Effects of Epinephrine on Coronary Microvascular Diameters

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This study was designed to examine the hypothesis that epinephrine has nonuniform effects on coronary microvascular diameters. Measurements of coronary microvascular diameter were completed in anesthetized, open-chest cat preparations in which the epicardial microcirculation was viewed through an intravital microscope using stroboscopic epi-illumination. Images of coronary microvessels were digitized and analyzed on a video monitor. With arterial pressure controlled, measurements in the absence and presence of β-adrenergic blockade (propranolol 1 mg/kg) were obtained during epinephrine infusion (1–2 μg/kg/min). In the absence of β-adrenergic blockade, epinephrine produced a 25% increase in myocardial perfusion. Under these conditions, coronary vasodilation was observed in all classes of coronary arterial and arteriolar vessels. In the presence of β-adrenergic blockade, epinephrine produced a significant decrease in myocardial perfusion (−20%). Nonuniform effects on diameter were observed in arterial and venous segments of the coronary circulation. These data are consistent with the view that in the absence of β-adrenergic blockade, the functional coronary hyperemia associated with epinephrine administration is produced by uniform coronary arterial and arteriolar dilation. In the presence of β-adrenergic blockade, with metabolic effects controlled, epinephrine produced a decrease in myocardial perfusion, which is related to a nonuniform decrease in coronary microvascular diameters. Such heterogeneous effects on microvascular diameters result in a redistribution of coronary microvascular resistance. (*Circulation Research* 1987;61(suppl II):II-47–II-53)

Stimulation of cardiac sympathetic nerves or catecholamine infusion produces β-adrenergic receptor–mediated increases in heart rate and myocardial contractility, which result in an increase in coronary blood flow. Concurrent with the metabolic coronary hyperemia, there is activation of α-adrenergic receptors, which produces coronary vasoconstriction.[1,2] Although there is substantial information regarding pharmacologic and metabolic coronary hyperemia as well as α-adrenergic constriction at the macrovascular level in the coronary circulation, there is a paucity of information regarding the microvascular sites at which such dilation and constrictor mechanisms may occur.[1,3]

Attempts to examine segmental α-adrenergic constriction in the coronary circulation have been confined to studies that simultaneously measure large epicardial coronary artery resistance and total coronary vascular resistance. In the intact animal, Kelley and Feigl[4] examined segmental α-adrenergic coronary constrictor mechanisms in large coronary arteries. Large coronary arteries constricted during sympathetic nerve stimulation or norepinephrine infusion following β-adrenergic blockade. The percent increase in large coronary artery resistance was similar in magnitude to that in total coronary vascular resistance, which suggested that proximal and distal segments of the coronary circulation respond uniformly to α-adrenergic stimulation. Vatner et al[5] reported that infusion of the α-adrenergic agonist methoxamine in conscious dogs increased both epicardial coronary artery resistance and total coronary vascular resistance. These studies unfortunately could not distinguish possible nonuniform constriction in the distal coronary microcirculation.

Segmental α-adrenergic constriction has been inferred from studies in isolated blood vessels. These in vitro studies have suggested that the α-adrenergic receptors:β-adrenergic receptors ratio decreases from large epicardial coronaries to small epicardial vessels.[6–8]

The effects of sympathetic, α-adrenergic constriction on the distribution of microvascular resistance have been assessed in other vascular beds. Baumbach and Heistad[9] found that sympathetic stimulation constricted large cerebral arteries but not small cerebral blood vessels. In skeletal muscle, sympathetic nerve stimulation produces greater constriction of large arterioles and small arteries than that observed in small arteriolar vessels.[10–12] Bohlen et al[13] reported that nerve stimulation produced preferential constriction of intestinal small arteries and large arterioles.

In the aggregate, these various studies in the coronary circulation and other vascular beds suggest the possibility that α-adrenergic receptor activation may produce nonuniform constriction in the microcirculation. It was our intent to document the precise location(s) of α-adrenergic constriction in the coronary microcirculation and to contrast this to the microvascu-

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lar location(s) of metabolic coronary hyperemia. Our approach was to measure coronary microvascular diameters in the arterial and venous circulations during epinephrine infusion in the absence of β-adrenergic blockade. Since epinephrine will produce metabolic (functional) coronary hyperemia in the absence of β-adrenergic blockade, these measurements would document sites of such coronary vasoregulation. To eliminate the confounding metabolic vasodilator (β_1-adrenergic receptor) and direct vasodilator (β_2-adrenergic receptor) actions of epinephrine, microvascular caliber measurements during β-adrenergic blockade were also completed. These measurements enable precise documentation of the microvascular sites in the coronary vasculature that are receptive to α-adrenergic constriction.

Materials and Methods

General Preparation

Mongrel cats ($n=32$) of either sex were sedated with ketamine (2 mg/kg i.m.) and anesthetized with sodium pentobarbital (30 mg/kg i.m.). Each animal was placed on a homeothermic blanket to maintain body temperature at 37.5° C. The femoral artery and veins were catheterized for hemodynamic measurements, fluid and drug administration, and arterial blood gas analyses. The femoral arterial catheter was advanced retrograde to the aortic arch. A solid-state transducer (Millar, Houston, Tex.) was situated in the left ventricle via the right carotid artery for measurements of left ventricular (LV) pressure and LV dP/dt.

To eliminate the cardiac movement attributable to pulmonary inflation, high-frequency jet ventilation was used. An 18-gauge cannula was introduced into the trachea and advanced to the carina. An expiratory tracheal tube was positioned under 1–3 cm of water. This ventilatory system consisted of a pressure source (compressed air) regulated with a pressure valve at 3–7 PSI. A solenoid valve, triggered from LV dP/dt, was connected to the pressure valve. The tracheal cannula connected to this solenoid was open for only 10–20 msec during a respiratory cycle. With the jet ventilation system, pulmonary inflation produced no discernible effects in cardiac motion because of the small tidal volume. Arterial blood gases and pH were analyzed frequently and maintained within physiologic limits by varying the duration that the solenoid was open, the position of the cannula in the trachea, and/or the pressure to the solenoid.

Following these procedures, the heart was exposed by a midsternal split and partially stabilized by a pericardial cradle. The left atrium was catheterized for microsphere injections. Snares were placed around the inferior vena cava and descending thoracic aorta for control of arterial pressure during the interventions.

Microvascular Preparation

To accomplish measurements of microvascular diameter in the beating heart, an intravital microscope (Leitz Ploemopak) coupled to a silicone-intensified tube video camera (General Electric) was used. A stroboscopic light source (Chadwick-Helmuth, 250-watt xenon arc, El Monte, Calif.) was flashed once per heart cycle (middiastole) at the same point in time during successive cardiac cycles. A computer that received the LV dP/dt signal was used to set and maintain the trigger point for the strobe light during middiastole. Since the heart was illuminated for only a short period of time (15–25 msec) during each cardiac cycle, the epicardial surface appeared to be motionless when viewed through the microscope. A heat filter was used to minimize damage to the epicardial microcirculation from the stroboscopic light source, and a polarizing filter was used to reduce the glare from the epicardial surface. To enhance visualization of the smaller coronary microvessels, fluorescein-isothiocyanate dextran (MW 149,700) was administered as a bolus into the left atrium (Figure 1). Under these conditions, the vessel lumens appear white and the background dark. The fluorescein molecule was activated and visualized using fluorescence techniques and filters (Leitz H2 filter) in conjunction with the Ploem system. This procedure was instrumental for precise visualization of smaller coronary microvessels as well as identification of arterial and venous microvessels. Following injection of the labelled dextran, the arteries and veins would illuminate sequentially, i.e., arteries would be illuminated first and, because of the transit time for plasma flow, the veins would be illuminated a few seconds later. The microscope objectives used for this preparation were the Leitz A6 (6×) and Leitz L10 (10×) with numerical apertures of 0.18 and 0.22, respectively. When these objectives were used in conjunction with 10× magnification eyepieces, the resulting magnification was either 60× or 100×, respectively.

Diameter measurements were made from vessels in the coronary arterial and venous circulations during middiastole. Our image acquisition and analysis system consisted of a frame grabber (Imaging Technology, Inc., Woburn, Mass.) that digitized the image from the camera. These images could be displayed on a high-resolution video monitor (Panasonic) and stored in a computer (PDP 11/73) on a hard disk or transferred to magnetic tape for permanent storage.

Vessel measurements were accomplished by retrieving video images from the computer and displaying them on the high-resolution video monitor. Cursors were aligned with the vessel edges using a digitizing tablet (Summagraphics Corp., Fairfield, Conn.), and a computer program was used to calculate the vessel diameter in microns. Each measurement was repeated several times and represents the mean of 4–8 measurements. Our system was calibrated using a standard micrometer grid and 1.0- and 2.5-μm spherical beads. The resolution of our measurements was 2.6 μm for the 10× objective and 4.6 μm for the 6× lens. Arterial coronary microvessels were separated into four diameter classes: 10–50 μm (IV A), 51–100 μm (III A), 101–200 μm (II A), and >200 μm (I A). Venous vessels were placed in three diameter classes: 10–50 μm (III V), 51–100 μm (II V), and >100 μm (I V).

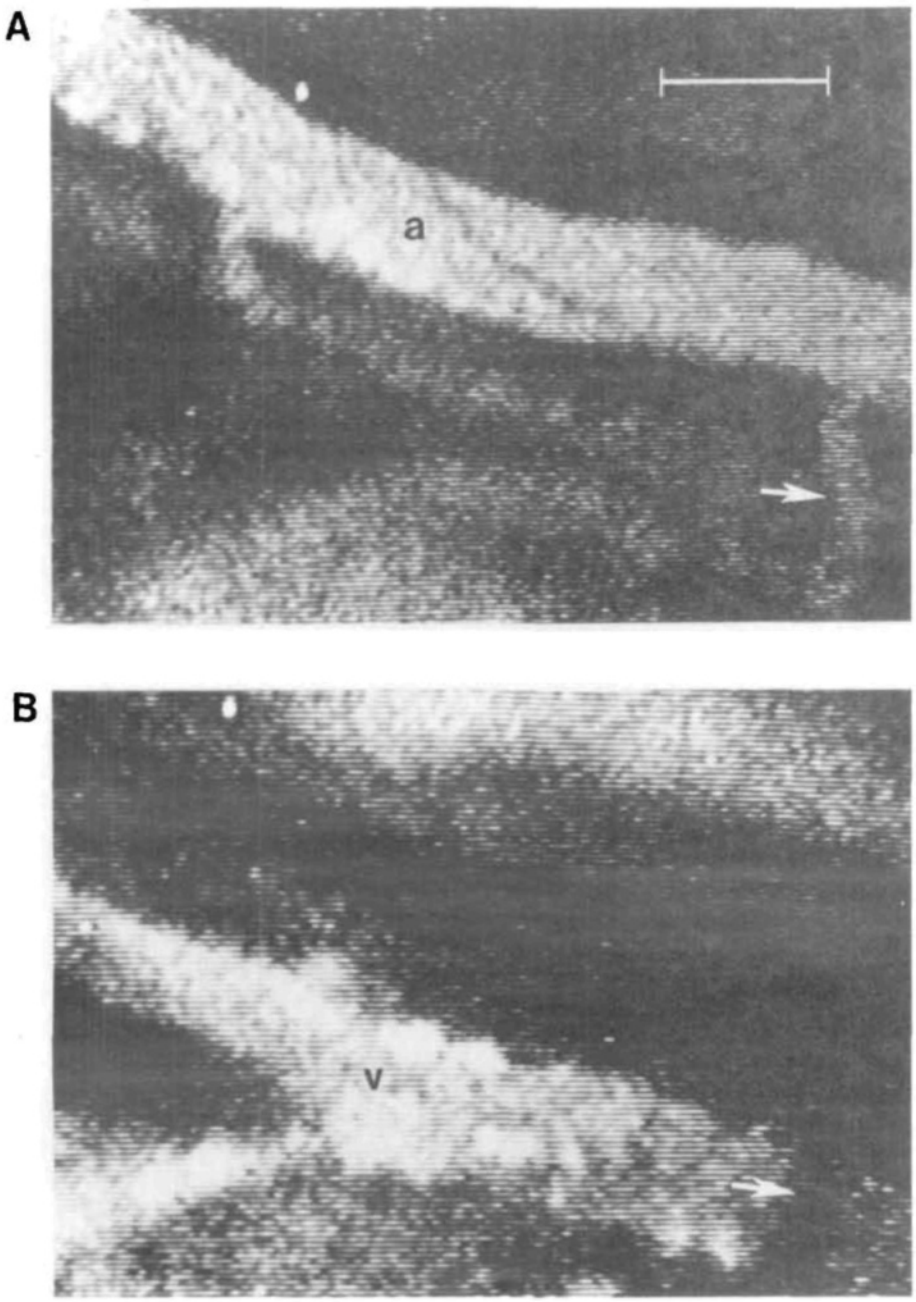

FIGURE 1. *Sequential images of coronary arterioles* (Panel A) *and venules* (Panel B) *following a bolus intra-atrial injection of fluorescein-isothiocyanate dextran. Initially, arterioles* (a) *are illuminated, then venules* (v). *Arrow points to 28-μm arteriole that is illuminated with dextran in Panel A and is seen as shaded area over coronary venule in Panel B. Venules are slightly out of focus because of curvature of heart. Bar, 100 μm.*

Protocol

Measurements of microvascular diameters in the different groups of vessels were completed under four conditions: control (baseline experimental conditions), epinephrine infusion (1–2 μg/kg/min), β-adrenergic blockade (propranolol, 1 mg/kg), and epinephrine infusion during β-adrenergic blockade. In some experiments, only the first two measurements were possible, while in other experiments, only measurements during β-adrenergic blockade were completed. Control measurements, in the absence and presence of β-adrenergic blockade, were repeated during all experiments. Following epinephrine infusion, any vessel that did not return to a diameter within 10% of the original control measurement (pre-epinephrine) was excluded from final analysis. Arterial pressure was maintained at baseline values during the experimental interventions with adjustments of the aortic or inferior vena cava snares and was maintained relatively constant at ±5 mm Hg.

Following measurements of coronary microvascular caliber, measurements of myocardial perfusion were completed with nuclide-labelled microspheres (15 μm diameter labelled with ^{46}Sc, ^{85}Sr, ^{113}Sn, ^{153}Gd, ^{141}Ce, or ^{95}Nb). Microspheres (1×10^6) were agitated, injected into the left atrium, and flushed with 2 cc of warm saline. Prior to and for 1.5 minutes after the microsphere injection, arterial blood was collected with a constant withdrawal pump from the femoral arterial line at a rate of 0.5 ml/min. Blood reference samples were placed in counting vials to determine nuclide activity. After killing the animal, the heart was removed, tissue samples from the left ventricle excised,

and the sections were divided into subepicardial and subendocardial portions and weighed. Since microvascular diameter measurements were restricted to the subepicardium, only measurements of subepicardial perfusion are reported. Myocardial perfusion/100 g (MBF) was calculated from:

$$\text{MBF (ml/min/100 g)} = [(\text{Cm})\ (\text{Wr})/\text{Cr}] \times 100$$

where Cm is nuclide activity/tissue g wt, Wr is withdrawal rate of the pump, and Cr is total nuclide activity in the blood reference sample. Nuclide activity was determined on an automated Germanium well-type gamma counter. We have recently reported the accuracy and calculation of myocardial perfusion via a computer with a Germanium counting system.[14] With the high-energy resolution of the Germanium detector, nuclide energy spectra do not overlap, and only background corrections are required.

Data Analysis

All hemodynamic variables (LV pressure; LV dP/dt; and systolic, diastolic, and mean arterial pressures) were recorded on a Gould brush recorder. These variables, along with myocardial perfusion measurements and coronary microvascular diameter measurements, were compared using t tests (paired t tests were used for the diameter comparisons). The Bonferroni correction factor was used for multigroup comparisons of the hemodynamics, e.g., heart rate during control, epinephrine, β-adrenergic blockade, and epinephrine with β-adrenergic blockade. All data are presented as mean ± SEM, and $p<0.05$ was used as the probability level for statistical significance.

Results

Hemodynamics and myocardial perfusion during the experimental interventions are shown in Table 1. Prior to β-adrenergic blockade, epinephrine infusion increased both heart rate and myocardial perfusion. β-Adrenergic receptor blockade resulted in a decrease in heart rate from that in the unblocked control state. Epinephrine infusion following β-adrenergic blockade resulted in only modest changes in hemodynamic parameters. Myocardial perfusion, however, decreased significantly.

Figures 2 and 3 show the effects of epinephrine on coronary arterial and arteriolar diameters in the absence and presence of β-adrenergic blockade. In the absence of β-blockade, epinephrine produced a substantial increase in diameters in all classes of arterial and arteriolar vessels. Under these conditions, measurements from I A and II A vessels were combined because there was not a sufficient number of measurements per individual class for statistical testing. After β-adrenergic blockade, epinephrine produced a significant decrease in diameter of the largest coronary arteries (I A), large arteriolar vessels (III A), and smallest coronary arterioles (IV A).

Figure 4 shows the effects of epinephrine infusion on microvascular diameters in the coronary venous microcirculation. In the absence of β-adrenergic blockade, epinephrine did not produce significant changes in the diameters of the two smallest groups of venules but did produce a significant diameter reduction in coronary veins greater than 100 μm in diameter. During β-adrenergic blockade, epinephrine did not significantly influence the diameter of veins less than 50 μm in diameter but did produce significant decreases in diameter of venules between 50–100 μm and veins greater than 100 μm in diameter.

Discussion

This study produced two major findings. First, functional coronary hyperemia produced by epinephrine is characterized by dilation throughout the coronary arterial circulation. Second, epinephrine produces heterogeneous effects on coronary microvascular diameters during β-adrenergic blockade. Specifically, epinephrine produced a decrease in diameter in coronary arteries larger than 200 μm and in coronary arterioles less than 50 μm. Also, coronary venules, especially those larger than 100 μm, exhibited a marked decrease in diameter during epinephrine infusion. Since coronary microvessels showed different degrees of diameter

Table 1. Hemodynamics and Myocardial Perfusion

	Control	Epinephrine	β-Adrenergic blockade	β-Adrenergic blockade + epinephrine
Heart rate (beats/min)	192 ± 3 (24)	237 ± 3* (24)	158 ± 2 (19)	175 ± 4†‡ (19)
Systolic pressure (mm Hg)	113 ± 4 (24)	107 ± 10 (24)	103 ± 5 (19)	116 ± 5† (19)
Diastolic pressure (mm Hg)	78 ± 3 (24)	78 ± 2 (24)	76 ± 8 (19)	85 ± 14 (19)
Mean arterial pressure (mm Hg)	92 ± 4 (24)	87 ± 4 (24)	88 ± 13 (19)	95 ± 7 (19)
Myocardial blood flow (ml/min/100 g)	188 ± 25 (8)	238 ± 21* (8)	185 ± 13 (7)	148 ± 13†‡ (7)

*$p<0.05$, epinephrine vs. control.
†$p<0.05$, epinephrine + β-adrenergic blockade vs. β-adrenergic blockade.
‡$p<0.05$, epinephrine + β-adrenergic blockade vs. epinephrine.
n, Number of observations (in parentheses); mean ± SEM.

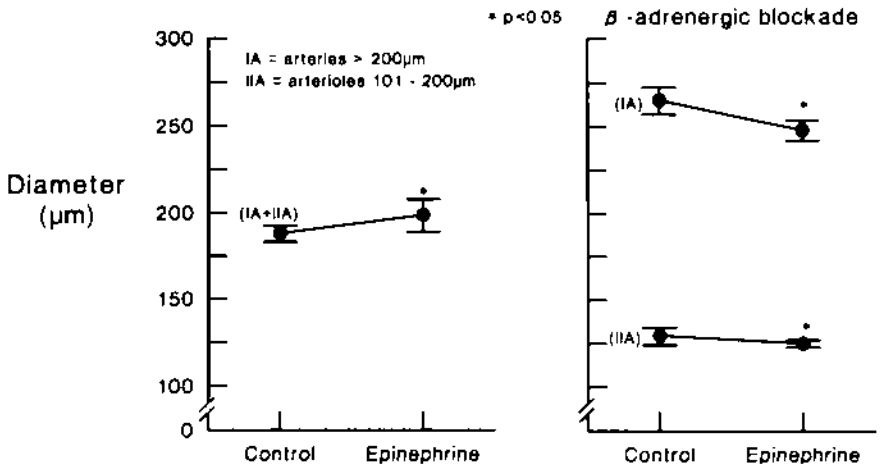

FIGURE 2. *Coronary arterial (I A) and large arteriolar (II A) responses to epinephrine in absence and presence of β-adrenergic blockade. In absence of β-blockade, coronary artery and arterial vessels were lumped into one group because of insufficient sample size in each group. Sample sizes: in absence of β-adrenergic blockade, I A+II A (n=7); in presence of β-adrenergic blockade, I A (n=7), II A (n=8).*

change to a common stimulus (epinephrine), one implication of these results is that there may be independent regulatory mechanisms for the control of vasomotor tone at different levels in the coronary microcirculation.

Our data interpretations, results, and conclusions depend critically on the accuracy of our measurements and the viability of our preparation. Our measurement system is calibrated with a micrometer grid, and we have determined the resolution to be approximately 4.6 μm for the 6× objective and 2.6 μm for the 10× objective. Thus, only very small changes in microvascular caliber (within the range of 1 μm) would be undetected. Many of the significant differences observed were in the range of 7–20 μm, which are easily detected with the resolution of our system.

Another criticism regarding the study could be related to the viability of the epicardial microcirculation. As we have pointed out previously,[15] our method maintains the environment of the epicardial surface. With this procedure, vascular tone is similar to that when the pericardium is closed. Moreover, any measurement in which the control microvascular diameter following an intervention did not return to within 10% of the previous control was excluded from final analysis. This occurred in approximately 15% of our preparations. Such criteria ensured that measurements were not obtained from a preparation that was deteriorating during the course of the experiment.

A limitation to our data interpretations regarding nonuniform effects on coronary microvascular diameters produced by epinephrine relates to the redistribution of microvascular pressures produced by such effects. It was not possible to distinguish between active and passive changes in coronary microvascular diameters. For instance, the observed decrease in diameter of the IV A vessels could be related to active vasoconstriction and/or a passive decrease in diameter, attributable to a decrease in distending pressure. Without pressure measurements, which were not completed in this study, it is not possible to distinguish the mechanism for a decrease in microvascular diameter. Also, we have assumed that coronary capacitance has an equivalent effect on our microvascular diameter measurements during each of the interventions. Although this assumption may not be absolutely correct, because the rate of pressure change in the coronary vasculature is directly related to heart rate, our measurements were made at similar distending pressures, i.e., the same "capacitive charge." With these limitations in mind, the discussion of our data is accordingly restricted to changes in microvascular diameters rather than microvascular constriction or dilation.

There are many additional factors that complicate

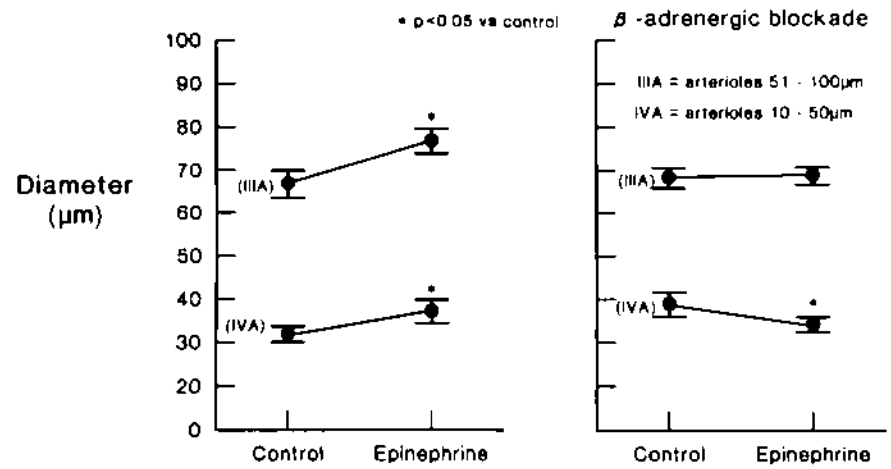

FIGURE 3. *Coronary arteriolar responses to epinephrine in absence and presence of β-adrenergic blockade. Sample sizes: in absence of β-adrenergic blockade, III A (n=6), IV A (n=5); in presence of β-adrenergic blockade, III A (n=7), IV A (n=6).*

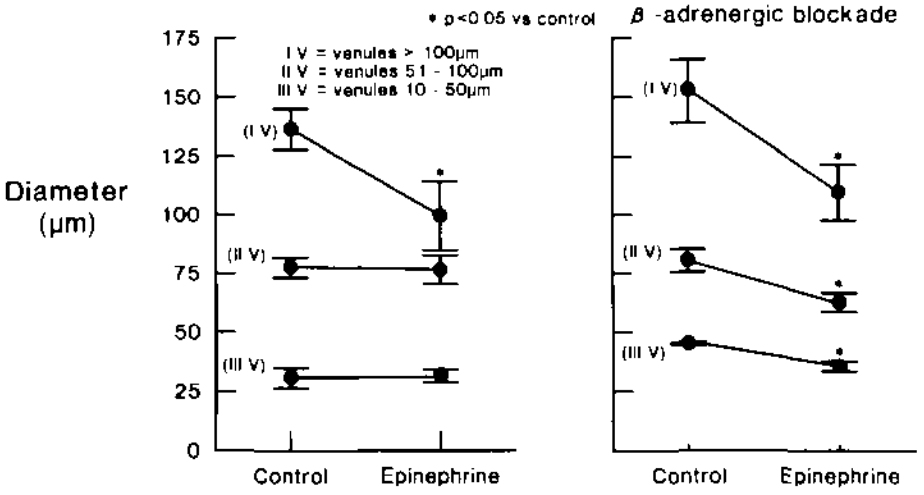

FIGURE 4. *Coronary venular responses to epinephrine in absence and presence of β-adrenergic blockade. Sample sizes: in absence of β-adrenergic blockade, I V (n = 14), II V (n = 11), III V (n = 16); in presence of β-adrenergic blockade, I V (n = 14), II V (n = 11), III V (n = 13).*

the interpretation of the data. Specifically, microvascular diameters would be influenced by both direct actions of epinephrine and indirect actions related to changes in myocardial metabolism and possible reflex changes that could have occurred as a result of systemic hemodynamic changes (although arterial pressure was controlled). Also, since substantial changes in myocardial perfusion were observed during the various interventions (Table 1), some of the actions of epinephrine may be indirectly related to flow-mediated vasoactive changes. Thus, the effects of epinephrine on the coronary microcirculation are related most likely to a combination of direct and indirect effects.

Another factor that influences our data interpretations concerns our classification of the coronary circulation into four different classes of arterial vessels and three different classes of venous vessels. Our classification scheme was not based on arbitrary designation; it was based on functional responses to different constrictor and/or dilator stimuli[15,16] and on varied anatomic characteristics of different-sized blood vessels.[17] We emphasize, however, that knowledge of the functional organization of coronary microvessels is limited. With acquisition of additional information, such a classification scheme may likely change.

There is a great deal of evidence that documents functional hyperemia in the coronary circulation.[1,3] There have been few studies that have addressed specific sites at which functional coronary hyperemia occurs. Large coronary arteries were found to be responsive to changes in metabolic demands.[18,19] Reduction of myocardial oxygen consumption with propranolol not only reduced coronary blood flow but also decreased the diameter of large coronary arteries.[18] Furthermore, Macho et al[19] found that stimulation of myocardial metabolism with β-adrenergic agonists produced concomitant functional coronary hyperemia and large epicardial artery vasodilation. It is also possible that a component of the diameter increase observed during epinephrine infusion in the coronary microcirculation may be related to flow-mediated dilation. Our results extend observations obtained in the conscious dog[18,19] to the microcirculation, namely, that coronary arteries (in our preparation vessels >200 μm in diameter) and arterioles were responsive to metabolic stimuli. All of these vessels dilated considerably when metabolic demands were augmented during epinephrine administration. Our results also reveal that such coronary metabolic hyperemic responses are uniform throughout the coronary arterial system.

The responsiveness of coronary circulation to α-adrenergic agonists, such as epinephrine, has been well documented. Numerous studies have evidenced that pharmacologic α-adrenergic receptor coronary constriction can be produced by infusion of catecholamines following β-adrenergic blockade.[1,3,20–27] In addition to these studies regarding pharmacologic α-adrenergic coronary constriction, there have been other reports in the literature that have documented that physiologic levels of circulating catecholamines also can produce coronary constriction.[28,29] Despite this large body of literature describing α-adrenergic constriction in the coronary circulation, there have been few studies that have addressed segmental control of resistance at specific sites in the coronary circulation.

An important implication of our results is that there are different regulatory mechanisms for the control of vasomotor tone in different vessels in the coronary circulation. In coronary arteries and large coronary venules (I A and I V), neurohumoral control mechanisms may dominate. In smaller coronary arterioles (III A), the regulatory mechanism may be myogenic and/or metabolic because these vessels were not responsive to α-adrenergic constriction produced by epinephrine. It is interesting to speculate that different regulatory mechanisms at different levels in the coronary microcirculation may contribute to the integrative control of oxygen delivery to the myocardium under various types of physiologic stresses, e.g., exercise.

In summary, this report documents that functional coronary hyperemia is produced by dilation throughout the coronary arterial vasculature. If the metabolic influences of epinephrine are controlled via β-adrenergic blockade, nonuniform decreases in diameter in various segments of the coronary microcirculation are observed. Based on these functional differences to epi-

nephrine among different classes of coronary microvessels, we suggest that there may be different regulatory mechanisms at various levels in the coronary microcirculation.

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