Effect of I-Epinephrine on the Coronary Circulation in Human Subjects with and without Coronary Artery Disease

By Jay M. Sullivan, M.D., and Richard Gorlin, M.D.

ABSTRACT

The effects of intravenous infusion of epinephrine on the coronary circulation of 21 human subjects, 8 with and 13 without coronary artery disease, have been studied. The response to epinephrine was similar in the two groups. Epinephrine increased cardiac output, stroke volume, and systolic ejection rate significantly without significant change in blood pressure. Myocardial O\textsubscript{2} consumption increased in relation to increased kinetics of contraction. Coronary flow increased significantly without change in coronary arteriovenous O\textsubscript{2} difference, suggesting that the vasodilatory response to epinephrine in man is secondary to augmented myocardial metabolic demands.

ADDITIONAL KEY WORDS epinephrine myocardial O\textsubscript{2} consumption coronary blood flow coronary artery disease

In a recent review of the coronary circulation, Berne pointed out conflicting reports concerning the effects of catecholamines on the coronary vasculature (1). On the basis of experiments in intact animals, it is generally agreed that epinephrine increases coronary blood flow through a poorly understood dilator effect secondary to increased metabolic activity of the myocardium (2). The direct effect of epinephrine on the smooth muscle of the coronary arteries remains a subject of investigation. Studying the coronary circulation in dogs, Parratt demonstrated that epinephrine and isoproterenol decreased coronary vascular resistance, while norepinephrine increased resistance. Block of beta-adrenergic receptors resulted in reduction of the isoproterenol effect, reversal of the epinephrine effect and potentiation of the norepinephrine effect, suggesting that there are beta-adrenergic receptor sites in the coronary vasculature (3). Zuberbuhler and Bohr have demonstrated that epinephrine and norepinephrine induce relaxation of isolated muscle strips taken from canine coronary arteries of small diameter, but they induce either relaxation or contraction in strips taken from larger coronary vessels (4). Recently, Pitt and his co-workers have demonstrated the presence of both alpha- and beta-adrenergic receptors in the coronary arteries of the dog, independent of the adrenergic receptors of the myocardium (5).

Previous reports from our laboratory have shown that isoproterenol acts as a primary dilator of the coronary arteries in man (6) and that norepinephrine acts as a primary vasoconstrictor (7). Information about the effect of another naturally occurring catecholamine, epinephrine, on the human coronary circulation is lacking and might be useful in the choice of agents for treatment of patients with low cardiac output. Since these are frequently patients with coronary artery disease, knowledge of the effects, if any, of epinephrine on a diseased coronary vascular bed.
might also prove to be of value. This study reports the effects of intravenous infusion of epinephrine on the coronary circulation of human subjects with and without coronary arterial lesions as determined by coronary cinearteriography.

Methods

Twenty-one patients were studied during cardiac catheterization for diagnostic purposes. The patients were divided into two groups. Group 1 served as a control and was composed of eight patients with mild mitral stenosis (calculated valve areas ranging from 1.2 to 2.0 cm²), three with systolic murmurs without evidence of organic heart disease at catheterization, and two with the syndrome of angina pectoris but with normal coronary arteriograms. Only the last two patients had clinical or electrocardiographic evidence of coronary artery disease. Group 2 was composed of eight patients with either intractable angina pectoris or typical angina pectoris of premature onset; all had electrocardiograms consistent with coronary artery disease and all had significant stenotic or occlusive lesions demonstrated by coronary arteriography. Recent work in this laboratory has shown an excellent correlation between coronary cinearteriographic interpretation and post-mortem observation (8).

There were 9 women and 4 men in the control group; they were 26 to 63 years old (mean age, 42 years). There were one woman and seven men in group 2; they were 35 to 53 years old (mean age, 44 years).

Patients were studied in the fasting state. Meperidine, 50 mg, and sodium pentobarbital, 75 mg, were given intramuscularly 30 min before cardiac catheterization. A polyethylene cannula was placed in a brachial artery by the Seldinger technique (9). A no. 7 Goodale-Lubin catheter was placed in the coronary sinus and advanced to the left lateral margin of the heart, where sampled blood was assumed to be representative of blood from the left ventricular myocardium (10). A no. 8 Sones catheter was placed in a brachial artery and advanced into the left ventricle during the study period. When indicated, coronary cinearteriography was performed by the Sones technique (11). Pressures were measured with Statham P23D strain gauges and recorded on a Sanborn 560 photographic recorder. Cardiac output was measured by the indicator dilution technique with indocyanine green dye, with injection into the left ventricle and sampling from the brachial artery (12). Coronary flow was measured by left ventricular injection of 85Kr in saline with integrated sampling from the coronary sinus after a 15-sec equilibration period (13). Values for each sample were plotted semilogarithmically, yielding mono-exponential decay slopes. Earlier reports from this laboratory have pointed out that this method is reproducible within 5% in subjects over 5 min at rest (14). Blood O₂ content and capacities were determined in duplicate by the method of Van Slyke and Neill (15). Systolic ejection period and systolic and diastolic mean pressures were measured from brachial arterial pressure pulses. Myocardial O₂ consumption/100 g of left ventricle was calculated as the product of coronary flow and myocardial A-V O₂ difference (ml/liter). Mean systolic ejection rate, pressure × time/min, left ventricular work and coronary and systemic vascular resistances were calculated as described elsewhere (8, 16). Observations were made at rest and during a steady 15- to 20-min intravenous infusion of l-epinephrine (1.5 to 3.5 µg/min) at a time when heart rate and blood pressure had been stable for at least 5 min. Two patients with coronary disease and one control patient were studied at doses of 1.5 and 2.5 µg/min. Results were subjected to paired analysis with each patient serving as his own control. Student's t-test was used to determine significance; a P value of less than 0.05 was considered significant.

Results

Mean values for all determinations in the control and coronary disease groups are shown in Table 1. Data from one representative patient with coronary artery disease are shown in Figure 1. The two groups responded in essentially the same manner to epinephrine. The rate of infusion did not appear to affect the basic response of the coronary circulation. Three patients received a graded infusion without change in the relation between coronary flow and myocardial O₂ extraction. There was no difference in response between individual patients related to difference in infusion rates (range 1.5 to 3.5 µg/min).

Discussion

In the physiologic state, coronary blood flow is regulated by several physical factors; primarily these are aortic pressure, coronary arteriolar caliber, relative length of systole and diastole, and the mechanical effects of the myocardium around the coronary arteries (1). Ordinarily, all of these factors are overshadowed by a regulation imposed by...
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CORONARY FLOW
ml/100 ml

ARTERIAL AND CORONARY
VENOUS O₂ CONTENT
ml/100 ml

MYOCARDIAL O₂ CONSUMPTION
ml/100 ml

CVR
dyne. sec. cm⁻² x g⁻¹

HEART RATE
beats/min

SYSTEMIC ARTERIAL PRESS.
mm Hg

SER
cal/sec cm²/m²

FIGURE 1
Effect of graded infusion of epinephrine. Note the constant coronary A-V O₂ difference during the period of increased coronary blood flow and myocardial O₂ consumption. O₂ consumption; CVR = mean diastolic coronary vascular resistance; SER = mean systolic ejection rate; A-V/A = fraction of O₂ extracted from coronary arterial blood.

The metabolic demands of the heart which results in a constant A-V O₂ difference across the heart during changing physiologic circumstances (17).

It has been shown in man that sympathomimetic drugs can override the metabolic demands of the myocardium. Isoproterenol results in an increase in coronary blood flow in excess of the O₂ requirements of the heart (6). Norepinephrine effects either no change or only a moderate increase in coronary blood flow, an increased O₂ extraction, a widened A-V O₂ difference, and decreased coronary venous O₂ content; calculated coronary vascular resistance remains unchanged or increased (7).

To be considered a vasodilator, an agent must increase flow out of proportion to any rise in perfusion pressure (18). This was the case with epinephrine, which resulted in a 37% increase in coronary blood flow although there was no change in arterial systolic pressure and a slight fall in diastolic pressure. The relative time of systole and diastole did not change significantly. Assuming that the constant left ventricular end-diastolic pressure reflected a constant left ventricular volume, and having demonstrated no change in left ventricular systolic pressure, one cannot implicate a major change in mean left ventricular intramyocardial tension as a mechanical factor regulating coronary flow in this study.

Of the mechanical performance factors measured, only mean ejection rate (and thus secondarily stroke and cardiac output) increased with epinephrine. This suggested that myocardial oxygen consumption rose in relation to augmented kinetics of contraction.

Having determined that the overall effect of epinephrine in the intact human subject is one of coronary vasodilation, the question remains whether this is primary or secondary to the increased O₂ requirements of the heart. Vasodilation is believed to be primary if the A-V O₂ difference across a vascular bed narrows, indicating that flow rose more than energy demand, and secondary if A-V O₂ difference remains constant (13). In this study, despite a significant increase in coronary blood flow and myocardial O₂ consumption, coronary A-V O₂ difference, coronary venous O₂ content, and percent extraction of O₂ by the myocardium did not change significantly. This is virtually identical to the response of the coronary circulation during exercise (6). Epinephrine in the intact human subject probably acts primarily to increase cardiovascular performance with coronary vasodilation occurring as a secondary phenomenon. It lacks the primary coronary vasoconstrictor effect of norepinephrine and the marked chronotropic effect of isoproterenol. Although it causes selective vasoconstriction in certain regions of the body, epinephrine may be a less dangerous agent to the heart itself in the treatment of low output states in subjects with coronary artery disease.

Circulation Research, Vol. XXI, December 1967
### Effects of Epinephrine on the Coronary Circulation (Average Results)

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*Not significant.

**Acknowledgments**

We are grateful to Drs. M. V. Herman, M. D. Klein, and F. J. Lane for their contributions to individual case studies, and to Mrs. K. Dahl for statistical computations.

**References**

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8 Patients with coronary artery disease

-2 8 Patients  with coronary artery disease


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Circ Res. 1967;21:919-924
doi: 10.1161/01.RES.21.6.919

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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