased epicardial NADH fluorescence within 1-2 seconds of a coronary artery occlusion. This indicates a decrease in the reduction of oxygen at the terminus of the electron transport chain, due to a fall in mitochondrial oxygen tension. Thompson et al. (1980) used a quick-freeze biopsy technique to measure myocardial adenosine and its degradation products at various points in the cardiac cycle of isolated perfused guinea pig hearts. The sum of the concentrations of adenosine, inosine, and hypoxanthine was significantly increased at mid-systole, compared to diastole. With the addition of an inhibitor of adenosine deaminase or of adenosine uptake, a significant rise in the concentration of adenosine itself was demonstrated at mid-systole. In addition, it should be noted that the oscillations of these metabolites were large in comparison to their mean levels; for example, the mid-systolic sum of adenosine, inosine, and hypoxanthine was more than double the diastolic level. The cyclic production of vasoactive metabolites, coincident with tension development and the major portion of myocardial oxygen consumption (Monroe, 1964), supports the metering of coronary vascular resistance to myocardial metabolism on a beat-to-beat basis. Recent data from this laboratory (Schwartz et al., 1981) demonstrated that myocardial reactive hyperemia in the conscious dog follows occlusion of a coronary artery for fractions of a single diastole. The onset of reactive hyperemia was always delayed until the occurrence of the first post-occlusion systole, suggesting that a metabolic deficit was set up by the brief occlusion, but not sensed until the more rapid myocardial oxygen consumption and energy utilization of the succeeding systole.
Since the interventions employed in this study yielded results inconsistent with a passive mechanical, myogenic, or neural basis, since cardiac metabolic demand was undoubtedly increased, and since existing evidence in the literature supports the notion of rapid changes in cardiac metabolism, it is most likely that the current observations reflect a metabolic mechanism whereby coronary vascular resistance is metered to cardiac metabolic demand on a beat-to-beat basis. However, the definitive proof of such a mechanism awaits the identification of a specific chemical mediator released in response to this intervention in sufficient quantity to account for the observed vascular responses.

Acknowledgments

We express our gratitude to Kirby Cooper and Eric Fields for surgical preparations, Donald G. Powell and the staff of the Durham Veterans Administration Medical Center Illustration Service, J. Michael Taylor and the staff of the Durham Veteran Administration Medical Center Animal Care Facility, Susan Brazzamano and Marjorie Grubb for their help, and to Mary Jane Porterfield for skillful preparation of the manuscript.

We are especially grateful to Dr. Judith C. Rembert for her invaluable assistance in the pilot studies and her help in perfecting the methodology.

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Circ Res. 1982;50:38-46
doi: 10.1161/01.RES.50.1.38

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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