Adrenergic Receptor Activity in the Coronary Arteries of the Unanesthetized Dog

By Bertram Pitt, M.D., Eric C. Elliot, M.D., and Donald E. Gregg, Ph.D., M.D.

ABSTRACT

Both α- (vasoconstrictor) and β- (vasodilator) receptor activity was demonstrated in the coronary arteries of the unanesthetized dog independent of adrenergic receptors in the myocardium. In the β-receptor blocked animal, α-adrenergic receptor activity was demonstrated after intravenous and intracoronary injections of epinephrine and norepinephrine by the occurrence of coronary vasoconstriction which could be eliminated by blocking α-adrenergic receptors as well. Coronary vasoconstriction was also seen prior to β-receptor blockade after intravenous phenylephrine and, on occasion, after intracoronary injections of norepinephrine. β-adrenergic receptor activity was demonstrated in several instances after intravenous or intracoronary injections of catecholamines by an initial vasodilatation which could be eliminated by β-adrenergic receptor blockade and which occurred before there was any change in myocardial or systemic hemodynamics. The role of this independent adrenergic receptor activity in the control of the coronary circulation remains to be determined.

ADDITIONAL KEY WORDS

intracoronary injections  vasoconstrictor
vasodilator myocardium  phenylephrine
catecholamines  norepinephrine
block of α- and β-receptors  systemic hemodynamics

Considerable controversy has existed concerning the effects of catecholamines on the coronary circulation. In part, this is due to indirect methods for the measurement of coronary blood flow and the use of open chest anesthetized animals in which varying degrees of hypoxia and myocardial failure often coexist. Although there is general agreement that catecholamines can cause an increase in coronary blood flow (1), this has been attributed by some to myocardial stimulation and subsequent metabolic vasodilatation rather than to a direct effect on the coronary arteries (2, 3). The recent demonstration of β-adrenergic receptor activity as manifested by coronary relaxation in isolated coronary artery strips (4), and in the non-beating heart (5, 6), as well as α-receptor activity as manifested by coronary constriction in isolated coronary artery strips (4), and vasoconstriction in the open chest animal with β-receptors blocked (7-9) has renewed interest in the primary action of the catecholamines on the coronary vasculature.

The present study was undertaken in an attempt to determine whether α- and β-adrenergic receptor activity could be demonstrated in the coronary arteries of the unanesthetized dog, using chronically implanted electromagnetic flow transducers and adrenergic blocking agents.

Methods

The standard animal preparation and methods used for analysis of data in our laboratory have been described previously (10) and will be briefly reviewed below. Electromagnetic flow...
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TABLE 1
Intravenous Injections at Fixed Ventricular Rate before β-Receptor Blockade

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transducers were placed around the left circumflex coronary artery and central aorta to measure phasic and mean coronary blood flow and cardiac output. Zero coronary blood flow was obtained by a polyethylene snare located distal to the coronary flow transducer. Central aortic pressure was obtained through a chronically implanted polyvinyl catheter. Intravenous injections were made through a chronically implanted jugular venous catheter. Coronary flow and cardiac output were determined by planimetric integration of the phasic flow tracings.

In one group of 4 dogs weighing 16 to 23 kg, surgical heart block was produced 2 to 4 weeks prior to the implantation of flow transducers, either by a modification of the Starzl technique (11) or by electrocoagulation of the atrioventricular node, and the heart was paced thereafter with a variable rate pacemaker. One of these animals did not have an aortic flow transducer.

In another group of 3 dogs of similar weight with intact conducting system, a coronary arterial catheter was implanted into the left circumflex coronary artery distal to the coronary flow transducer and snare by the Herd-Barger technique (12). Two of these animals did not have an aortic flow transducer.

All animals were trained to lie quietly and were studied 1 to 12 weeks postimplantation in the resting state.

Results

Intravenous injections at fixed ventricular rates (Table 1)

In the 4 animals with fixed ventricular rates, isoproterenol (0.5 μg/kg iv) led to a 46% increase in mean coronary blood flow 20 to 30 sec after injection. This was accompanied by a marked fall in mean aortic pressure (32% below control) resulting in a decrease in mean and late diastolic coronary vascular resistance of 58 and 35%, respectively. Cardiac output rose 22% above control and was associated with a decrease in systolic ejection period. The increase in coronary blood flow was accomplished by increasing stroke systolic coronary flow while stroke diastolic coronary flow remained unchanged or fell slightly in 3 animals. After β-adrenergic receptor blockade with intravenous propranolol (1 to 2 mg/kg), isoproterenol had no effect on mean or late diastolic coronary vascular resistance in 3 animals, while in the fourth there was a slight increase in resistance.
Epinephrine (1.0 μg/kg iv) led to a 194% increase in coronary blood flow 20 to 30 sec after injection. This was done by increasing both stroke systolic and diastolic coronary flow. Mean aortic pressure rose 27% above control while mean and late diastolic coronary vascular resistance fell 52 and 46% respectively. The effects on cardiac output were small. After β-adrenergic receptor blockade with intravenous propranolol, epineph-

![Diagram of hemodynamic effects of epinephrine before and after β-adrenergic receptor blockade with propranolol.](image1)

**Figure 1**

Hemodynamic effects of epinephrine, 1 μg/kg iv before and after β-adrenergic receptor blockade with propranolol (1 mg/kg). Conducting system previously blocked and heart paced at 52 beat/min. H.R. = heart rate. ECG = electrocardiogram lead II. ABP = phasic aortic blood pressure curve (numbers indicate mean pressure, mm Hg, but mean pressure line should be ignored). LCF = phasic left circumflex flow curve; numbers indicate mean flow (ml/min). LDCR = late diastolic coronary resistance; numbers just above zero coronary flow line (dotted) represent aortic blood pressure (mm Hg) divided by coronary flow (ml/min) just before isometric contraction. CO = cardiac output (ml/min). Paper speed, 75 mm/sec. Vertical time lines, 0.1 sec.

![Diagram of hemodynamic effects of phenylephrine.](image2)

**Figure 2**

Hemodynamic effects of phenylephrine, 1 μg/kg iv. Conducting system previously blocked and heart paced at 52 beat/min. Order of curves and abbreviations same as in Figure 1. Mean pressure lines on phasic pressure curves should be ignored. Paper speed, 75 mm/sec. Vertical time lines, 0.1 sec.
Intracoronary Injections before β-Receptor Blockade

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Rine had a variable effect on coronary blood flow but consistently increased both mean and late diastolic coronary vascular resistance (13 and 22%).

In some experiments with intravenous catecholamines, coronary vascular resistance fell before any change occurred in systemic or myocardial hemodynamics. In a representative animal with a fixed ventricular rate, epinephrine (1.0 μg/kg iv) led to a 69% rise

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in mean coronary blood flow and a fall in mean and late diastolic coronary vascular resistance before there was any change in aortic pressure, cardiac output, systolic ejection period, mean or peak ventricular ejection rates (Fig. 1). After β-adrenergic receptor blockade with intravenous propranolol, epinephrine led to a 24% fall in coronary blood flow despite a rise in mean aortic pressure of 10 mm Hg.

The results with norepinephrine (1.0 μg/kg) were qualitatively similar to those with epinephrine. However, the increase in coronary blood flow (51%) and fall in mean and late diastolic coronary vascular resistance (15% each) after norepinephrine were less than with epinephrine. After β-adrenergic receptor blockade with intravenous propranolol, the increase in mean coronary resistance (23%) and late diastolic coronary vascular resistance (26%) was greater with norepinephrine than with epinephrine.

Coronary vasoconstriction could also be demonstrated prior to β-adrenergic receptor blockade. Phenylephrine (1.0 μg/kg) was given intravenously with ventricular rate again held constant; it led to a fall in coronary blood flow 26% below control despite an increase in mean aortic pressure of 10 mm Hg (Fig. 2).

Following α-adrenergic receptor blockade with intravenous dibenzyline (1 mg/kg) in 2 animals, epinephrine and norepinephrine caused a fall in coronary vascular resistance. In 1 dog with α-receptors blocked, intravenous epinephrine (1 μg/kg) led to an increase in coronary blood flow from a control of 34 to 63 ml/min (85% above control) while mean aortic pressure fell from 80 to 65 mm Hg (19% below control). This resulted in a fall in mean and late diastolic coronary vascular resistance of 58 and 59%. Cardiac output increased from 3800 to 4300 ml/min (13% above control) while the heart rate was held constant at 71 beat/min. After α-adrenergic receptor blockade with intravenous dibenzyline, and β-adrenergic receptor blockade with intravenous propranolol (1 to 2 mg/kg), epinephrine and norepinephrine either had no effect on coronary vascular resistance or led to a small fall in resistance. In the other animal cited above, epinephrine (1 μg/kg) increased coronary blood flow from 35 to 43 ml/min (23% above control) while mean aortic pressure increased from 85 to 105 mm Hg (24% above control). Mean coronary resistance remained unchanged while late diastolic coronary vascular resistance fell 16%. Cardiac output fell from 3150 to 2350 ml/min (25% below control) while the heart rate was held constant at 71 beat/min. These results are in contrast to the coronary vasoconstriction seen with epinephrine after β-adrenergic receptor blockade alone (Table 1).

**INTRACORONARY INJECTIONS (TABLE II)**

The direct effects of the catecholamines on the coronary circulation were evaluated in 3 dogs with intact conducting systems. Repeated intracoronary injections of isotonic...
saline (0.03 ml) led to a maximum 15% increase in coronary blood flow and 15% fall in coronary resistance. In a representative animal (Fig. 3), control recordings were obtained with the dog in the resting state. Isotonic saline was then given through the chronically implanted coronary artery catheter, and led to a fall in late diastolic coronary vascular resistance from 3.3 to 3.0 units (9% below control), 5 sec after injection.

Intracoronary isoproterenol injections (0.6 µg in 0.03 ml isotonic saline) led to a 70% increase in mean coronary blood flow 4 to 5 sec after injection. Mean and late diastolic coronary vascular resistance fell 30 and 35% respectively. Heart rate, aortic pressure, systolic ejection period, and cardiac output changed less than 5% at this time. After β-adrenergic receptor blockade with intravenous propranolol (1 mg/kg), isoproterenol in a dose equal to that used previously, failed to elicit a significant rise in coronary blood flow or fall in coronary vascular resistance. In the same animal as shown in Figure 3,
isoproterenol led to a rise in coronary blood flow and fall in late diastolic coronary vascular resistance from 3.4 to 1.7 units at 5 sec, and to 1.4 units at 7 sec after injection (55% below control) while mean aortic pressure, heart rate, cardiac output, mean ventricular and peak ventricular ejection rates, and tension-time index calculated according to method of Sarnoff et al. (13) were not increased from control values (Fig. 4). Ten seconds after injection, myocardial effects first became noticeable, and at 25 sec, were manifested by a decrease in systolic ejection period from 0.20 to 0.15 sec (25% below control), along with an increase in peak ventricular ejection rate (18% above control) and mean ventricular ejection rate (43% above control).

Intracoronary injections of epinephrine (0.6 µg in 0.03 ml isotonic saline) increased mean coronary blood flow 55%, and decreased mean and late diastolic coronary vascular resistance 33 and 31% respectively, 4 to 5 sec after beginning injection without any increase in heart rate, aortic pressure or change in systolic ejection period. After β-adrenergic receptor blockade, epinephrine led to an increase in mean and late diastolic coronary vascular resistance of 29 and 24% respectively. In the experiment shown in Figure 5, epinephrine caused an initial coronary vasodilatation before any significant change in myocardial or systemic hemodynamics. Twelve seconds after injection, there was a further decrease in late diastolic coronary vascular resistance. The coronary vasodilatation seen at this time was accompanied by myocardial effects as manifested by a decrease in systolic ejection period. After β-adrenergic receptor blockade, epinephrine (0.6 µg) led to a small increase in mean and late diastolic coronary vascular resistance.

After α-adrenergic receptor blockade with intravenous dibenzylene (1 mg/kg), intracoronary epinephrine and norepinephrine caused an initial coronary vasodilatation. In 1 animal, epinephrine (0.6 µg) led to an initial increase in coronary blood flow from 24 to 32 ml/min (35% above control) while mean aortic pressure increased slightly from 100 to 103 mm Hg, 4 to 5 sec after injection. This resulted in a fall in mean and late diastolic coronary vascular resistance of 24 and 28% respectively. Cardiac output and heart rate remained unchanged. After the administration of propranolol (1 mg/kg) to the α-receptor blocked animal, epinephrine and norepinephrine had no effect on coronary vascular resistance. In the animal cited above, epinephrine (0.6 µg) led to a slight fall in mean aortic pressure from 101 to 98 mm Hg, while coronary blood flow remained unchanged at 24 ml/min. Mean coronary resistance fell 2% while late diastolic resistance was unchanged.

Discussion

The results of the present investigation are consistent with the presence of both α- and β-adrenergic receptors in the coronary arteries of the unanesthetized dog, independent of adrenergic receptors in the myocardium. The finding of coronary vasoconstriction after intravenous and intracoronary injections of epinephrine and norepinephrine in the β-receptor blocked animal, and its elimination by α-adrenergic receptor blockade, suggests the presence of α-(vasoconstrictor) adrenergic receptors in the coronary arteries. These results are consistent with the findings of Zuberbuhler and Bohr (4) that epinephrine and norepinephrine cause contraction of isolated coronary artery strips after β-receptor blockade. Similarly Doutheil et al. (7), Gaal et al. (9), and Parratt (8) have demonstrated α-receptor activity after β-receptor blockade in the anesthetized open chest dog. Our finding of coronary vasoconstriction after intravenous phenylephrine and, in some instances, after intracoronary norepinephrine in the unanesthetized animal, is further evidence for the presence of α-receptors in the coronary arteries and suggests that these receptors can influence coronary flow in the absence of β-receptor blockade.

The increase in coronary flow after intravenous catecholamine injection was accompanied by changes in aortic pressure and
cardiac output, and could be attributed, at least in part, to myocardial stimulation and subsequent metabolic vasodilatation. There were, however, several instances in the unanesthetized dog with fixed ventricular rate, in which intravenous catecholamines caused an increase in coronary blood flow before any change in aortic pressure, systolic ejection period or cardiac output. Similarly, initial coronary vasodilatation after intracoronary isoproterenol, epinephrine and, in some instances, after norepinephrine, which can be eliminated by β-adrenergic receptor blockade, suggests the presence of β-adrenergic receptors in the coronary arteries. The initial coronary vasodilatation occurred 3 to 5 sec after beginning intracoronary injection of catecholamines before any significant increase in systemic or myocardial hemodynamic effects. Control intracoronary injection with isotonic saline led to a maximum 15% increase in coronary blood flow as compared to a greater than 100% increase in some experiments with isoproterenol and epinephrine. The increase in coronary blood flow seen 10 to 12 sec after intracoronary injection of catecholamines can be attributed both to a direct effect on the coronary vessels and to secondary metabolic vasodilatation. Myocardial effects were manifested on the coronary flow pattern by a shortening of the systolic flow period and, on occasion, by backflow during late systole. The positive chronotropic effect usually seen after catecholamines was minimized in our preparation by injection distally into the left circumflex coronary artery thereby bypassing the sinus node artery which usually originates from the right coronary artery (14).

Klocke et al. (15) found that catecholamines in physiologic concentrations failed to increase significantly the myocardial oxygen consumption in the arrested heart and Sonnenblick et al. (16) found that myocardial oxygen consumption is directly related to the speed of ventricular contraction. Therefore, it is unlikely that the initial coronary vasodilatation seen in our experiments before any increase in myocardial or systemic hemodynamics was due to an increase in myocardial oxygen consumption and subsequent metabolic vasodilatation. Catecholamines in physiologic concentrations in nonbeating hearts can cause coronary vasodilatation (5, 6); this adds further evidence that catecholamine-induced vasodilatation is, at least in part, due to a direct effect upon the vessels themselves. The conflicting reports on the direct effects of epinephrine and norepinephrine on the coronary vasculature, reviewed by Berne (1), can be explained by the presence of both α- and β-adrenergic receptors in the coronary circulation. Although we have not seen any initial coronary vasoconstriction after epinephrine prior to β-receptor blockade, it is possible that this may occur under certain conditions. Zuberbuhler and Bohr (4) have reported that in isolated coronary artery strips there are relatively more β-adrenergic receptors present in the small coronary vessels, and more α-receptors in the larger coronary vessels. The effects of the administration of an agent with both α- and β-adrenergic receptor activity such as epinephrine or norepinephrine may, therefore, depend on the relative proportion and distribution of α- and β-adrenergic receptors in the coronary vessels of a given animal, the route of administration, and on the experimental conditions affecting sympathetic tone such as anesthesia, hypoxia, and myocardial failure during open chest experiments.

Similar studies in the completely denervated heart have shown that sympathetic nervous impulses are unnecessary for the performance of the heart under certain physiologic conditions (17). These studies make it unlikely that adrenergic receptors in the coronary arteries are essential to life. They may, however, play an important role in modifying the physiologic and pathophysiologic adaptation of the coronary circulation.

References


Adrenergic Receptor Activity in the Coronary Arteries of the Unanesthetized Dog
BERTRAM PITT, ERIC C. ELLIOT and DONALD E. GREGG

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