SUMMARY Recent studies from this laboratory have indicated that sympathetic α-receptor-mediated coronary vasoconstriction can compete with local metabolic vasodilation to reduce the oxygen supply to the myocardium. In vitro studies from other laboratories on isolated coronary vessel strips suggest that large epicardial vessels are the dominant site of adrenergic α-receptor activity. In this study we used anesthetized, open-chest dogs to test the hypothesis that α-receptor-mediated vasoconstriction occurs predominantly in epicardial vessels, which are partially removed from the metabolic milieu in the myocardium. Adrenergic β-receptor blockade was achieved by propranolol (3 mg/kg, iv). The circumflex coronary artery was pump-perfused at constant pressure to minimize passive changes in large vessel resistance. Pressure was measured at the tip of the perfusion cannula sealed in the circumflex artery, and in an apical branch of the circumflex artery. Large vessel resistance was calculated as the pressure gradient along the vessel segment divided by the coronary flow. Intracoronary injections of nitroglycerin were used as an independent measure of the vasomotor responsiveness of the large vessel segment. Adrenergic α-receptor activation was produced by intracoronary bolus injections of norepinephrine and by electrical stimulation of the left stellate ganglion. Alpha-receptor stimulation caused an increase in total coronary vascular resistance; however, the relative increase in the resistance of the large vessel was only about 60% of that seen for the entire coronary bed. These data suggest that, contrary to the proposed hypothesis, adrenergic α-receptor-mediated vasoconstriction in the large coronary vessels is not proportionally greater than that observed in the total coronary vascular bed.

The purpose of the present study was to test the hypothesis that α-receptor vasoconstriction occurs predominantly in epicardial vessels by comparing the relative change in large epicardial vessel resistance to the change in total coronary vascular resistance during α-receptor vasoconstriction. Adrenergic α-receptor coronary vasoconstriction was produced by intracoronary bolus injections of norepinephrine or stimulation of the left stellate ganglion in a β-receptor-blocked, beating heart preparation. Contrary to the proposed hypothesis, the increase in epicardial vessel resistance was found to be proportionally less than that observed for the entire coronary vascular bed.

Methods

General Preparation

Mongrel dogs (22-34 kg) were premedicated with morphine sulfate (2.5 mg/kg, sc) and anesthetized with α-chloralose (100 mg/kg, iv) supplemented with a continuous infusion (10 mg/kg per hour, iv) during the experiment. The dogs were ventilated with room air by a positive pressure respirator (Harvard model 607), with an expiratory pressure of 5 cm H₂O. End-expiratory carbon dioxide was monitored continuously with an infrared absorption analyzer (Beckman LB-2) and maintained between 4.5% and 5% by adjustment of the ventilation rate and tidal volume. Metabolic acidosis during chlo-
ralose anesthesia was counteracted by an intravenous infusion of 150 mm sodium bicarbonate (5 ml/kg per hour, iv).\textsuperscript{23} Rectal temperature was held at 37°C with a heating pad and temperature controller (Yellow Springs 73A). Blood pressure was measured in the aorta with a polyethylene catheter (no. 260) and a strain gauge pressure transducer (Statham P23Dd). Heart rate was measured continuously with a cardiotachometer triggered from the pressure pulse.

**Intermediate Pressure Measurement (P\textsubscript{i})**

A left thoracotomy at the 6th intercostal space was performed, and the pericardium was opened and sutured to the chest wall to form a cradle for the heart. A small apical branch of the left circumflex coronary artery was dissected free from the epicardium and ligated distally with 5-0 silk. The vessel was incised, a 0.23-mm in diameter monofilament nylon thread was inserted proximally, and the tip of a 2-cm-long, no. 10 polyethylene tubing (0.28-mm internal diameter (i.d.)) was advanced over the nylon thread into the vessel and tied in place in a modification of the Seldinger\textsuperscript{24} technique. The tubing had an outside diameter of 0.60 mm and fitted into the cannulated vessel snugly; thus, the small vessel had an inside diameter of approximately 0.6 mm. The tubing was joined to a 28-cm length of no. 190 polyethylene tubing (1.19 mm i.d.) by telescoping small sections of polyethylene tubing of increasing diameters, and this tubing was in turn coupled to a manometer (Statham P23ID) via a 1.5-cm-long, 18-gauge needle (0.84 mm i.d.) and a three-way stopcock. Pressure was measured with a bridge amplifier (Hewlett Packard 8805B). This system had a natural frequency of 9 Hz and a damping coefficient of 1.3 when tested with a sinusoidal pressure generator\textsuperscript{25} and approximated as a lumped system with a single natural frequency.\textsuperscript{26}

**Coronary Perfusion at Constant Pressure**

The dogs were anticoagulated by initial administration of heparin, 750 U/kg, and supplemental infusion of 250 U/kg per hour via the intravenous drip. A thin-walled metal coronary perfusion cannula (a modification of the coronary flowmeter described by Smith et al.\textsuperscript{27}) was inserted via the right carotid artery, passed through the left coronary ostium, and wedged in the left circumflex artery. By this arrangement, dissection and incision of the proximal circumflex coronary artery were avoided and the autonomic innervation to the vessel coursing in the adventitia was left undisturbed.

Pressure was measured through a small, stainless steel inner tube with an opening at the side of the distal end of the perfusion cannula. The proximal end of this tube connected to a manometer (see Proximal Pressure Measurement, below) which was used to control a servocontrolled pump. Blood from the left femoral artery passed through the servo-controlled roller pump (modified Sarnes 3500), a 5-ml windkessel, and an extracorporeal electromagnetic flowmeter (Zepeda SWF3), and thence to the perfusion cannula (Fig. 1). This arrangement enabled maintenance of constant perfusion pressure inside the circumflex coronary artery (less than 1 mm Hg change during experimental maneuvers), and thus coronary blood flow was dependent solely on coronary vasomotion. Perfusion pressure was set 25–50 mm Hg above mean aortic pressure so that adequate perfusion was provided and the possibility of flow from collateral channels was lessened.

The seal between the cannula and the circumflex coronary artery was tested several times during the experiment by stopping pump flow and measuring the proximal pressure in the circumflex coronary artery; if it fell promptly to a value below 20 mm Hg, the seal was considered tight. At the end of the experiment, with the circumflex coronary artery perfused at the same pressure as during the experiment (25–50 mm Hg above mean aortic pressure), 3 ml of a saturated solution of crystal violet in 1 n

![](https://example.com/figure1.png)

**Figure 1** Schematic diagram of experimental preparation. Circumflex branch of left coronary artery was pump-perfused at a constant pressure through a stainless steel cannula. Roller pump in coronary perfusion line was servocontrolled to maintain constant pressure in circumflex artery. P\textsubscript{p} = proximal pressure at tip of perfusion cannula; P\textsubscript{i} = intermediate pressure at an apical branch of circumflex artery. A: Enlargement of perfusion cannula tip wedged in circumflex branch with small inner tube for pressure measurement.
ammonium hydroxide were injected into the coronary perfusion line. Retrograde leakage of blood around the wedged cannula tip was readily detected by endothelial staining in the circumflex coronary artery proximal to the cannula tip at postmortem examination. Experiments with any evidence of leakage were rejected. The stained portion of the myocardium was cut out postmortem and weighed, and flow was expressed as milliliters per minute per 100 g of myocardium. The flowmeter zero was checked repeatedly during the experiment. The flowmeter was calibrated by timed volume collections immediately after each experiment, using the dog’s blood. Mean flow was recorded with a low-pass filter with a 2.0-second time constant.

**Proximal Pressure Measurement (Pp)**

The proximal end of the stainless steel intracoronary pressure-measuring tube (33 cm long, 0.65 mm i.d.) was connected to a manometer (Statham P23ID) via a 30-cm length of no. 260 polyethylene tubing (1.78 mm i.d.), a 1.5-cm-long, 18-gauge needle (0.84 mm i.d.), and a three-way stopcock. Pressure was measured with a bridge amplifier (Hewlett Packard 8805B). This pressure-measuring system had a natural frequency of 20 Hz and a damping coefficient of 0.3. A Y-connection directed the same proximal pressure to a second manometer, which was used to control the pump servomechanism. In this way, the signal to the servocontrol manometer was not interrupted when the proximal pressure manometer system was calibrated before and after each experimental maneuver.

**Pressure Gradient Measurement (Pp-Pi)**

The proximal and intermediate coronary pressure manometers were adjusted carefully to within 1 mm of the same hydrostatic level at the level of the right atrium. The gradient between proximal and intermediate coronary pressures (Pp-Pi) was determined continuously by an electronic subtraction circuit. This circuit also had provision for fine balancing of the zero and gain calibrations of the pressures. Proximal and intermediate pressure pulsation amplitudes were matched by a variable low-pass filter so that oscillation of the computed pressure gradient during each cardiac cycle was minimized with no effect on the mean pressure gradient.

Before and after each experimental maneuver, the zero and gain stabilities of the entire measurement system (manometers, amplifiers, subtraction circuit, and oscillograph) were checked by turning the appropriate stopcocks and subjecting both manometers to atmospheric pressure and then to a pressure reservoir bottle with air pressure equal to the proximal coronary pressure (typically 140 mm Hg). Under both these conditions there was no pressure difference between the two manometers, and the acceptable error in recorded pressure gradient was less than 0.1 mm Hg (see section on Experimental Criteria). The mean pressure difference was recorded with a gain permitting resolution of 0.05 mm Hg and a low-pass filter with a 2.0-second time constant.

The pressure gradient across the entire coronary vascular bed (proximal pressure minus right atrial pressure) was simply taken as the proximal pressure servocontrolled to a constant level (± 1 mm Hg). The right atrial pressure was assumed to be zero in the open-chest preparation. The mean proximal coronary pressure was recorded with a 2.0-second time constant.

**Drugs**

Atropine sulfate was diluted with saline to a concentration of 1 mg/ml for intravenous administration. Propranolol was diluted with saline to a concentration of 4 mg/ml for intravenous administration. Nitroglycerin was diluted in a solution of normal saline and ethylenedinitrilotetraacetic acid disodium salt (10⁻⁵ EDTA) to a concentration of 4 µg/ml for intracoronary administration. Norepinephrine was similarly diluted to a final concentration of 10 µg/ml for intracoronary administration. Intracoronary bolus injections of nitroglycerin and norepinephrine were from 0.1 to 0.4 ml. Injection of the same volumes of the saline EDTA vehicle were without detectable effect.

**Experimental Design**

The purpose of the experiment was to determine the relative α-receptor vasoconstriction response of large and small coronary vessels, independent of other factors controlling coronary blood flow. A principal determinant of coronary vascular resistance is myocardial oxygen metabolism, which in turn is dependent on heart rate, myocardial tension development, and contractility. Accordingly, the experiment was designed to minimize alterations in heart rate, aortic blood pressure, and myocardial contractility. Parasympathetic effects were prevented with atropine (0.5 mg/kg, iv). Adrenergic β-receptor activity was blocked with propranolol (3 mg/kg, iv, plus 1 mg/kg per hour in the iv drip). Alpha-receptor vasoconstriction was elicited by bolus intracoronary injection of 1–4 µg of norepinephrine or by electrical stimulation of the left stellate ganglion (15 Hz, 3 msec, 3–5 V). The dose of intracoronary norepinephrine and the level of sympathetic nerve stimulation were chosen to preclude changes in coronary blood flow greater than 35% of control.

**Data Analysis**

Large vessel pressure gradient (Pp-Pi), coronary flow, proximal coronary pressure, intermediate coronary pressure, aortic pressure, and heart rate were recorded on an oscillograph (Brush 200). Resistance calculations were made every 5 seconds during the 15 seconds before intracoronary injection or stellate stimulation (time zero), and every 2.5 seconds during the first 30 seconds of the response, and every
15 seconds during the next 60 seconds.

Total coronary vascular resistance was calculated as the proximal coronary pressure divided by the flow per 100 g of myocardium, and the large vessel resistance as the measured pressure gradient (Pp-Pi) divided by the flow for each time point. The control resistance was determined as the average of the three values (−15, −10, −5 seconds) before the experimental maneuver. The percent changes (Δ%) in total resistance (RT) and large vessel resistance (RL) were calculated from these control values for each dog.

The average ratio between the change in large vessel resistance and that in total resistance (Δ%RL/Δ%RT) during each vasoconstrictor response was calculated as the slope

\[ b = \frac{\sum_{i=1}^{n}X_iY_i}{\sum_{i=1}^{n}X_i^2} \]

of the regression line, \( Y_i = \Delta%RL \) vs. \( X_i = \Delta%RT \), constrained through zero, for each set of time points during the response. There were nine time points for the norepinephrine responses (times 7.5 seconds through 27.5 seconds) and seven time points for the stellate stimulation responses (times 5.0 seconds through 20.0 seconds). These slopes for the individual vasoconstrictor responses of 11 dogs are listed in Table 1.

**Experimental Criteria**

The criteria for an acceptable experiment were as follows. Proximal coronary perfusion pressure was between 25 and 50 mm Hg greater than mean aortic pressure. The spontaneous fluctuations in resistance during the control period before α-receptor activation were less than 2% of baseline (see section on Data Analysis). The change in coronary blood flow during intracoronary norepinephrine infusion or stellate ganglion stimulation did not exceed 35% of control. The heart rate was regular and changed by no more than 10 beats/min, and mean aortic pressure changed no more than 20 mm Hg during an experimental maneuver.

An independent evaluation of the vasomotor reactivity of the large vessel was made based on the response to intracoronary injections of nitroglycerin (0.4–1.6 μg) before and after the experimental activation of coronary α-receptor vasoconstriction. Adequate responsiveness was established by large vessel vasodilation during the initial decrease in total resistance (type A) due to nitroglycerin. Experimental preparations which demonstrated an increase in large vessel resistance (type B) in response to nitroglycerin were discarded (see Results).

The instrumentation drift in the measured large vessel pressure gradient (Pp-Pi) was less than 0.1 mm Hg between the calibration done immediately before and immediately after the experimental maneuver. The leeway of 0.1 mm Hg was that which was practical with careful technique after several hours warm-up of the equipment. Ling et al.\(^{29}\) describe a method for measuring coronary pressure gradient with an accuracy of 0.001 mm Hg, but it requires averaging during steady state, and this could not be done during α-receptor activation in the present study. A minimum large vessel pressure gradient of 2.0 mm Hg was arbitrarily set as 20 times the stability criterion. The 2.0 mm Hg pressure gradient was the most difficult criterion to meet, since it depended on how small a vessel could be cannulated on the surface of the beating heart. Finally, the criteria for a tight seal of the coronary perfusion cannula, described in the section on Coronary Perfusion, were met.

**Results**

A small coronary branch was cannulated in 35 dogs; however, data from 11 of these dogs are presented here. Fourteen experiments were rejected because of a pressure gradient less than 2 mm Hg, five experiments were eliminated because of an

<table>
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<tr>
<th>Table 1</th>
<th>Vasocostriction Responses to Norepinephrine and Sympathetic Stimulation</th>
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<tbody>
<tr>
<td>Control heart rate (beats/min)</td>
<td>Control aortic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Dog</td>
<td>138</td>
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<tr>
<td>2</td>
<td>125</td>
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<td>3</td>
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<td>11</td>
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<td>Mean</td>
<td>138</td>
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<td>SE</td>
<td>4</td>
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<tr>
<td>95% Confidence interval</td>
<td>0.450–0.842</td>
</tr>
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</table>
inadequate response to nitroglycerin, and the remainder were rejected for failure to meet other experimental criteria listed above.

The large vessel resistance determined in this study averaged 2.1% of the total coronary vascular resistance (Table 1). This is the resistance of the branched epicardial circumflex coronary artery which had a proximal internal diameter of approximately 3.5 mm and an internal diameter of approximately 0.6 mm at the intermediate pressure-measuring point. The results are expressed as the percent change in resistance of the large vessel segment and the percent change in total coronary resistance.

Nitroglycerin

There were two distinct response patterns of segmental coronary vascular resistance to intracoronary injection of nitroglycerin. The first (response A) consisted of brief coronary vasodilation with both the total and large vessel resistances decreased, followed by a return to the control level of total resistance but a prolonged decrease in large vessel resistance (Fig. 2).

The second (response B) consisted of a brief coronary vasodilation with a fall in total vascular resistance but a rise in calculated large vessel resistance, followed by a return to the control level of both total and large vessel resistances (Fig. 3). The brief increase in large vessel resistance observed in the type B response is thought to be artifactual and indicative of a poorly responding large vessel segment.

Norepinephrine

A representative record of the response of segmental coronary vascular resistance to intracoronary injection of norepinephrine is shown in Figure 4. The main response lasted 30 seconds and was followed by minor oscillations near the control value. Flow decreased by 26%, whereas aortic blood pressure and heart rate were nearly constant. The average changes in large vessel and total coronary vascular resistances in seven dogs are presented in Figure 5. Total coronary vascular resistance increased by 40% and large vessel resistance increased by 28% at the peak of the response.

Stellate Stimulation

A representative record of the response of segmental coronary vascular resistance to stellate stimulation is shown in Figure 6. Heart rate and aortic pressure were nearly constant, whereas coronary flow decreased by about 11%. The average changes in large vessel and total coronary vascular resistances in seven dogs are presented in Figure 7. Total vascular resistance increased by 23% and large vessel resistance increased by 12% at the peak of the response.

Relative Magnitude of Large Vessel and Total Vascular Response

It was assumed that there was a constant relationship between the percent change in large vessel resistance and the percent change in total coronary resistance following sympathetic stimulation or norepinephrine injection (see Data Analysis). A line was fitted by linear regression to the data points for each response. The slopes of these lines (Table 1) averaged 0.64 for the norepinephrine group and 0.61 for the stellate stimulation group. When a 95% confidence interval is calculated, the mean slopes for the population lie between 0.45 and 0.84 and between 0.25 and 0.97, respectively. Thus, the relative magnitudes of the large vessel α-receptor vasoconstrictor responses to norepinephrine and sym-

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Effects of intracoronary injection of nitroglycerin (0.8 μg). Both large vessel resistance ($R_L$) and total resistance ($R_T$) decreased markedly immediately after the injection, but the decrease in large vessel resistance was sustained, whereas total coronary resistance quickly returned to near control values. This pattern of resistance changes, called Response A, should be compared with those seen in Figure 3, following a similar injection of nitroglycerin. Resistance is expressed as percent change from the respective preinjection value calculated as the average of the values −15, −10, and −5 seconds before the injection. Proximal perfusion pressure ($P_{pj}$) was constant at 143 mm Hg.
pathetic stimulation are probably somewhat less than the total coronary vascular responses.

Discussion

Assumptions

The major assumption in this study is that changes in blood flow measured for the entire left circumflex coronary artery reflect the changes in
flow that occur in the branched path between the proximal and intermediate pressure-measuring points. That is, if a 20% decrease in flow was measured at the inlet of the circumflex coronary artery, then a 20% decrease in flow occurred in the vessels between the proximal and intermediate pressure-measuring points. Studies with radioactive tracer microspheres indicate some variability in blood flow to different geographical areas of the left ventricle under control conditions, but it probably is reasonable to assume a similarity in percent change in flow to various branches of the circumflex artery.

**Pressure- and Flow-Dependent Artifacts**

The intention of the present experiment was to study the changes in large epicardial vascular resistance due to contraction of the vascular smooth muscle in these vessels; however, other factors can cause changes in the observed resistance. The two major sources of possible artifacts are changes in flow and changes in vascular transmural pressure.

Since epicardial vessels are distensible elastic tubes, a change in transmural distending pressure will result in a corresponding change in vessel radius. Small changes in radius have large effects on vascular resistance (radius to the fourth power for steady laminar flow). Thus, a decrease in transmural pressure from passive narrowing of the tube rather than active smooth muscle vasoconstriction will result in an increase in the calculated resistance of the large vessels.

The flow-dependent artifact is related to energy losses associated with nonlaminar flow patterns. Disturbed flow with eddies and transient vortex formations is likely in the branched epicardial vessels in the beating heart. An increase in flow is likely to increase these disturbances and the associated energy loss and to increase the measured pressure gradient. Since resistance is calculated as the ratio of the pressure gradient divided by the flow \( \frac{P_p - P_i}{F} \), this effect will result in an increase in the calculated segmental resistance independent of active vasomotion.

Pressure- and flow-dependent artifacts probably were observed in previous pharmacological studies on segmental coronary vascular resistance. Cohen and Kirk and Fam and McGregor measured the pressure gradient between an inflow cannula \( P_p \) and a small epicardial artery \( P_i \) in a preparation perfused at constant flow. With flow pumped at a constant rate, vasoconstriction in the distal coronary bed results in an increase in the proximal transmural pressure, and vasodilation results in a fall in the proximal transmural pressure. These workers observed a transient initial increase in the pressure gradient and in the calculated large vessel resistance in response to intracoronary nitroglycerin. Cohen and Kirk attributed the unexpected increase in large vessel resistance to the transient fall in transmural pressure caused by vasodilation.
of the overall vascular bed from nitroglycerin. They also observed the converse effect with infusion of the vasoconstrictor angiotensin, a paradoxical transient decrease in the large vessel resistance.

Takeda and co-workers and Kamitani and co-workers perfused the isolated heart at constant pressure, infused the coronary vasodilators adenosine and dipyridamole to increase coronary blood flow, and observed an increase in the calculated resistance of large vessels. Although active vasoconstriction in these vessels cannot be ruled out, it seems likely that the increase in resistance resulted in part from an increase in energy loss associated with the augmented flow. Winbury and co-workers measured the pressure gradient between the root of the aorta and a distal epicardial branch of the left anterior descending artery but made no attempt to control either perfusion pressure or flow rates. They observed an initial transient increase in the resistance of the large vessel segment in response to intravenous nitroglycerin and a sustained decrease in large vessel resistance when the systemic blood pressure and coronary flow had returned to control values.

In the present study the circumflex bed was perfused at servocontrolled constant pressure, because in pilot studies the paradoxical transient increase in large vessel resistance seen by Cohen and Kirk, Fam and McGregor, and Winbury et al. in response to nitroglycerin was not observed with this preparation (vida infra). The assumption is that nitroglycerin is unlikely to cause constriction of any vascular smooth muscle; thus, the constant pressure perfusion preparation was less subject to serious artifact.

With constant perfusion pressure, in the present study, coronary vasoconstriction resulted in a decrease in coronary blood flow. The change in flow remains as a possible source of error in calculating large vessel resistance. A decreased flow may result in less disturbed flow and smaller energy losses; thus, the large vessel's calculated vasoconstriction may appear to be smaller than it really is. Decreases in flow greater than 35% of control were excluded from this study, so the dependence on flow of the calculated resistance of the large vessel should not be large, but its magnitude cannot be determined from these experiments.

Taken together, the possible artifacts will probably result in an underestimation of large vessel vasoconstriction rather than an overestimation. The data are reasonably homogeneous, and care has been taken to avoid large artifacts; thus it may be concluded that epicardial α-receptor vasoconstriction is less, or not much greater, than that found in the total coronary vascular bed. Epicardial α-receptor vasoconstriction might be as much as two times that found in the total coronary circulation, but it seems unlikely that it is five or ten times as large.

**Nitroglycerin**

The prolonged (over 30-second) decrease in the large coronary vessel resistance seen in the present study (Nitroglycerin A, Fig. 2) confirms similar results from many previous in vivo investigations on this topic. It may be noted that, during this late large vessel vasodilation, the potential artifacts from changes in flow and pressure are minimal because they have returned to control level.

**Adrenergic α-Receptor Vasoconstriction**

Contrary to the studies on isolated strips of coronary vessel, the present study did not show that large coronary vessels have a greater α-receptor vasoconstrictor response than small coronary vessels, whether activated by intracoronary norepinephrine or sympathetic nerve stimulation. It is difficult to evaluate the negative findings from isolated vessels, since this type of preparation may give responses opposite to those found in the intact circulation; e.g., acetylcholine induces contraction of isolated coronary vessels. The magnitude and direction (constriction or dilation) of the response of isolated coronary vessels to catecholamines is also very dependent on the potassium ion concentration in the bathing solution.

Torres and Brandi studied the resistance response of myocardial circulation in the beating heart by a modified radioactive 133Xe-washout technique. Control coronary blood flow was estimated by the washout of a 0.2-ml depot of 133Xe in saline injected directly into the myocardium and compared with the results after the addition of catecholamines to the saline. Local injection of myocardial β-receptor agonists resulted in increased blood flow, but α-receptor vasoconstriction was not observed with phenylephrine or a combination of propranolol and norepinephrine. The principal site of action of such an intramyocardial depot injection is not known. It is possible that the increased rate of indicator washout injected with β-receptor agonists reflects opening of precapillary sphincters secondary to increased myocardial oxygen consumption. The absence of α-receptor vasoconstriction may reflect an insensitivity of precapillary sphincters to α-receptor vasoconstricting agents.

A possible problem is that large vessels may respond more slowly than small vessels. If this is the case, then α-receptor vasoconstriction to a bolus injection of norepinephrine would be smaller for large vessels than for small vessels. It is also possible that bolus injection of norepinephrine resulted in a situation in which norepinephrine did not attain an equilibrium with the α-receptors of the large vessels. We were unable to employ constant norepinephrine infusion in this study because, when it was attempted, norepinephrine spilled out of the coronary circulation and caused an increase in arterial pres-
sure, which in turn caused an increase in myocardial oxygen consumption and a metabolic vasodilatation of small vessels. This reservation is probably answered by the results with sympathetic nerve stimulation, since the stellate ganglion was stimulated until a steady response was obtained. The results with intracoronarynorepinephrine injection and sympathetic nerve stimulation are quite similar (Table 1), indicating that large vessel responses are not unduly slow in the in situ coronary circulation with a functioning vasovasorum.

In conclusion, the relative α-receptor vasoconstriction in large epicardial coronary vessels was only about 60% of that observed for the entire coronary vascular bed with either intracoronary bolus injection of norepinephrine or sympathetic nerve stimulation. Since the resistance in the segment of large epicardial vessel studied in these experiments averaged 2.1% of the total coronary vascular resistance, large vessel α-receptor vasoconstriction would account for only a small fraction of the total vasoconstriction. Thus, the epicardial vessels which are partially removed from the metabolic milieu within the myocardium are not the dominant site of sympathetic coronary vasoconstriction. The coronary circulation appears to resemble other vascular beds in this respect.

Acknowledgments

We thank Stephanie Lathrop and Fellner Smith for expert technical assistance.

References

Staircase in Frog Ventricular Muscle

Its Dependence on Membrane Excitation and Extracellular Ionic Composition

JEAN-MICHEL CHESNAIS, FREDERIC KAVALER, THOMAS W. ANDERSON, AND EDOUARD CORABOEUF

SUMMARY Staircase was studied in frog ventricle strip preparations where it was possible to alter extracellular ionic composition extremely rapidly in the diastolic interval between beats. Several findings strongly indicate that staircase in this tissue is a result of progressively increasing calcium influx per beat, rather than a beat-by-beat augmentation of an intracellular calcium pool which contributes to activation. After a steady state of force development, the very next beat could be graded, from approximately zero force to the steady state value attained during the staircase progression, by grading the calcium concentration of a new Ringer’s solution switched to perfuse the muscle in the diastolic period immediately before that beat. Also, action potentials, elicited during the “quiescent” period in the virtual absence of contraction (in 0.025 mm calcium Ringer’s solution), markedly increase force development and accelerate the staircase seen upon return to normal Ringer’s solution. Staircase is augmented and accelerated by prior exposure of the muscle, during the quiescent period, to calcium-poor media and markedly suppressed by prior exposure to sodium-poor media. Tetrodotoxin, in a dose that markedly slows the action potential upstroke, has no effect on staircase. Finally, staircase is seen to occur during a train of depolarizations (by voltage clamp) to inside positive levels greater than the equilibrium potential for sodium. It is concluded that changes in intracellular sodium concentration will alter the staircase response and may contribute to its genesis, but that this cannot be the sole cause of staircase.

STAIRCASE and the frequency-force relationship of myocardium have been attributed variously to modifications in the pattern of calcium uptake and release by the sarcoplasmic reticulum and of calcium entry and extrusion through the sarcolemma. Hajdu has suggested that the Bowditch’s staircase (also called “potentiation” or “PIEA”) takes its origin from sarcolemmal function, and Woodworth’s staircase (“restitution” or “NIEA”) from the sarcoplasmic reticulum. Several observations of the contractile behavior of frog ventricular muscle, in particular the effects of rapid alterations in extracellular calcium concentration and the inotropic effect of caffeine, are most easily understood as indicating that mechanical activation in this tissue is primarily mediated by transsarcolemmal calcium movements. Niedergerke et al. have recently summarized other items of experimental support for this view, as well as results indicating the presence of a mechanism which “acts in the cell interior, involving a calcium-dependent process of an as yet unknown nature.” The present study of staircase in frog ventricle strips describes experiments which use a technique for rapid alteration of the ionic composition of the extracellular fluid. The results presented below further underscore the extracellular origin of activator calcium in this tissue and provide information as to the possible ionic nature of intracellular processes modulating activation.

Methods

Strips of frog ventricle, 0.8-1.0 mm thick and about 5 mm long, were cut close to and parallel to the atroioventricular groove. Each strip was drawn...
Segmental alpha-receptor-mediated vasoconstriction in the canine coronary circulation.
K O Kelley and E O Feigl

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