Considerable evidence indicates that an adrenergic vasoconstrictor mechanism exists in the coronary vascular bed. In the classification advanced by Ahlquist, the sites mediating this response are termed alpha receptors. Whether or not an adrenergic dilator mechanism exists also in the coronary vessels remains controversial, since it is unclear whether the decrease of coronary resistance that occurs during adrenergic stimulation of the myocardium represents a direct effect of catecholamines on the vessels or is a consequence of the increased myocardial activity. The present study was undertaken to examine the reaction of the coronary vessels to isoproterenol, an agent known to effect vasodilatation in other vascular beds by stimulation of so-called beta receptors. The effects of isoproterenol were studied first in the beating canine heart; then, in order to eliminate its stimulating action on the myocardium, its effects were also studied in the isolated perfused canine heart arrested with potassium. The findings indicate that the coronary vessels of the dog do contain an intrinsic adrenergic dilator mechanism.

Methods

I. STUDIES OF THE INTACT BEATING HEART

Six mongrel dogs weighing between 21.4 and 29.2 kg and averaging 24.4 kg were premedicated with morphine sulfate, 2.5 mg/kg, and anesthetized with alpha-chloralose, 60 to 130 mg/kg. Ventilation was maintained with a positive displacement pump through an endotracheal tube, the chest was opened through a median sternotomy, and the left main coronary artery was isolated. Heparin was then administered in an initial dose of 5 mg/kg and subsequent hourly doses of 2.5 mg/kg. Blood from the left femoral artery was routed through an extracorporeal electromagnetic flowmeter probe to a Gregg cannula which was tied into the left main coronary artery. In one experiment (animal no. 4), the left circumflex artery was cannulated. A plastic catheter was inserted into the coronary sinus through the right atrial appendage and blood was withdrawn by a finger pump at a constant rate and returned to a femoral vein. The rates of withdrawal ranged from 30 to 40 ml/min and were always less than half of the left coronary artery inflow, ensuring that an appreciable fraction of the coronary sinus blood passed around the catheter, and preventing contamination of the sampled blood with right atrial blood. A Beckman macroelectrode for measuring oxygen tension \( P_{O_2} \) was inserted into the withdrawal circuit near the right atrium, and the \( P_{O_2} \) in the blood withdrawn from the coronary sinus was measured with a Beckman model 160 analyzer and recorded continuously. The transit times from the catheter tip in the coronary sinus to the oxygen electrode ranged from 12 to 30 seconds and averaged 20 seconds. The temperatures of the blood in the right atrium and at the site of the oxygen electrode were monitored with thermistor probes, and were found relatively constant, variations being 0.4°C or less during any experiment. The electrode was calibrated as described elsewhere at a temperature within 1°C of the temperature in the coronary sinus drainage line. Mean arterial blood pressure was measured in the right femoral artery with a Statham pressure transducer, and recorded continuously with heart rate, mean left coronary inflow and coronary sinus \( P_{O_2} \) on a direct-writing oscillograph.

Isoproterenol was infused intravenously for periods of one to three minutes by a constant infusion pump, at doses ranging from 0.1 to 0.3 \( \mu \)g/kg/min. The volume of the infusate was always less than 5 ml/min.

*Medicon, model A-2308.
ADRENERGIC CORONARY DILATATION


II. STUDIES OF THE ISOLATED, PERFUSED ARRESTED HEART

Hearts from 20 mongrel dogs weighing between 11.2 and 31.0 kg and averaging 18.3 kg were studied using sodium pentobarbital anesthesia, 30 mg/kg. The preparation is illustrated in figure 1. A small bubble oxygenator* was primed with whole blood from a donor animal and supplied with a gas mixture containing 97% O2 and 3% CO2. Blood leaving the oxygenator passed through an occlusive roller pump† a heat exchanger, and a blood filter, to a cannula tied into the left subclavian artery. The descending aorta and brachiocephalic arteries were occluded and the pump output was thus directed into the ascending aorta and thence through the coronary arteries. The inferior vena cava, superior vena cava, and pulmonary artery were ligated and the coronary outflow was drained through a cannula introduced into the right atrium and ventricle through the azygos vein. The coronary venous blood drained into a graduated cylinder with a pressure transducer connected to an opening at its base above a stopcock. By opening and closing the stopcock the rate of fluid accumulation in the cylinder could be recorded repeatedly. In a few experiments coronary outflow was also recorded with a Shipley-Wilson rotameter. A drainage tap just below the stopcock allowed coronary outflow to be collected and discarded during drug infusions. In this preparation right heart outflow represents total coronary flow minus left Thebesian drainage, and a small catheter (not shown in figure 1) was inserted into the left ventricle to decompress this chamber. In none of the experiments was appreciable aortic regurgitation present.

Coronary perfusion pressure was measured with a Statham pressure transducer connected to a catheter inserted into the aortic arch via the brachiocephalic artery. Right ventricular temperature was monitored with a thermistor probe inserted through the right atrial appendage. In some experiments a Beckman oxygen macro-electrode was inserted into the coronary outflow line just outside the right atrium and the coronary venous Po2 was measured with a Beckman model 160 analyzer and recorded continuously. The electrode was calibrated and the temperature at its location monitored as in the intact beating heart. Temperature at the electrode varied by no more than 0.4°C during an experiment. The pH and Po2 of blood leaving the oxygenator were measured at 37°C with an Instrumentation Laboratories analyzer (model 113), and corrected to the temperature of blood in the right ventricle.10 The pH values ranged between 7.3 and 7.4, and the Po2 values between 20 and 34 mm Hg.

After the preparation had been completed, cardiac arrest was induced by adding KCl to the blood in the oxygenator. Since the heart was isolated, it was not necessary to administer additional KCl after the initial dose. Serum K levels, measured in 18 of the 20 experiments, averaged 20 meq/liter (range 9 to 36 meq/liter). The absence of contractile activity was verified with a Walton-Brodie strain gauge arch sutured to the right ventricle and calibrated at a high sensitivity. Coronary perfusion pressure, coronary outflow, strain gauge arch activity and, when applicable, coronary venous Po2 were recorded continuously on a direct-writing oscillograph. In nine experiments the oxygen content of blood entering and leaving the heart was measured by conventional Van Slyke technique before and at the completion of an isoproterenol infusion, and myocardial O2 uptake was calculated from the arteriovenous O2 difference and coronary blood flow.

*Abbott pulmo-pack, model 4546.
†Ilmco model 1009-P.

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In this preparation, the occlusive pump always delivered blood to the coronary bed at a constant rate, and alterations in coronary vascular resistance were indicated therefore by changes of the perfusion pressure. When perfusion pressure was decreased abruptly, the measured coronary outflow sometimes increased slightly and briefly. These increases of flow were due to the discharge through the coronary bed of a small fraction of the blood originally contained between the occlusive pump and the coronary resistance vessels. They are of interest because of their transient effects on venous $P_{O_2}$, as mentioned below.

Isoproterenol was injected into the coronary vascular bed by means of a no. 20 gauge needle inserted through a rubber diaphragm into the perfusion line. Single injections of between 0.01 $\mu$g and 10.0 $\mu$g, or constant infusions of between 0.044 and 10.8 $\mu$g/min were given. The volume of all single injections was 0.1 ml, and the volume of all infusions less than 1.30 ml/min. In seven animals isoproterenol was given before and after administration of the beta adrenergic blocking agent nethalide in doses ranging from 5 to 35 mg.

**Results**

1. **INTACT BEATING HEART**

The results obtained in all six animals are summarized in table 1 and a typical experiment is reproduced in figure 2. In each experiment, isoproterenol infusion increased coronary blood flow and this was accompanied by an increased $P_{O_2}$ in coronary sinus blood. The increases of $P_{O_2}$ occurred despite tachycardia and reduced or unchanged systemic arterial pressures. The increases of flow and $P_{O_2}$ were both statistically significant ($P < 0.01$).

2. **ISOLATED PERFUSED ARRESTED HEART**

The effects of graded doses of isoproterenol on coronary vascular resistance, as evidenced by changes of perfusion pressure, were studied in 11 hearts which had been arrested with KCl. Coronary blood flow varied from 42 to 99 ml/min and averaged 72. Control perfusion pressures varied from 43 to 145 mm Hg and averaged 87. Isoproterenol lowered the perfusion pressure consistently, the magnitude of the decline depending on the dosage. With injections of 0.01, 0.10, 1.0, and 10.0 $\mu$g of the drug, the maximum decreases from the control pressure averaged $3 \pm 0.8^\circ$ (SEM), $8 \pm 1.2^\circ$, $14 \pm 1.5^\circ$, and $26 \pm 3.9^\circ$ respectively. No change of coronary arterial pressure occurred in response to control injections of saline. Coronary venous $P_{O_2}$ was recorded in six of the eleven experiments. With the abrupt decreases of perfusion pressure which usually followed the injection of
### TABLE 1

| Dog no. | Isoproterenol dose (μg/kg/min) | Mean arterial pressure (mm Hg) | Heart rate (beats/min) | Coronary venous PO<sub>2</sub> (mm Hg) | Right atrial temp (°C) | Left coronary inflow (ml/min) | Coronary sinus PO<sub>2</sub> (mm Hg) | P vs. Control
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*In these experiments, the donor animals had undergone bilateral adrenalectomy one hour prior to exsanguination.

### TABLE 2

| Dog no. | Isoproterenol dose (μg/kg/min) | Coronary outflow (ml/min) | Perfusion pressure (mm Hg) | Control | End of infusion | Coronary venous PO<sub>2</sub> (mm Hg) | Mucosal O<sub>2</sub> content (vol %) | Myocardial O<sub>2</sub> uptake (cc/100 g/min) | P vs. Control
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*In these experiments, the donor animals had undergone bilateral adrenalectomy one hour prior to exsanguination.
isoproterenol, coronary venous P_{O_2} increased momentarily. These increases corresponded temporally with the transient increases of coronary outflow described above. With doses of isoproterenol of 0.01 and 0.10 µg, the momentary increase of P_{O_2} was followed by a return to, but not below, the control value. With doses of 1.0 and 10.0 µg, the momentary increase of P_{O_2} was usually followed by a decrease below the control level (fig. 3). It is of interest, however, that the initial response to both large and small doses of isoproterenol was always the same, i.e., a reduction of perfusion pressure accompanied by transient increases of coronary outflow and of coronary venous P_{O_2}.

Isoproterenol was administered by constant infusion in 11 hearts. The results are shown in table 2. In every instance the infusion decreased perfusion pressure, which reached a stable level in two to four minutes (fig. 4, upper half). The decreases were dose-dependent and ranged from 8 to 30% of the control values. In the nine experiments in which the O_2 contents of blood entering and leaving the heart were determined, the infusions did not consistently increase the O_2 extraction or calculated myocardial O_2 uptake, in spite of relatively high coronary venous O_2 contents (average 17.1 vol %). Coronary venous P_{O_2}, monitored in four of the eleven experiments, also showed no consistent changes.

The effects of beta adrenergic blockade on the response of perfusion pressure to isoproterenol were investigated in seven hearts by determining the response to an injection or infusion of isoproterenol before and after administration of the blocking agent nethalide. In each case the original reduction of perfusion pressure following isoproterenol was completely or almost completely eliminated by the nethalide (fig. 4).

**Discussion**

Present knowledge of the role played by neural and neurohumoral factors in the regulation of coronary blood flow has been summarized by Berne. It is now established that neural and humoral adrenergic stimuli can...
cause coronary vasoconstriction. While it is also clear that coronary dilatation occurs during adrenergic stimulation of the myocardium, a definitive separation between a direct effect of catecholamines on the coronary vessels and a secondary effect of myocardial stimulation has not been possible. In the present studies, the administration of isoproterenol always decreased coronary resistance. Although the decreases of resistance in the beating heart could have been due to a primary effect of isoproterenol on the coronary vessels, the possibility that they were related to metabolic or mechanical consequences of myocardial stimulation, or to extracardiac neural or humoral effects, could not be eliminated.

Potassium-arrested, isolated hearts were studied to exclude these other possibilities, because decreases of coronary vascular resistance in such preparations could not have been due to metabolic effects dependent upon increased myocardial contractile activity, to mechanical consequences of myocardial stimulation, or to extracardiac effects. Several other findings also argue against the possibility that the decreases of vascular resistance in either preparation were metabolic in origin. In the beating heart, the decreases were always accompanied by elevations of coronary sinus $P_{O_2}$, despite reduced or unchanged levels of systemic arterial pressure, suggesting that the degree of coronary vasodilatation exceeded the augmentation of metabolic requirements. In the presumed absence of arteriovenous shunts, the increases of coronary sinus $P_{O_2}$ also imply the absence of a reduced myocardial $P_{O_2}$, which might have been expected had the fall of coronary vascular resistance occurred on a metabolic basis. In the arrested heart, isoproterenol infusion produced no consistent change of myocardial $O_2$ uptake, as determined by conventional Van Slyke technique, and the coronary blood flow was set at such a level that the coronary venous $O_2$ content was always well above the levels associated with coronary vasodilatation.

The venous $P_{O_2}$ recordings in the arrested hearts facilitated detection of extremely subtle changes in the level of myocardial oxygenation and myocardial oxygen uptake. For example, with a venous $P_{O_2}$ above 100 mm Hg, an increase of $O_2$ extraction of only 0.15 volumes per cent would have lowered $P_{O_2}$ by approximately 10 mm Hg. When isoproterenol was infused continuously, $P_{O_2}$ did not change in a consistent manner and, since coronary flow was the same at the completion as at the start of the infusion, myocardial oxygen uptake also did not change. When isoproterenol was injected, and the initial phase of the reduction of perfusion pressure was accompanied by transient increases of coronary flow and venous $P_{O_2}$, it may be presumed that myocardial $P_{O_2}$ was not initially lowered by the drug. With usage of smaller doses of isoproterenol, when the venous $P_{O_2}$ did not decrease below the control level after the transient increase of flow, it also seems likely that myocardial $O_2$ uptake did not increase.

In considering the relevance of findings in a metabolically isolated, potassium-arrested heart to those in the intact heart, a recent study on isolated strips of small coronary arteries by Zuberbuhler and Bohr has interest. They found that epinephrine and norepinephrine induced relaxation at markedly elevated levels as well as at normal extracellular levels of potassium, that this relaxation occurred with concentrations of catecholamines below normal plasma levels, and that it was reversibly blocked by nethalide. On the other hand, Berne has described a coronary vasoconstrictor response to these agents in the potassium-arrested dog heart.

The finding, in the arrested heart, that coronary venous $P_{O_2}$ decreased during the late phase of vasodilatation following large doses of isoproterenol, suggests that large doses of catecholamines can increase resting oxidative metabolism. This possibility has been suggested previously and is presently being investigated. However, on the basis of the evidence discussed above, a metabolic consequence of myocardial stimulation could not have been solely responsible for the de-
creases of resistance observed in the present studies. It is therefore concluded that the coronary vessels are supplied with an intrinsic adrenergic mechanism for vasodilatation, which is mediated through so-called beta receptors. The role of this mechanism under normal physiological conditions remains to be clarified.

Summary

The question of whether the coronary blood vessels contain an intrinsic adrenergic mechanism for vasodilatation has been examined by studying the response of the coronary vessels of the dog to isoproterenol. Initially, coronary blood flow, coronary sinus $P_{O_2}$, mean arterial pressure, and heart rate were measured continuously in anesthetized, open-chest animals. When isoproterenol, 0.1 to 0.3 $\mu$g/kg/min, was given intravenously, coronary flow and coronary sinus $P_{O_2}$ always increased in spite of tachycardia and a reduced or unchanged arterial pressure. Although this response suggested a primary vasodilating effect of isoproterenol, a vasodilatation consequent to increased myocardial activity or an extracardiac factor could not be eliminated. Accordingly, additional studies were performed in an isolated heart arrested with potassium and perfused with whole blood at constant rates of flow. Isoproterenol was given by single injections and constant infusions and always produced a decrease of perfusion pressure. These decreases could be blocked by nethalide and, as indicated by measurements of myocardial oxygen uptake and coronary venous $P_{O_2}$, did not depend upon increased myocardial metabolism or decreased myocardial oxygenation. With injections of 0.01, 0.1, 1.0, and 10.0 $\mu$g of isoproterenol, the decreases averaged respectively 3, 8, 14, and 26% of the control pressures. It is concluded that the coronary vessels of the dog do contain an intrinsic adrenergic mechanism for vasodilatation.

References

An Intrinsic Adrenergic Vasodilator Mechanism in the Coronary Vascular Bed of the Dog
FRANCIS J. KLOCKE, GERARD A. KAISER, JOHN ROSS, Jr. and EUGENE BRAUNWALD

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