Differential Response of Large and Small Coronary Arteries to Nitroglycerin and Angiotensin

AUTOREGULATION AND TACHYPHYLAXIS

By Michael V. Cohen and Edward S. Kirk

ABSTRACT

Large proximal and smaller distal coronary arteries respond differently to pharmacologic agents, but the role of autoregulation is not known. We examined this role in dogs by cannulating the main left coronary artery and a distal left anterior descending artery branch. With coronary flow held constant, the distal coronary artery pressure and the gradient from proximal to distal artery were proportional to the small and the large vessel resistance, respectively. At normal perfusion pressure, nitroglycerin injected directly into the coronary artery caused a transient fall in small vessel resistance and a prolonged decrease in large vessel resistance. During ischemia, when small vessels autoregulated and small vessel resistance was minimal, nitroglycerin lowered only large vessel resistance. Angiotensin injected directly into the coronary artery increased small and large vessel resistance; the slower response of large vessel resistance followed a passive dilation caused by increased perfusion pressure. Continuous infusions of nitroglycerin and angiotensin maintained dilation and constriction of large vessels, respectively, but small vessels demonstrated tachyphylaxis. Only adenosine infusion maintained dilation in both large and small vessels. In response to varying perfusion, small vessels autoregulated and large vessels responded passively to changes in perfusion pressure. We concluded that small coronary arteries respond to cardiac metabolism and demonstrate escape from prolonged dilation and constriction. Conversely, large vessels respond continuously to sustained mechanical and pharmacologic stimuli independently of the nutritional state of the myocardium.

KEY WORDS coronary artery tone autoregulatory escape dog vascular resistance coronary artery perfusion adenosine coronary pharmacodynamics distensibility of coronary vessels

The coronary arterial tree can be divided functionally into two major categories of vessels. Larger conductive vessels lie primarily on the epicardial surface, and smaller precapillary resistance vessels lie in close proximity to the contracting myocardial fibers. The two types of vessels can be studied by arbitrarily cannulating a small distal branch of an epicardial artery (1, 2). At normal perfusion pressures, the resistance of the larger segments of vessel extending from the coronary ostium to the cannulated branch constitutes less than 10% of the total coronary resistance (1, 2). Thus, significant changes in total coronary resistance primarily reflect alterations in the smaller vessels, and regulation of coronary blood flow becomes a function of these smaller vessels.

Although the resistance of larger arteries can be altered by vasoactive agents, the response may differ significantly from that of small vessels. Nitroglycerin, for example, causes prolonged vasodilation of larger coronary arteries but has only a transient vasodilator effect on small coronary vessels (1, 2). Furthermore, in vitro experiments with helical strips of coronary arteries have confirmed a differential response of large and small arteries to vasodilators (3) and to catecholamines (4). Winbury's (5) hypothesis concerning the mechanism by which nitroglycerin relieves myocardial ischemia is based partly on this differential mode of action.

Although large coronary vessels are apparently not dilated during reactive hyperemia (2, 6), their role in autoregulation is not defined. Accordingly, the physiological and the pharmacologic properties of small and large coronary arteries were studied during autoregulatory responses. In addition, the
effect of ischemia on the response of these vessels to the vasodilators nitroglycerin and adenosine was systematically studied. The potent vasoconstrictor angiotensin was also administered to better define the range of responses of large and small coronary arteries.

**Methods**

Experiments were performed on 12 mongrel dogs. Seven dogs were anesthetized with sodium pentobarbital (27.5 mg/kg, iv), and 5 dogs were anesthetized with a chloralose-urethane-propylene glycol mixture (10 g-100 g-100 ml [1.5 ml/kg], iv). Additional amounts were administered as required to maintain prolonged anesthesia. A polyvinyl catheter was introduced into the thoracic aorta via a femoral artery for measurement of systemic pressure. Following endotracheal intubation and mechanical ventilation with an intermittent positive-pressure respirator using 100% oxygen, a left thoracotomy was performed. Anticoagulation was produced with 20,000 units of heparin and maintained by injection of 10,000 units every 1–2 hours.

The experimental preparation is diagramed in Figure 1. The main left coronary artery was cannulated with a modified Gregg cannula which was introduced into the left subclavian artery and securely tied in place just proximal to the bifurcation of the left coronary artery. The coronary vascular bed was perfused by blood from a femoral artery. The perfusion tubing also contained an extracorporeal flow probe attached to a Biotronex 410 electromagnetic flowmeter, a side arm for measurement of proximal coronary pressure with a Statham transducer, and a site for intracoronary drug injection. During administration of the experimental drugs, constant-flow perfusion was achieved with the aid of a Sigmmotor pump. At all other times, the coronary bed was autoperfused at the dog’s normal aortic pressure.

A small distal branch of the left anterior descending or the left circumflex coronary artery was isolated. The branch was ligated distally, and the central portion was cannulated with either a 20- (0.88 mm, o.d.) or a 22- (0.71 mm, o.d.) gauge blunted needle connected by a short polyethylene catheter to a pressure transducer to record distal coronary pressure. The cannulated branch was only slightly larger than the cannulating needle. To facilitate cannulation, short periods of cardiac arrest were induced by stimulation of the vagus nerve in the neck. The transducers recording proximal and distal coronary pressure were selected to have identical linearity over a range of pressures from 0 to 200 mm Hg. The amplified outputs from these transducers were connected to the input of a differential amplifier. By carefully adjusting the gain of the transducer preamplifiers, the proximal-distal pressure gradient could be recorded. At frequent intervals throughout an experiment, the two pressure transducers were connected to the same pressure source to check for zero baseline and linearity drifts. In this manner changes in the pressure gradient exceeding 0.5 mm Hg could be detected unequivocally at all pressure levels. Systemic pressure, coronary flow, proximal and distal coronary pressures, and proximal-distal gradient were continuously recorded on a multichannel oscillograph.

The resistance of the perfusion system from the location of the proximal coronary pressure gauge to the tip of the Gregg cannula was determined with blood to be 0.05 mm Hg min/ml over the range of flows encountered in these experiments. All values for proximal coronary pressure used in calculations were corrected for this pressure drop, but the original uncorrected data is presented in the figures.

A solution of nitroglycerin was prepared by dissolving 0.8-mg tablets in saline to make a final concentration of 0.6 μg/μlter. The standard intracoronary bolus injection was 12–18 μg, and the continuous infusion was 0.34–0.37 mg/min. A solution of adenosine was prepared each time just prior to use. The final concentration was 1 μg/μlter in saline, and 30-μg boluses were injected directly into the coronary artery. Adenosine was also administered as a constant intracoronary infusion of 0.58 mg/min. The bolus doses of nitroglycerin and adenosine were selected on the basis of their ability to maximally lower total coronary vascular resistance as determined by dose-response curves in preliminary experiments. Angiotensin was prepared by dissolving the powder in saline to a final concentration of 0.5 μg/μlter. The bolus intracoronary dose was 1 μg; a continuous infusion of 0.008 mg/min was administered to some experimental dogs. A Harvard Apparatus constant infusion pump was used to administer continuous intracoronary infusions of these three agents.

The distal coronary pressure represents the pressure in the smaller coronary arteries beyond the site of distal cannulation, and the proximal-distal pressure gradient represents the pressure drop along the large coronary arteries proximal to the cannulation. At constant coronary flow, the distal coronary pressure and the proximal-distal gradient are proportional to the small (R_s) and large (R_L) coronary artery resistances, respectively. Therefore, changes in pressure directly reflected changes in resistance. Coronary venous pressure was assumed to be negligible, and all transducers were positioned at the level of the right atrium.
The changes in $R_L$ and $R_S$ were documented in detail during steady-state conditions following sequential lowering of the coronary perfusion pressure in two dogs. Changes in coronary vascular resistance in response to an intracoronary injection of nitroglycerin at normal and decreased perfusion pressure were noted in all dogs. In those dogs with responsive large coronary segments, adenosine was similarly tested. The effect of intracoronary injections of angiotensin on $R_L$ and $R_S$ was examined in seven of these dogs. A continuous intracoronary infusion of nitroglycerin was administered to six dogs, a continuous infusion of adenosine was administered to four dogs, and a continuous infusion of angiotensin was demonstrated in two dogs.

An additional four dogs without a distal coronary cannula were studied. The effect of a continuous intracoronary infusion of nitroglycerin on coronary flow was determined, and the subsequent tolerance of the coronary vasculature to intracoronary bolus injections of nitroglycerin was demonstrated.

All results are expressed as means ± SE. Student's $t$-test for independent observations was used to determine the significance of differences (7).

Results

Sequential lowering of perfusion pressure elicited reproducible changes in coronary resistance as demonstrated in one representative experiment in Figure 2. As perfusion pressure was decreased from 90 to 40 mm Hg, the small vessels dilated to maintain coronary flow. This autoregulatory response was systematically documented with pressure-flow curves in two dogs, but evidence of this mechanism was observed in all dogs studied. In contrast to the marked decline in $R_S$, $R_L$ gradually increased as perfusion pressure fell.

In 3 of the 12 dogs, large coronary arteries did not respond to nitroglycerin. At normal coronary flows, the proximal-distal pressure gradient in these 3 dogs averaged 4.5 mm Hg. The site of distal cannulation was altered two or three times in each dog. Although the site affected the magnitude of the recorded gradient, it did not appear to alter the absence of a response to nitroglycerin. In the other 9 dogs, the proximal-distal pressure gradient averaged 6.8 ± 1.5 mm Hg under control conditions. In these dogs, the degree of response to nitroglycerin also did not depend appreciably on the size of the branch chosen for distal cannulation. Injection of an intracoronary bolus of nitroglycerin had a characteristic effect which is illustrated in Figure 3. At normal perfusion pressure (90 mm Hg) (Fig. 3, left), nitroglycerin produced prompt dilation of small vessels, and $R_S$ fell from 1.50 mm Hg min/ml to 0.92 mm Hg min/ml. This dilation was transient, lasting 2 minutes. In contrast, nitroglycerin induced a transient rise in the proximal-distal pressure gradient and then a slow decline associated with a drop in $R_L$ from 0.10 to 0.02 mm Hg min/ml. The large vessel alterations receded slowly, and 2.5 minutes after the administration of nitroglycerin the gradient was still significantly reduced. The lowered gradient persisted for 8.5 minutes. Myocardial ischemia (coronary perfusion pressure 30 mm Hg) (Fig. 3, right) induced dilation of the small vessels, and $R_S$ fell to 1.1 mm Hg min/ml. Intracoronary injection of nitroglycerin further decreased $R_S$ to 0.89 mm Hg min/ml. Thus, $R_S$ reached approximately the same minimum resistance after the administration of nitroglycerin in both the control and ischemic situations. In contrast, lowering of perfusion pressure raised $R_L$ to 0.11 mm Hg min/ml. The subsequent response of $R_L$ to nitroglycerin was similar to that at normal perfusion pressure, i.e., a decrease from 0.11 to 0.03 mm Hg min/ml.

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Effect of Drugs on Small and Large Coronary Artery Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proximal coronary pressure (mm Hg)</th>
<th>Proximal-distal pressure gradient* (mm Hg)</th>
<th>Rs (%)</th>
<th>Rl (%)</th>
<th>Rs time to max change (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin (18 µg)</td>
<td>115.3 ± 8.0</td>
<td>6.8 ± 1.5</td>
<td>-36.8 ± 4.1</td>
<td>-54.0 ± 6.9</td>
<td>6.2 ± 0.51</td>
</tr>
<tr>
<td>Adenosine (30 µg)</td>
<td>120.9 ± 11.7</td>
<td>5.3 ± 1.5</td>
<td>-53.2 ± 4.9</td>
<td>34.0 ± 13.7</td>
<td>10.0 ± 1.01</td>
</tr>
<tr>
<td>Angiotensin (1 µg)</td>
<td>93.1 ± 9.2</td>
<td>4.8 ± 1.5</td>
<td>108.7 ± 23.7</td>
<td>69.3 ± 27.6</td>
<td>17.0 ± 1.61</td>
</tr>
</tbody>
</table>

All values are means ± SE. All drugs were administered by intracoronary injection. Statistical evaluation of drug response at ischemic pressure relative to change at normal perfusion: *s = P < 0.01 and w = P > 0.5. Rₗ = small coronary artery resistance and Rₗ = large coronary artery resistance.

*Measurements prior to drug injection.

†Changes in resistance relative to predrug resistance levels.

‡Time interval between drug administration at normal perfusion pressure and maximum change in Rs or Rl.

§Adenosine-induced dilation of large vessels is often obscured at normal perfusion pressure and is seen maximally at ischemic pressure; therefore, the time to maximum change of Rs and Rl after adenosine administration is noted under ischemic conditions.

Results of all studies are summarized in Table 1. For all experimental dogs, Rs averaged 6.0 ± 1.4% of total coronary resistance at normal perfusion pressure, although the contribution of Rs to total resistance increased to 12.2 ± 3.9% at the lower pressure. At normal perfusion pressure, administration of nitroglycerin reduced Rs by 37% and Rl by 54%, indicating significant dilation. Ischemia, induced by reducing coronary flow an average of 28%, was accompanied by an autoregulatory dilation of the small vessels, resulting in a 29.6 ± 5.8% fall in Rs. Under these conditions, nitroglycerin again dilated both large and small vessels; however, the responsiveness of the small vessels was muted and significantly less than that seen at control coronary flows (P < 0.01). The large vessels displayed...
similar responses to nitroglycerin at both levels of coronary flow ($P > 0.5$). Large vessel responses persisted for 4–9 minutes.

The response of large and small vessels to adenosine is represented in Figure 4. This powerful vasodilator decreased perfusion pressure by 90 mm Hg as a result of a reduction in $R_s$ to 40% of control (Fig. 4, left). However, $R_L$ in this experimental dog did not change appreciably. When coronary perfusion pressure and flow were reduced to ischemic levels (Fig. 4, right), the small vessels dilated and became less responsive to injection of adenosine, which then lowered perfusion pressure by only 18 mm Hg. However, a dilatory effect of adenosine on large vessels now became evident. In the dogs receiving adenosine injected directly into the coronary artery, two distinct, large vessel responses were therefore apparent (Table 1). At normal levels of perfusion, the dilation of small vessels and the resultant lowering of perfusion pressure was marked, but large vessel resistance characteristically did not decrease and often increased. In contrast, under conditions of ischemia when the response of the small vessels was muted and perfusion pressure fell minimally, the large vessels always showed a marked dilation.

Angiotensin produced vasoconstriction of both large and small coronary arteries. In the representative record shown in Figure 5, $R_s$ rose by 80%. After an initial decrease which coincided with maximum constriction of the small vessels, $R_L$ increased 108%. The increase was gradual, and the peak value was not reached for almost 2 minutes. Small vessels...
returned to control or were slightly dilated within 2 minutes. As with all responses of large vessels, the changes in $R_L$ were prolonged and did not return to control levels for more than 5 minutes. The response to angiotensin in all dogs is summarized in Table 1.

Continuous intracoronary infusion of vasoactive agents revealed striking differences in the responses of the large and small coronary vessels. Figure 6 represents the effect of a continuous nitroglycerin infusion in one dog. With constant coronary flow, nitroglycerin elicited the expected dilation of the small vessels. However, despite continuation of the infusion, $R_L$ gradually returned toward control. After an initial transient increase in $R_L$, coincident with the large fall in coronary pressure, $R_L$ fell to 40% of control and remained at this level for the duration of the infusion. When coronary flow was allowed to vary (Fig. 7), a similar loss of responsiveness of the coronary resistance vessels to continuously infused nitroglycerin was observed. Furthermore, subsequent intracoronary injections of nitroglycerin failed to elicit a significant dilation, although the response to adenosine persisted. The small coronary arteries also became tachyphylactic when they were exposed to a constant intracoronary infusion of angiotensin (Fig. 8); however, $R_L$ did not begin to decline until after discontinuation of drug administration. The small vessels were able to maintain a prolonged and unvarying change in tone only in response to a constant adenosine infusion (Fig. 7). Again the large vessels demonstrated prolonged responsiveness to the administered drug.

**Discussion**

Autoregulation of coronary resistance vessels is characterized by relative independence of coronary blood flow and perfusion pressure and is one of the most striking compensatory features of this vascular bed. For example, Mosher et al. (8) observed an average change in flow of only 7% over a range of perfusion pressures from 70 to 150 mm Hg. The twofold change in coronary vascular resistance that occurs must involve changes in the resistance of small coronary vessels, in as much as they account for more than 90% of the total coronary resistance at normal pressures. Our experiments showed that large vessels, in contrast to small coronary segments, failed to demonstrate an autoregulatory response. To maintain constant coronary flow, small vessels constricted when perfusion pressure was increased, whereas the same increase in pressure was accompanied by passive distention of the large vessels (Fig. 2). Although Winbury et al. (2) attempted to define the response of large vessels to varying coronary perfusion, the steady-state pressure-flow curves in their experimental preparations did not demonstrate autoregulation of coronary flow. However, they, as well as Fam and McGregor (6), demonstrated that large coronary vessels are not dilated during reactive hyperemia. Thus, our results, considered with those of others, suggest that the large coronary vessels are not responsive to the level of myocardial metabolism.

We used constant coronary flow and intracoronary administration of drugs to demonstrate the differential effect of interventions on small and large coronary arteries. Fam and McGregor (1) used this approach in only two animal preparations. Their primary experimental observations, as well as those of Winbury et al. (2), were made in animals with unregulated coronary flow that were receiving drugs intravenously. Constant coronary flow allowed us to directly monitor changes in vascular resistance. Moreover, intracoronary administration of drugs permitted the use of small doses that have only minor effects on systemic hemodynamics.
The coronary bed is composed of several major coronary vessels which subdivide in parallel fashion into progressively smaller branches. The choice of a given branch for the site of our distal cannulation was often governed by convenience, and the division of the coronary vessel into "large" vessels proximal and "small" vessels distal to this level is somewhat arbitrary: large vessels may extend beyond the level of cannulation. However, the marked difference in the quality and duration of the response of vessels proximal and distal to the cannula suggests that the contribution of large vessels to the observed responses of the distal vessels is negligible. Cannulation of the distal vessel converts it to an end vessel, and the monitored pressure is that at the branching just proximal to the cannula. It was assumed that the pressure at this site was representative of the pressure in all vessels at this anatomic level. Furthermore, we, as well as other investigators (1, 2, 6), assumed that the induction of ischemia and the administration of vasoactive drugs did not change the proportion of coronary flow delivered to the left anterior descending coronary artery and its distal branches. Only sparse evidence exists to justify this assumption (9).

The passive response of large vessels to significant pressure alterations is seen in Figures 3-6 and 8. Concomitant with a significant early fall in distal coronary pressure induced by vasodilators (Figs. 3, 4, and 6), $R_t$ transiently increased. A transient increase after the administration of nitroglycerin was also noted by Fam and McGregor (1) in their experimental preparations in which coronary flow was held constant. These observations are consistent with the increase in large vessel resistance that occurred when perfusion pressure was lowered sequentially (Fig. 2). Conversely, with an abrupt rise in distal coronary pressure after the administration of angiotensin (Figs. 5 and 8), $R_t$ initially decreased. These changes in large vessel resistance in a direction opposite to that of the distending pressure are consistent with those of a passive, distensible vascular bed (10).

Vasodilatory responses of large and small coronary arteries to nitroglycerin have been studied both in vivo (1, 2) and in vitro (3, 11). Our studies confirmed the ability of nitroglycerin to dilate both
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Effect of a continuous intracoronary (IC) infusion of angiotensin on distal left anterior descending (LAD) artery pressure and main left coronary artery (LCA)–distal LAD pressure gradient. The small vessels rapidly developed tolerance to the infused drug, whereas the large vessels maintained the drug-induced constriction. The infusion was continued for the duration of the record.

FIGURE 8

The differential effect of angiotensin on $R_L$ and $R_S$ has not previously been reported. The small vessels constricted and $R_S$ increased markedly, but it returned to control level within 2 minutes (Fig. 5). Large vessels were also constricted. As noted with nitroglycerin and adenosine, this large vessel response was also slow to develop and quite prolonged.

To further examine the characteristics of small and large coronary artery segments, nitroglycerin, adenosine, and angiotensin were infused continuously into the coronary arteries. The small resistance vessels rapidly developed tolerance to nitroglycerin (Figs. 6 and 7), a previously unappreciated observation (13). However, the large vessels remained dilated for the duration of the infusion (Fig. 6). Similarly, the small vessels escaped from the vasoconstrictor effects of angiotensin, but the large vessels remained constricted (Fig. 8). Only the physiological mediator adenosine (14) was able to maintain prolonged dilation of small as well as large coronary artery segments. Thus, small coronary vessels demonstrate rapid tolerance to the prolonged effects of vasodilator and vasoconstrictor agents.

The mechanism of tachyphylaxis in these experiments is not clear. The documentation of tachyphylaxis only in those vessels capable of autoregulation makes autoregulatory escape an attractive
hypothesis, but it is not obvious how an autoregulatory mechanism might alter coronary tone when coronary blood flow is constant. However, vasoactive agents can change capillary exchange without changing blood flow, presumably by altering precapillary sphincter tone (15, 16). Thus, autoregulatory escape could result from the operation of a feedback mechanism in which changes in capillary exchange might alter the washout of a vasoactive metabolite.

Angiotensin might produce tachyphylaxis in the coronary vasculature by binding and blocking receptor sites. Helical strips of coronary arteries placed in a bath to which angiotensin is added rapidly develop tachyphylaxis which is subsequent-ly partially reversed by the administration of angiotensinase (17). Conversely, helical strips of coronary arteries do not appear to develop tolerance to nitrates (3).

The clinical significance of the demonstrated arteriolar tolerance to infusions of nitroglycerin is unknown. A benefit of coronary vasodilation to ischemic myocardium has only been shown to result from the response of coronary collateral vessels (18). Therefore, further evaluation of the clinical importance of myocardial vessel tolerance to nitroglycerin must await assessment of tachyphylaxis of collaterals.

Our studies imply that large coronary vessels do not participate in autoregulatory responses and are not involved in escape from pharmacologic stimuli, whereas small coronary artery segments do autoregulate and demonstrate tachyphylaxis to vasoactive substances. Small vessel responses appear to preserve myocardial integrity, and large vessels respond to stimuli without apparent modification by myocardial metabolic requirements. This setting tends to minimize the physiological importance of the large coronary artery segments other than as conduit channels. Whether large vessels are important to the beneficial clinical effect of nitroglycerin has not been directly answered by this study. Drug-induced changes in large vessel tone would be important in those patients with recurrent spasm of proximal coronary arteries (19).

References


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