Regulation of Large Coronary Arteries by Increases in Myocardial Metabolic Demands in Conscious Dogs

PILAR MACHO, THOMAS H. HINTZE, AND STEPHEN F. VATNER

SUMMARY In order to assess the effects of increasing myocardial metabolic demand on the large epicardial coronary arteries, we measured left circumflex coronary artery diameter (ultrasonic transit time technique) and blood flow in conscious dogs with chronically implanted transducers. Myocardial oxygen consumption was increased by pacing-induced tachycardia and aortic constriction, and monitored by multiplying left circumflex coronary arterial blood flow by coronary arterio-venous oxygen content difference. Increase of heart rate by 90 beats/min caused myocardial oxygen consumption to increase by 34 ± 4.3% (1 SEM); coronary blood flow at constant arterial pressure to increase by 32 ± 6.8%; and coronary diameter to increase by 0.07 ± 0.01 mm, P < 0.01. Aortic constriction, producing a 53 ± 5.1% increase of left ventricular systolic pressure, caused myocardial oxygen consumption to increase by 49 ± 7.2%, coronary blood flow to increase by 50 ± 6.0%, and coronary diameter to increase 0.13 ± 0.03 mm, P < 0.01. The increases in coronary artery diameter were gradual, not immediate, in onset and not altered by β-adrenergic blockade. Thus, increased myocardial metabolic demand dilates large epicardial coronary arteries, but with a slower response time than the rapid dilation of the smaller resistance vessels.

It is widely recognized that coronary arteriolar vessels are exquisitely sensitive to changes in myocardial metabolic demands (Berne and Rubio, 1979). It is not known whether large coronary vessels also are regulated by changes in myocardial metabolic demands. This topic has not been examined adequately due to lack of appropriate techniques, despite considerable clinical interest in view of the critical role played by large coronary vessels in the ischemic heart. The goal of the present investigation was to determine for the first time, using direct and continuous measurements, the effects of increasing myocardial metabolic demands, caused by increasing either cardiac frequency or afterload, on large and small coronary vessels in conscious dogs. Conscious dogs were studied in order to eliminate the potentially confusing effects of anesthetics and recent surgical manipulation on coronary vasoactivity (Vatner and Braunwald, 1975).

Methods

Mongrel dogs (n = 20) were anesthetized with pentobarbital Na, 30 mg/kg. Transducers were implanted through a thoracotomy in the 5th left intercostal space. Two miniature 7-MHz ultrasonic transducers (2 × 1 mm, 12 mg) were implanted on opposing surfaces of the left circumflex coronary artery, 3-6 cm from its origin. The ultrasonic transducers were covered with Insl-X (Insl-X Products Corp.) and attached to a Dacron (Dupont, de Nemours and Co., Inc.) backing. The Dacron was sutured to the outer adventitia of the coronary artery using Ethicon 6-0 suture (Ethicon, Inc.). An electromagnetic (Zepeda Inst.) or Doppler flow transducer was implanted distally on the same vessel in 14 dogs. An hydraulic occluder was implanted distal to the electromagnetic flow probe to establish zero blood flow. Pacing electrodes were implanted on the right atrium. Miniature pressure gauges (Königsberg Instruments, Inc.) were implanted in the left ventricle and descending thoracic aorta and heparin-filled Tygon (Norton Co., Plastics and Synthetics Div.) catheters were implanted in the left atrium and descending thoracic aorta. In five dogs, an hydraulic occluder was implanted around the ascending aorta. In four dogs at a subsequent operation using pentobarbital, Na, 30 mg/kg, and a right thoracotomy, a Tygon catheter was implanted in the coronary sinus. In one of these dogs, a pair of miniature ultrasonic crystals was implanted on opposing surfaces of the right coronary artery.

Left ventricular (LV) pressure was measured with the implanted miniature gauge, which was calibrated in vitro with a mercury manometer and cross-calibrated in vivo with measurements of pressure from the aortic and left atrial catheters. Coronary blood flow was measured with a Benton square wave electromagnetic flowmeter (Benton Instruments, Cupertino, CA), or a Doppler ultrasonic...
Flowmeter. In the experiments using the electromagnetic flowmeter, zero blood flow was assessed by inflating the implanted hydraulic occluders. Phasic coronary arterial diameter was measured instantaneously and continuously with an improved ultrasonic dimension gauge (Patrick et al., 1974; Pagani et al., 1978; Vatner et al., 1980). This instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of 1.5 × 10^6 mm/sec between the 7-MHz piezoelectric crystals, thus giving a record of instantaneous external coronary arterial diameter. To measure these relatively small dimensions accurately, the instrument used in this study was further modified to minimize the acoustic disturbance generated by the electrical excitation of the transmitting crystal. This was accomplished by placing 1000-ohm rheostats in parallel with crystals at the exciter output and receiver input. These rheostats were adjusted to minimize the ringing observed in the receiving crystal, without substantially affecting the amplitude of the received echo. In addition, the basic 1-MHz repetition rate of the dimension gauge was changed to 2 MHz. This doubled the amplitude of the output voltage and also permitted precise calibrations in 0.5-μsec steps. The frequency response of the dimension gauge is flat to 100 Hz. The drift of the instrument is minimal, i.e., less than 0.01 mm in 6 hours. To further ensure data reliability, repeated calibration references were obtained regularly throughout the experiments, and the received ultrasonic signal was monitored continuously on an oscilloscope. Any major changes in alignment of the crystals was detected in the received signal and invalidated the experiment. Measurements of arterial and coronary sinus O_2 content were made using a Lex O_2 Con (Lexington Instruments, Waltham, MA) oxygen analyzer.

The experiments were conducted 1-2 weeks after operation in healthy conscious dogs lying quietly. Measurements of left circumflex coronary arterial diameter, aortic root pressure, LV pressure, and heart rate were continuously recorded during control conditions and interventions. The various interventions were carried out on different experimental days.

The effects of increasing heart rate by electrical stimulation of the atria were examined. In two dogs, heart rate was varied rapidly and transiently (within 5 seconds) over a wide range (from 90 to 240 beats/min) with an electronic pacemaker. Values of coronary diameter were plotted against LV end-diastolic pressure for these beats. In 11 dogs, a control period was recorded when pacing the heart at a rate just above the spontaneous rate. Then heart rate was increased by steps of 30 beats/min up to an increase of 90 beats/min. Each step was held for 3 minutes. In four dogs pretreated with propranolol, 1 mg/kg, electrical pacing was insti-

The data were recorded on a 14-channel tape recorder (Bell and Howell Co., Datatape Div.) and played back on two multichannel oscillographs (Gould-Brush). Mean pressures and coronary diameters were assessed using RC-filters with 2-sec time constants. LV dP/dt was derived by differentiating the LV pressure signal with a Philbrick operational amplifier (Teledyne Philbrick), connected as a differentiator and having a frequency response of 700 Hz. A triangular signal with known slope (rate of change) was substituted for the pressure signal to calibrate the differentiator directly. Heart rate was measured continuously with a cardiotachometer triggered by the LV pressure pulse. Although external coronary diameter was measured continuously, the internal radius was calculated by determining at autopsy the thickness and mass of a coronary artery with known length from the point at which the piezoelectric crystals were located. Thus, wall volume could be calculated as the quotient of mass and density (d = 1.06 g/cm³). After the wall volume, one wall thickness value, and external diameter were known, the internal changing diameter and cross-sectional area (CSA) were calculated.

Late diastolic coronary resistance (LDCR), which reflects primarily small coronary vessel resistance, was calculated as the quotient of late diastolic arterial pressure and late diastolic coronary blood flow. An index of MVO_2 was calculated from the product of O_2 extracted across the heart and left circumflex coronary blood flow. Since only a fraction of total coronary blood flow was measured, i.e., left circumflex coronary blood flow, the values do not represent total MVO_2, but rather an index of MVO_2. Mean and SEM were calculated for...
all variables. Data were analyzed using analysis of variance (Armitage, 1973).

Results

Results are expressed as percent change from control (mean ± SEM). Control values can be found in the tables and figures. Coronary blood flow, LDCR, coronary diameter, and CSA refer to the left circumflex coronary artery.

I. Effects of Increasing Heart Rate (Table 1)

When heart rate was increased transiently and rapidly (in less than 5 seconds) by electrical stimulation from 90 to 240 beats/min, mean arterial and LV systolic pressures, coronary diameter and CSA did not change. Whereas LV end-diastolic pressure fell from 12.4 to 2.5 mmHg.

When heart rate was increased and held at an elevated level, mean coronary diameter and CSA began to rise in 9.6 ± 2.7 sec and reached a plateau by 1 minute (Fig. 1). Steady state values collected at 1-3 minutes after attaining the elevated rate are presented. When heart rate was elevated by 90 beats/min, mean arterial and LV systolic pressures did not change significantly, and LV dP/dt rose slightly, but not significantly. Mean coronary blood flow increased progressively, rising by a maximum of 32 ± 6% (Fig. 2). LDCR fell by 38 ± 4% while mean coronary diameter and CSA increased significantly by 1.57 ± 0.3% and 8.20 ± 1.8%, respectively (Fig. 3). Arterial and coronary sinus O2 contents did not change significantly from control values of 13.3 ± 0.4 and 2.7 ± 0.1 Vol%, respectively. MVO2 index increased by 34.0 ± 4.3% from a control value of 5.3 ± 0.6 ml O2/min.

In four experiments after β-adrenergic blockade, heart rate was elevated by 60 beats/min from 98 ± 4.8 beats/min. LV end-diastolic pressure fell from 10.4 ± 1.4 to 5.2 ± 1.1 mm Hg, and coronary diameter and CSA rose (P < 0.01) by 2.6 ± 0.4% and 11 ± 1.8%, respectively. In these experiments, LV end-diastolic pressure then was returned to 10.4 ± 1.4 mm Hg with saline infusion during pacing at the elevated rate. Under these conditions, mean coronary diameter and CSA rose further by 2.5 ± 1.1% and 10 ± 4.7%, respectively.

II. Effects of Aortic Constriction (Table 2)

During the steady state, i.e., 40-60 seconds after initiation of aortic constriction, heart rate was not significantly different from the control of 97 ± 5.4 beats/min, but this stimulus increased LV systolic pressure by 53 ± 5.1%, LV end-diastolic pressure by 14 ± 4.2%, mean coronary blood flow by 50 ± 6.0%, mean coronary diameter and CSA by 3.0 ± 0.7%, and 13 ± 3.1, respectively. Aortic root pressure did not change in one dog in which it was measured. (Fig. 4), but rose by 10 mm Hg in the other dog in which it was measured. Right coronary artery diameter, which was measured in one dog, rose initially with aortic constriction, but returned to control levels during maintained constriction. In contrast, left circumflex diameter in the same dog continued to rise (Fig. 5). Oxygen content did not change significantly from control values with aortic constriction in either the arterial (13 ± 0.5 Vol%) or coronary sinus (2.7 ± 0.1 Vol%) samples, whereas the MVO2 index rose by 49 ± 7.2%. The responses to aortic constriction were not altered significantly by β-adrenergic blockade.

Discussion

The effects of increasing myocardial metabolic demands have not been examined previously on direct and continuous measurements of coronary dimensions. The lack of information is due most likely to the absence of appropriate measuring devices. Recently we developed a technique to measure left circumflex coronary diameter directly and continuously in conscious dogs (Vatner, et al., 1980). We used this methodology in the current investigation and examined the extent to which large and small coronary vessels responded to changes in myocardial metabolic demands. Myocardial metabolic demands were elevated by increasing heart rate with electrical stimulation and by increasing afterload with aortic constriction. Effects on small coronary vessels were assessed by calculations of LDCR, whereas effects on large coronary vessels were assessed by calculations of CSA.

As expected, step increases in heart rate induced step-wise reductions in LDCR and appropriate el-

**Table 1: Effects of Increasing Heart Rate by 90 Beats/min**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Change from control during steady state increase in heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>100 ± 2.8</td>
<td>-0.8 ± 1.4</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>120 ± 3.2</td>
<td>1.4 ± 2.9</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>2597 ± 134</td>
<td>232 ± 90</td>
</tr>
<tr>
<td>Mean coronary blood flow (ml/min)</td>
<td>49.9 ± 5.8</td>
<td>16.5 ± 3.5*</td>
</tr>
<tr>
<td>Late diastolic coronary blood flow (ml/min)</td>
<td>61.5 ± 11.3</td>
<td>34.2 ± 9.7*</td>
</tr>
<tr>
<td>Mean coronary resistance (mm Hg/ml per min)</td>
<td>2.75 ± 0.83</td>
<td>-0.62 ± 0.13*</td>
</tr>
<tr>
<td>LDCR (mm Hg/ml per min)</td>
<td>1.38 ± 0.06</td>
<td>-0.53 ± 0.06*</td>
</tr>
<tr>
<td>Mean coronary diameter (mm)</td>
<td>3.95 ± 0.19</td>
<td>0.07 ± 0.01*</td>
</tr>
<tr>
<td>CSA (mm²)</td>
<td>6.50 ± 0.56</td>
<td>0.51 ± 0.11*</td>
</tr>
<tr>
<td>MVO2 index (ml O2/min)</td>
<td>5.92 ± 0.60</td>
<td>1.73 ± 0.22*</td>
</tr>
</tbody>
</table>

* Significant change from control (P < 0.01).
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200-

Increase Heart Rate

Hemodynamic Effects of Increasing Heart Rate

Aortic Pressure (mmHg)

Mean Pressure (mmHg)

Coronary Diameter (mm)

Mean Diameter (mm)

Heart Rate (beats/min)

FIGURE 1 The effects of increasing heart rate by approximately 60 beats/min on measurements of phasic and mean aortic pressure, phasic and mean left circumflex coronary diameter, and heart rate. There was a lag between the time of increased heart rate and maximal dilation of the left circumflex coronary artery.

evations in coronary blood flow and an index of \( MVO_2 \). However, commensurate increases in CSA were also observed. The dilation of the large coronary vessels was not secondary to enhanced arterial pressure, since that measurement did not change significantly. Moreover, it was unlikely to be related to \( \beta \)-adrenergic mechanisms, since this phenomenon still occurred after pretreatment with propranolol. Thus, it appeared that the large coronary arteries were responding to the changes in myocardial metabolic demands in a fashion similar to the resistance coronary vessels.

It was considered that the elevation in cardiac rate reduced cardiac size and consequently increased coronary artery diameter passively in response to the reduction in length of the artery tethered to the cardiac surface. Several types of evidence rule out this possibility. First, if the increase in coronary diameter with pacing was not due to relaxation of tone in the arterial wall, but rather to a passive increase in diameter, secondary pressure

FIGURE 2 The effects of increasing heart rate in steps of 30, 60, and 90 beats/min on measurements of heart rate, \( LV \, dP/dt \), mean arterial pressure, and mean coronary blood flow. Results are expressed as percent change from control. Control values (with heart rate constant at an average rate of 127 beats/min) are shown beneath the bars, and are in units of beats/min for heart rate, mm Hg/sec for \( LV \, dP/dt \), and mm Hg for mean arterial pressure and ml/min for coronary blood flow. Significant changes are denoted by the asterisks.

FIGURE 3 The effects of increasing heart rate in steps 30, 60, and 90 beats/min are shown on measurements of LDCR and CSA. Results are expressed as percent change from control. Control values (with heart rate constant at 127 beats/min) are shown beneath the bars and are in units of mm Hg/ml per min for LDCR and in mm\(^2\) for CSA. Significant changes from control are shown by asterisks.
to a reduction in vessel length, then the effect would be observed instantaneously with the decrease in cardiac size. In other words, as soon as the increase in heart rate caused cardiac size to diminish, an increase in coronary diameter would be observed. However, this was not the case. We used the measurement of LV end-diastolic pressure as an indicator of end-diastolic cardiac size. With step-wise increases in cardiac rate, there were almost immediate decreases in LV end-diastolic pressure, but the increases in coronary diameter lagged by an average of 10 ± 3 sec (Fig. 1). Similarly, when cardiac rate was rapidly and transiently elevated in 5 seconds, LV end-diastolic pressure fell substantially, but coronary diameter failed to change. Moreover, a series of experiments was carried out in which LV end-diastolic pressure was returned to control with saline infusion after heart rate had been elevated. Restoration of LV end-diastolic pressure with volume loading increased coronary CSA

![Figure 4](image_url)

**Figure 4** The effects of aortic constriction on measurements of LV pressure, LV end-diastolic pressure, mean aortic root pressure, and phasic and mean left circumflex coronary arterial diameter.

![Figure 5](image_url)

**Figure 5** The effects of aortic constriction on measurements of LV pressure (LVP), mean right coronary arterial diameter (RCD), phasic and mean left circumflex coronary arterial diameter (LCD). Since the phasic change in the right coronary arterial diameter was relatively small, only the mean data are shown. With maintained aortic constriction, left circumflex coronary diameter continued to rise, while right coronary diameter returned to baseline.

<table>
<thead>
<tr>
<th>TABLE 2 Effects of Aortic Constriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Mean coronary blood flow (ml/min)</td>
</tr>
<tr>
<td>Late diastolic coronary blood flow (ml/min)</td>
</tr>
<tr>
<td>Mean coronary diameter (mm)</td>
</tr>
<tr>
<td>CSA (mm²)</td>
</tr>
<tr>
<td>MVO₂ index (ml O₂/min)</td>
</tr>
</tbody>
</table>

Significant change from control *P < 0.01, †P < 0.05
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In summary, the results of the present investigation indicate an important role for regulation of large coronary vessels by changes in myocardial metabolic demands. Whereas, in the normal heart, the contribution of large coronary vessels to total coronary vascular resistance is small, about 5% (Winbury et al., 1969), their role in the presence of myocardial ischemia, with partial occlusion of a large coronary artery, assumes greater significance and changes in large vessel caliber may be crucial in regulation of the flow to the ischemic area.

Acknowledgments

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References


Hilton SM (1959) A peripheral arterial conducting mechanism underlying dilatation of the femoral artery and concerned in functional vasodilation in skeletal muscle. J Physiol (Lond) 149: 93–111


further, i.e., by 10%. Thus, the increases in coronary CSA that were observed with elevation of cardiac rate most likely reflected an effect secondary to augmented myocardial metabolic demands, rather than a passive change due to either a change in arterial pressure or reduction in length of the vessel.

Myocardial metabolic demands and consequently MVO₂ also were increased by aortic constriction. In these experiments, heart rate did not change significantly, but coronary diameter rose, as it did with elevation of cardiac frequency. In part, the increase in coronary diameter could be attributed to increases in arterial distending pressure. However, mean aortic pressure proximal to the aortic constriction was measured in two dogs and found to increase only slightly in one and not change in the other (Fig. 4). Moreover, in the experiment in which right coronary artery diameter was measured, this variable increased only transiently and then returned back toward control, whereas left circumflex coronary diameter continued to rise (Fig. 5). This is consistent with our hypothesis, since the right coronary artery perfuses only the right ventricle (Murray and Vatner, 1980), which was not exposed to the increased afterload and consequently enhanced myocardial metabolic demands with aortic constriction as occurs for the left ventricle.

The cellular mechanisms by which large coronary vessels are regulated by changes in myocardial metabolic demands is not clear. One possibility is that adjacent myocardial cells in vessel walls liberate metabolites (e.g., adenosine) with the increases in myocardial metabolic requirements, which then dilate coronary vessels. In support of this concept is a study conducted by Hilton (1959) in which dilation of the femoral artery was described following muscular contractions. Also of interest is a recent study of Honig and Frierson (1976) in which a reflex intrinsic to arterioles was considered responsible for post-contraction dilation of vessels in skeletal muscle. In the present investigation, it was observed that an elevation of MVO₂ caused by either increasing cardiac frequency or afterload was associated with a gradual dilation of the large coronary arteries (Fig. 1, 4, and 5). These observations are consistent with an ascending dilation theory.
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