α-Adrenergic Vasoconstrictor Tone Limits Right Coronary Blood Flow in Exercising Dogs

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In exercising dogs, increased myocardial O_2 consumption (MVO_2) of the left ventricle is met primarily by hyperemia, whereas increased O_2 extraction makes a greater contribution to right ventricular (RV) O_2 supply. We hypothesized that α-adrenergic vasoconstrictor tone limits right coronary (RC) blood flow during exercise, forcing increased O_2 extraction. This tone might also contribute to lesser RC vascular conductance at rest. Accordingly, RV O_2 balance was examined at rest and during graded treadmill exercise before and during α-adrenergic blockade with phentolamine (1 mg/kg, iv, $n = 6$). The transmural distribution of RC flow was measured with radiolabeled microspheres in 4 additional dogs. At rest, α-adrenergic receptor blockade did not significantly increase RC flow or conductance. During exercise, α-adrenergic blockade increased RC flow and conductance responses to increased RV MVO_2 by 25% and 60%, respectively. The transmural distribution of RC flow was not altered by exercise or by α-adrenergic blockade. Before α-adrenergic blockade, hyperemia provided 39%–66% of the additional O_2 consumed by the right ventricle during graded exercise; after α-adrenergic blockade, hyperemia contributed 74%–85%. After α-adrenergic blockade, the slope of the relationship between RC venous PO_2 and RV MVO_2 became less steep, reflecting less O_2 extraction due to enhanced hyperemia. Additional experiments were conducted on 5 anesthetized, open-chest dogs with constant RC perfusion pressure and β-adrenergic blockade. The RC flow response to intracoronary norepinephrine was shifted to the left compared with that measured in the left coronary circulation, consistent with observations in the conscious exercising dogs. In conclusion, α-adrenergic vasoconstrictor tone does not restrict resting RC blood flow, but during exercise, this tone transmurally blunts RC hyperemia and forces the right ventricle to mobilize its O_2 extraction reserve. This effect is more pronounced than has been reported for the left ventricle. Exp Biol Med 229:312–322, 2004

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As myocardial O_2 consumption (MVO_2) is elevated by graded treadmill exercise, O_2 supply is maintained differently between right and left ventricles (1). In the conscious state, left ventricular O_2 extraction is high (75%–82%) at rest (2–5), so only a small O_2 extraction reserve is available for increasing left ventricular O_2 supply during exercise. Thus, increases in left ventricular MVO_2 during exercise always produce concomitant increases in coronary blood flow (2, 3, 5–8). In contrast, right ventricular (RV) resting O_2 extraction is only ~50% (1, 9), so the right ventricle has a large O_2 extraction reserve as well as a substantial flow reserve to balance increased RV requirements for O_2 (1, 9, 10). In exercising dogs, we found that increased O_2 extraction is the primary mechanism for increasing RV O_2 supply until right coronary (RC) venous PO_2 falls to ~20 mmHg, the apparent threshold for both left and RC vasodilation (1). However, when RV MVO_2 is increased by acute pulmonary hypertension, RC flow increases as MVO_2 is elevated with no apparent venous PO_2 threshold for RC dilation (9, 11).

To account for these disparate findings, we hypothesize that RC dilation is blunted during exercise by augmented sympathetic-mediated vasoconstrictor tone. It is well-recognized that a coronary sympathetic vasoconstrictor tone exists in normal and atherosclerotic left coronary circulations during exercise (12–22). Although this tone does not prevent exercise-induced left coronary hyperemia, it does limit flow, and some studies have demonstrated improved left ventricular function during exercise after α-adrenergic receptor blockade (17, 21, 22). To date no studies have determined whether sympathetic-mediated vasoconstrictor tone restricts RC blood flow during exercise and to what extent this tone might affect RV O_2 demand/supply balance.

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Resting RC blood flow (1, 9, 10) is lower than generally reported for left coronary flow (15, 17, 20, 23). Since left and right coronary perfusion pressures are identical, the lesser conductance of the RC circulation at rest might be due, in part, to sympathetic-mediated vasoconstrictor tone, but this question has not been previously investigated.

In the current investigation, experiments were conducted in chronically instrumented, conscious dogs, which exercised before and after α-adrenergic blockade. A novel technique to collect RC venous blood from instrumented, conscious dogs (24) enabled us to measure RV MVO_2 and, thus, to determine the role of α-adrenergic vasoconstrictor tone in control of RC blood flow and RV O_2 demand/supply balance at rest and during graded treadmill exercise. Experiments were also conducted in anesthetized, open-chest, β-adrenergic–blocked dogs to further demonstrate the presence of α-adrenergic vasoconstriction in the RC circulation and to determine whether this RC vasoconstriction exceeds that observed in the left ventricle under similar conditions.

Materials and Methods

Studies Conducted in Chronically Instrumented Dogs. *Animal Instrumentation.* This investigation was approved by the Institutional Animal Care and Use Committee and was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the U.S. National Institutes of Health (NIH Publication No. 85-23, Revised 1996). Experiments were performed on 10 19–29 kg adult mongrel dogs of both sexes, which had been taught to run on a motorized treadmill.

Thirty minutes after preanesthesia treatment with Acepromazine (0.03 mg/kg sc), anesthesia was induced by thiopental sodium (5 mg/kg iv) and was maintained by mechanical ventilation with isoflurane gas (1%–3%) after endotracheal intubation. Under sterile conditions, a thoracotomy was performed in the fourth right intercostal space. A 17-gauge pressure-monitoring catheter was implanted into the ascending aorta to measure aortic blood pressure and obtain arterial blood samples. A nonbranching section of the RC artery was dissected free for 1–2 cm to affix a 2-mm diameter Transonic Systems Inc. flow transducer. A coronary venous catheter prepared from Micro-Renathane tubing was inserted into a superficial vein draining the RV myocardium, as described previously (9, 24). The venous catheterization site was in the central region of the RV free wall, well within the perfusion territory of the RC artery. A coextruded polyurethane catheter was implanted through a stab wound in the right ventricle, so that a 3F, high-fidelity, Mikro-tip catheter pressure transducer (Millar Instruments) could be inserted through it at the time of the experiment to measure RV pressure. This pressure transducer was introduced into the polyurethane RV catheter through a Tuohy-Borst hemostatic control valve (Mallinckrodt Medical), which allowed infusion of phentolamine while maintaining a fluid-tight seal around the Millar catheter (3, 4, 9).

At the conclusion of the instrumentation, catheters and wires were brought out of the thorax through the third and fifth right intercostal spaces, tunneled under the skin, and exteriorized between the shoulders through individual puncture wounds. The chest was closed, and the pneumothorax evacuated through a chest tube. An antibiotic (Clavamox, 13.75 mg/kg, twice daily, po) and aspirin (162–300 mg po) were given for 10 days after surgery. The RC venous catheter was attached to a 125-ml Access Technologies "C" Series Balloon Pump for continuous infusion (5.0 ml/hr) of heparinized saline (10 U/ml) from the time the venous catheter was implanted until the completion of experimentation, except for the times when venous blood samples were collected. After bandaging, the animal was fitted with a jacket (Alice King Chatham) to protect the catheters. The infusion pump was positioned in a pocket of the jacket.

Experimental Protocol and Data Collection. After the animals recovered from the surgical procedures, baseline measurements were obtained with the animal standing quietly in a sling. RC flow was measured with a Transonic Systems Inc. T206 series flowmeter. An external pressure transducer (Hewlett-Packard model 1290C) was positioned at midheart level and connected to the aortic catheter to measure systemic arterial pressure. Aortic pressure, RC blood flow, and RV pressure were recorded on a multichannel Hewlett-Packard chart recorder and an EMKA Technologies data acquisition system.

Arterial and RC venous blood samples were collected anaerobically and chilled on ice until analysis. O_2 content was measured with an Instrumentation Laboratory model 682 Co-Oximeter, and PO_2 was measured with an Instrumentation Laboratory Synthesis 30 blood gas analyzer. RV MVO_2 was computed by multiplying the RC arteriovenous O_2 content difference ($A\text{-}V\Delta O_2$) by RC blood flow, normalized per 100-gram tissue mass. RV lactate uptake was computed similarly using values for plasma lactate and plasma flow.

After baseline measurements were made, exercise was begun at 2 miles/hr and 0% incline (exercise 1). Exercise intensity was subsequently increased with treadmill speed at 3 miles/hr and 5% incline (exercise 2) and with treadmill speed at 4 miles/hr and 10% incline (exercise 3). The animal exercised for 3 mins at each intensity. Blood samples were taken and measurements recorded when RC flow had stabilized during the last minute at each exercise intensity. The animals were allowed to rest sufficiently between each exercise bout for hemodynamic variables to return to baseline. After the control experiments were conducted, phentolamine (1 mg/kg; Refs. 16, 18, 25) was administered via the RV catheter. The experimental protocol described above was repeated in 6 α-adrenergic–blocked animals beginning 10 mins after the drug injection.

To measure the transmural distribution of right and left coronary blood flow, a separate group of 4 dogs were instrumented as described above, with the addition of a catheter placed into the left atrial appendage for injection

of radioactive microspheres (26). RC venous samples were not collected from these animals. Between 1 to 2 million 15 μm-diameter microspheres, labeled with ^{141}Ce, ^{85}Sr, ^{95}Nb, or ^{46}Sc and suspended in 10% dextran and 0.014% Tween 80, were injected to measure regional coronary blood flow. Each microsphere dose was sonicated for 30 mins and vortexed prior to infusion. Control recordings were made and microspheres injected with the dogs standing quietly in a sling. A second species of microspheres was injected while the dogs were running at 4 miles/hr, 10% incline (exercise 3). Beginning 10 mins after phentolamine (1 mg/kg, iv) was administered, the third and fourth species of microspheres were injected at rest and during the same exercise intensity. Arterial reference blood samples were collected using the aortic catheter at a constant rate of 3 ml/min for 4 mins beginning at the time of microsphere injection.

After completion of the protocols, the animals were euthanized with pentobarbital sodium (30 mg/kg) followed by KCl sufficient to cause ventricular fibrillation. These agents were administered via the RV catheter. After the chest was opened, a catheter was inserted into the RC ostium and 15 ml of 2.5% Evans Blue dye was injected to delineate the RC-perfused territory. In all cases, the RC venous catheter was found to be positioned within the dyed RV wall. This dyed territory was then carefully excised and weighed, so that RC blood flow could be expressed per 100 grams of tissue. For measurements of regional coronary blood flow, tissue samples were taken from the dyed RV wall and from left ventricular regions perfused by the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LC). RV samples were divided into subendocardial and subepicardial layers, and left ventricular samples were divided into subendocardial, midmyocardial, and subepicardial layers. Tissue samples (approximately 1.6 g) and blood reference samples were analyzed for radioactivity using a Packard gamma counter. Regional coronary blood flow (ml/min) was calculated from Fr X Rt / Rr, where Fr is the arterial reference blood sampling rate (ml/min), and Rt and Rr are the radioactivities (counts/min) of the tissue and reference samples, respectively (26). Regional coronary flow was normalized by tissue sample weight and is reported as ml/min/100 g. The subendocardial/subepicardial flow ratio was calculated for each of the transmural samples.

Studies Conducted in Anesthetized Dogs. Additional experiments were conducted to further demonstrate the presence of α-adrenergic vasoconstriction in the RC circulation and to compare this RC vasoconstriction with that in the left coronary circulation ($n = 10$). Dogs were sedated with morphine (3 mg/kg, sc) and anesthetized with α-chloralose (100 mg/kg, iv). The animals were then intubated and ventilated (Harvard respirator) with room air and supplemental oxygen. Catheters were placed in the right femoral artery to withdraw blood for a pressure-controlled, extracorporeal, coronary artery perfusion system and right femoral vein for intravenous administration of supplemental anesthetic and propranolol. A catheter was also placed in the left femoral artery to measure arterial blood pressure.

A thoracotomy was then performed and the heart suspended in a pericardial cradle. The RC ($n = 5$) or left anterior descending coronary artery (LAD, $n = 5$) was isolated, and following heparinization (500 U/kg, iv), cannulated with a stainless steel cannula connected to the extracorporeal perfusion system. Coronary perfusion pressure was measured through a saline-filled catheter advanced to the orifice of the coronary cannula. Propranolol (2 mg/kg, iv) was then infused to inhibit norepinephrine-mediated activation of β-adrenergic receptors. Coronary perfusion pressure was maintained at 100 mm Hg throughout the experimental protocol. After 15 mins recovery, norepinephrine was infused into the coronary perfusion line (0.05–0.75 μg/kg/min), and coronary blood flow recorded when coronary constriction was maximal for each dose. At completion of the experiments, the perfused ventricular tissue was dyed and weighed, so that the norepinephrine infusion rate could be expressed as μg/min/g.

Statistical Analyses. All values are expressed as means ± SE. Results were analyzed with randomized block analyses of variance (ANOVA), that is, repeated measures design with all treatments performed on all dogs, to detect effects of 1) exercise and 2) α-adrenergic blockade. When significance ($P < 0.05$) was detected by ANOVA, a Student-Newman-Keuls multiple comparison test was performed. RC flow, conductance, and venous PO_2 were further examined by linear regression analysis using RV MVO_2 as the independent variable. For each dog, the slopes of these relationships were determined for the unblocked and blocked conditions. Respective slopes were compared using paired t tests. T tests were used to determine whether transmural flow ratios differed from 1.0. T tests were also used to determine whether flow during norepinephrine infusion differed from baseline. Differences between RC and LAD flow responses to norepinephrine were examined by ANOVA and the Student-Newman-Keuls test. Differences with $P < 0.05$ were considered statistically significant. All statistical analyses were performed according to Zar (27) using GB-Stat statistical software, version 9.0.

Results

Exercise Before α-Adrenergic Blockade. Hemodynamic and metabolic data collected at rest and during exercise are presented in Table 1 and Figure 1. In the untreated condition, heart rate (Table 1) increased by 25% to 147 ± 13 beats/min during exercise 1 and increased further during exercises 2 and 3, reaching 204 ± 15 beats/min at exercise 3. Mean aortic pressure (Table 1) tended to rise during exercise, although this change did not reach statistical significance. Peak RV pressure (Table 1) increased from 32 ± 1 mm Hg at rest to 46 ± 4 mm Hg during the most strenuous exercise. RV MVO_2 (Fig. 1A) was 4.7 ± 0.5 ml O_2/min/100 g at rest and increased to

Table 1. Hemodynamic Variables at Rest and During Graded Treadmill Exercise Before and After α-Adrenergic Blockade with Phentolamine

	Rest	Exercise			α-Adrenergic blockade (*P* value)	Exercise (*P* value)	Interaction (*P* value)
		Exercise 1	Exercise 2	Exercise 3			
Heart rate (beats/min)					<0.001	<0.001	0.402
Untreated	118 ± 9	147 ± 13†	175 ± 12†‡	204 ± 15†‡			
Phentolamine	155 ± 10*	197 ± 14*†	221 ± 11*†‡	247 ± 13*†‡			
Mean aortic pressure (mm Hg)					0.073	0.438	0.505
Untreated	108 ± 8	118 ± 10	121 ± 11	119 ± 14			
Phentolamine	104 ± 7	104 ± 11	109 ± 13	113 ± 16			
RV pressure (mm Hg)					0.116	<0.001	0.293
Untreated	32 ± 1	38 ± 3†	41 ± 3†	46 ± 4†			
Phentolamine	33 ± 3	44 ± 3*†	48 ± 3*†	51 ± 3†			
RV dp/dt_{max} (mm Hg/sec)					0.031	<0.001	0.854
Untreated	716 ± 69	1384 ± 337†	1508 ± 349†	1735 ± 334†			
Phentolamine	1359 ± 185*	1848 ± 274	2034 ± 174*†	2202 ± 191†			

Values are mean ± SE; $n = 6$. RV, right ventricular; † $P < 0.05$ vs. rest, same condition; ‡ $P < 0.05$ vs. prior, less strenuous exercise, same condition; * $P < 0.05$ vs. untreated condition, same exercise condition; exercise 1, 2 miles/hr, 0% incline; exercise 2, 3 miles/hr, 5% incline; exercise 3, 4 miles/hr, 10% incline.

10.1 ± 1.0 at exercise 3, a 115% increase in RV MVO_2 compared with rest. RC blood flow (Fig. 1B) was 51 ± 5 ml/min/100 g at rest and increased significantly to 83 ± 9 ml/min/100 g at exercise 3. When exercise-induced increases in RC perfusion pressure were taken into account by computing RC vascular conductance (conductance = RC blood flow/mean aortic pressure), no significant RC vasodilation was evident during exercise (Fig. 1C).

RC venous PO_2 decreased from 28.5 ± 1.4 mm Hg at rest to 22.2 ± 1.5 mm Hg during exercise 1 and declined further at each successive exercise intensity. At exercise 3, RC venous PO_2 reached 20.4 ± 1.1 mm Hg, a value similar to resting left coronary venous PO_2 (3, 5), and above the threshold for RC vasodilation during exercise (1). RV lactate uptake was 0.12 ± 0.04 μmol/min/g at rest and tended to rise during exercise, reaching 0.37 ± 0.12 μmol/min/g at exercise 3. Since there was no evidence of a shift to anaerobic metabolism, the increase in RV O_2 extraction, reflected by the observed decrease in RC venous PO_2, was sufficient to meet RV O_2 requirements.

Exercise After α-Adrenergic Blockade. Blockade of α-adrenergic receptors with phentolamine tended to increase RV MVO_2 at rest and significantly increased RV MVO_2 during each level of exercise (Fig. 1A). Mean aortic blood pressure tended to fall after α-adrenergic blockade ($P = 0.073$). Compared with respective untreated conditions, RV MVO_2 increased by 60% during exercise 1, 55% during exercise 2, and 59% during exercise 3. RC blood flow increased progressively during exercise and was significantly elevated compared with respective untreated exercise values (Fig. 1B). RC conductance was increased significantly at each exercise intensity after α-adrenergic blockade, although not at rest (Fig. 1C). RV lactate uptake at rest and during exercise did not differ significantly from respective untreated values.

Mechanisms of RV O_2 Balance. Systemic arterial O_2 content was 16.6 ± 0.5 ml O_2/100 ml blood at rest in the untreated condition. During exercises 1, 2, and 3, these values were 17.3 ± 1.1, 17.2 ± 0.9, and 17.3 ± 0.9 ml O_2/100 ml blood, respectively ($P > 0.05$). Phentolamine caused no significant changes in systemic arterial O_2 content, although values tended to be slightly lower than respective untreated values. Figure 2 provides further information on determinants of RV O_2 demand/supply balance at rest and during exercise-induced increases in O_2 demand before and after α-adrenergic blockade. With A-VΔO_2 on the *x*-axis and RC blood flow on the *y*-axis, the area within each rectangle represents RV MVO_2. Before α-adrenergic blockade, exercise caused a marked increase in A-VΔO_2, that is, RV O_2 extraction, which was evident at exercise 2. Percentage O_2 extraction (%O_2E; A-VΔO_2/arterial O_2 content × 100) was 56 ± 1% at the resting, untreated condition. Percentage O_2E increased significantly to 68 ± 4% at exercise 1, 70 ± 1% at exercise 2, and 71 ± 2% at exercise 3. Compared with the respective unblocked conditions, α-adrenergic blockade caused no significant change in A-VΔO_2, although A-VΔO_2 tended to become larger at rest and smaller during exercise, as shown in Figure 2. Percentage O_2E at rest increased significantly to 63 ± 2%. Exercise caused %O_2E to increase significantly, although these values did not differ significantly from respective, untreated exercise values. This figure clearly demonstrates that the exercise-induced increases in RV MVO_2 after α-adrenergic blockade were associated with large increases in RC flow.

Further analysis of the data presented in Figure 2 allowed us to define relative contributions of mechanisms

responsible for increasing RV O_2 supply to meet RV O_2 demand (1). Before α-adrenergic blockade with phentolamine, increased RC blood flow provided 39%, 57%, and 66% of the additional O_2 supply required for the increases in RV MVO_2 during exercises 1, 2, and 3, respectively. Thus, increased RV O_2 extraction supplied 61%, 43%, and 34% of the additional O_2 required at exercises 1, 2, and 3, respectively. After α-adrenergic blockade, exercise produced larger increases in RV MVO_2. Increases in RC blood flow contributed 74%, 83%, and 85% of the additional O_2 consumed at each respective exercise intensity. Clearly, the dependence of the right ventricle on its O_2 extraction reserve was reduced by α-adrenergic blockade.

Since RV MVO_2 was elevated by exercise and by α-adrenergic blockade during exercise, RC flow and conductance data were plotted as functions of RV MVO_2. Figure 3 shows that both RC flow and conductance varied linearly with RV MVO_2 before and after α-adrenergic blockade. α-Adrenergic blockade shifted these regression lines upward, making the slopes steeper ($P < 0.05$), such that the RC flow response to altered RV MVO_2 increased 25% after blockade, and the RC conductance response increased 60%. These data provide further evidence that sympathetic vasoconstrictor tone restricts RC blood flow during exercise.

A sensitive index of RV O_2 demand/supply balance is shown in Figure 4, where coronary venous PO_2 is plotted as a function of MVO_2 (1–4, 8, 9, 16, 28–30). RC venous PO_2 varied linearly with RV MVO_2 before and after α-adrenergic blockade (Fig. 4A); however, α-adrenergic blockade shifted the regression line upward, making the slope less negative ($P < 0.05$). This upward shift in the relationship between RC venous PO_2 and RV MVO_2 after α-adrenergic blockade is consistent with significant α-adrenergic vasoconstrictor tone during exercise in the untreated condition, which forces the right ventricle to utilize its large O_2 extraction reserve to balance increased RV myocardial requirements for O_2. This balance was confirmed by sustained RV lactate uptake during exercise. In addition, the difference between the untreated control slope and phentolamine-treated slope of the coronary venous PO_2 versus MVO_2 relationship was significantly greater in the right ventricle than in the left ventricle (data from Gorman *et al.*, Ref. 16; Fig. 4B).

Norepinephrine Dose-Response Relationships in Anesthetized Dogs. Figure 5 shows the effects of graded norepinephrine infusion on RC and LAD blood flow in β-adrenergic–blocked, anesthetized dogs. At all doses, norepinephrine caused significant depressions of RC flow. At the lowest dose of norepinephrine, this depression was markedly greater than that observed in similar left coronary experiments.

Effect of α-Adrenergic Blockade on Regional Myocardial Blood Flow. Table 2 presents values for regional RV and left ventricular blood flow and its transmural distribution at rest and during exercise 3 before and after α-adrenergic blockade. Exercise caused significant increases in flow to all right and left ventricular samples. In the untreated state, the resting RV subendocardial/subepicardial flow ratio was 1.26 ± 0.10 ($P = 0.08$ vs. uniformity), consistent with the preferential distribution of RC blood flow to the RV subendocardium reported previously (11, 31, 32). During exercise this ratio was 1.19 ± 0.05 ($P < 0.05$ vs. uniformity). α-Adrenergic blockade did not significantly alter the transmural distribution of RC flow at rest or during exercise.

In the left ventricle, resting flow in the untreated condition was significantly greater in the subendocardial layer

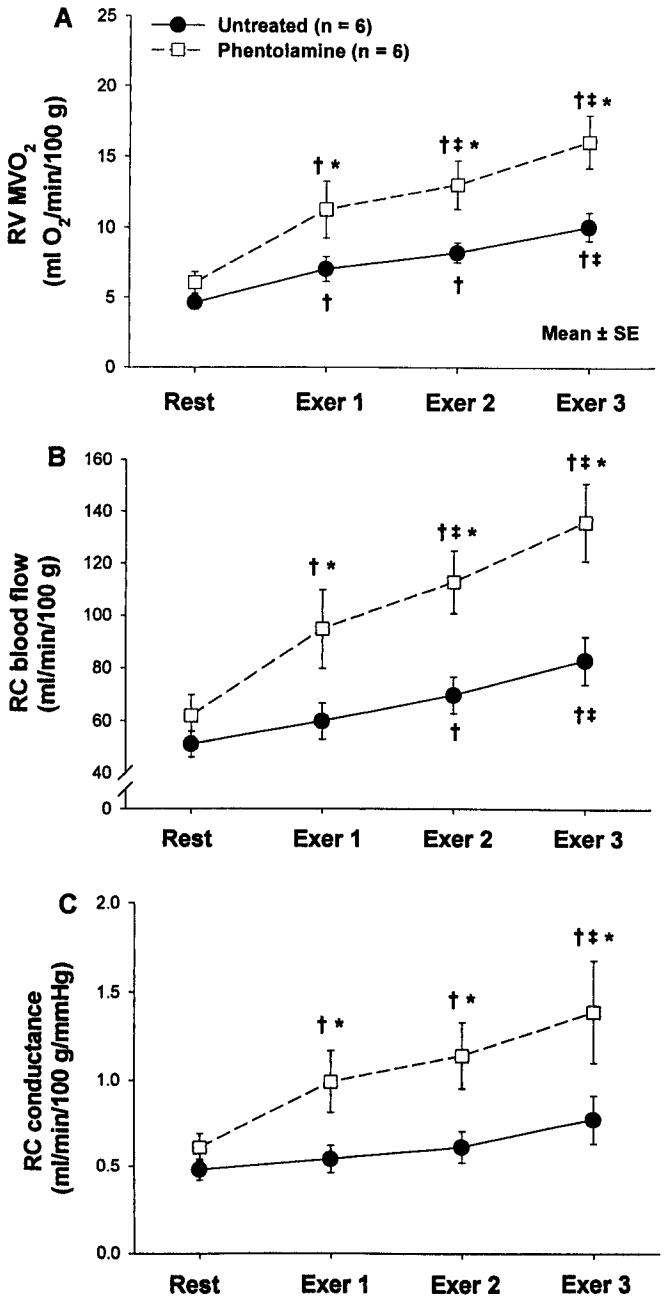

Figure 1. RV MVO_2 (Panel A), RC blood flow (Panel B), and RC conductance (Panel C) at rest and during three levels of treadmill exercise before and after α-adrenergic blockade with phentolamine. †Different from resting condition, $P < 0.05$; ‡Different from prior, less strenuous exercise level, $P < 0.05$; *Different from untreated condition, same exercise level, $P < 0.05$.

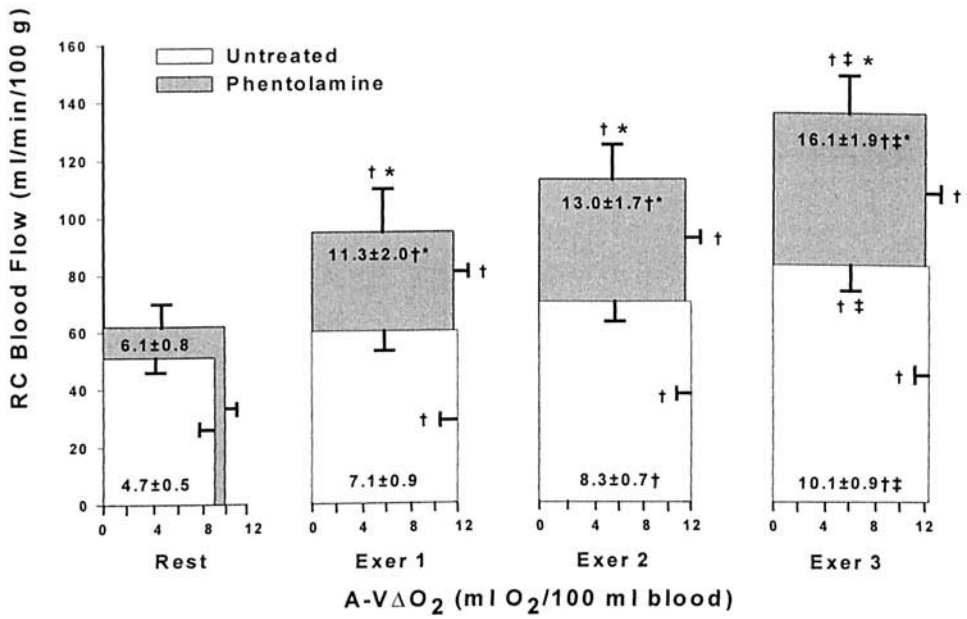

Figure 2. RV O_2 supply and consumption at rest and during three levels of treadmill exercise before and after α-adrenergic blockade. Area within each rectangle is RV O_2 consumption (MVO_2, ml O_2/min/100 g tissue) calculated from the product of arteriovenous O_2 content difference (A-VΔO_2, *x*-axis) multiplied by RC blood flow (*y*-axis) and divided by 100. Values of MVO_2 measured before and after α-adrenergic blockade are printed in the unshaded and shaded areas, respectively. The shaded area shows A-VΔO_2 and the incremental change in RC blood flow after α-adrenergic blockade. †Different from resting condition, $P < 0.05$; ‡Different from prior, less strenuous exercise level, $P < 0.05$; *Different from untreated condition, same exercise level, $P < 0.05$.

of both the LAD and LC regions (ratios of subendocardial to subepicardial flow > 1.0). During exercise in the untreated condition, the distribution of flow favored the subendocardial layer of the LC region, and tended to be greater in the subendocardial layer of the LAD region. After phentolamine, the ratio of subendocardial to subepicardial flow at rest decreased significantly in the LAD region and tended to decrease in the LC region. During exercise after phentolamine, this ratio tended to decrease in both regions. Compared with untreated exercise values, ratios of subendocardial to subepicardial flow during exercise after phentolamine decreased significantly in the LAD region and tended to decrease in the LC region.

Discussion

This report describes the first investigation of sympathetic vasoconstrictor tone in the RC circulation and its impact on RV O_2 balance during exercise. The most important finding of this investigation is that sympathetic vasoconstrictor tone blunts RC vasodilation during moderate treadmill exercise. Thus, exercise-induced increases in RV O_2 requirements are initially met by increased O_2 extraction, which is facilitated by a large resting RV O_2 extraction reserve. The RC sympathetic vasoconstrictor tone is transmurally uniform across the RV wall. Another important finding is the absence of significant RC sympathetic vasoconstrictor tone at rest.

Resting RC blood flow (1, 9, 10) is lower than generally reported for left coronary flow (15, 17, 20, 23), so RC conductance must be less than left coronary conductance. The mechanism responsible for this depression of RC conductance is presently unknown. While it is most likely that the low conductance of the RC circulation is directly related to the lesser O_2 requirements of the right ventricle, accentuated sympathetic-mediated constriction of the RC vasculature could be a contributing factor. Current findings demonstrate that this mechanism is not an important determinant of resting RC tone, since blockade of α-adrenergic receptors with phentolamine produced no significant increase in resting RC flow (Fig. 1B) or conductance (Fig. 1C). This new finding for the RC circulation is consistent with prior reports that sympathetic vasoconstrictor tone does not restrict resting left coronary flow (16, 19, 23).

Significant sympathetic vasoconstriction has been previously demonstrated in the left coronary circulation during exercise (12–22), and some investigators have observed improved left ventricular contraction following administration of α-adrenergic receptor blockers (15, 17, 21, 22). By restricting left coronary flow, these investigators suggested that sympathetic coronary vasoconstriction limits left ventricular function and cardiac output during exercise. However, Huang and Feigl (6) found that this coronary constrictor tone is beneficial during exercise, since it redistributes left coronary flow toward the subendocardium, the region of the left ventricular wall most vulnerable to underperfusion. To date there have been no investigations of sympathetic vasoconstriction in the RC circulation during exercise.

The absence of studies of this physiologically important topic most likely reflects the difficulty of collecting RC venous blood samples from conscious animals. This difficulty

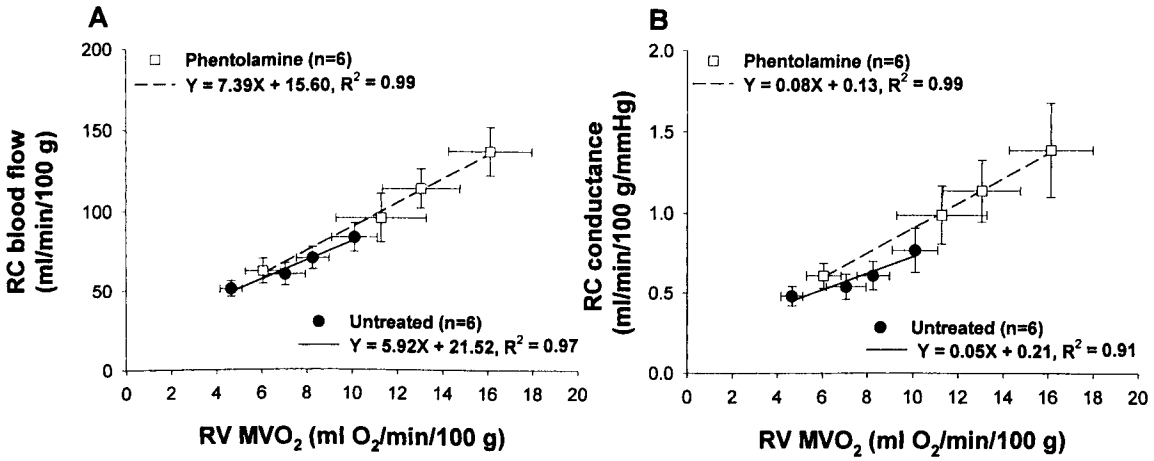

Figure 3. RC blood flow (Panel A) and RC conductance (Panel B) are plotted as functions of RV MVO_2 at rest and during graded treadmill exercise before and after α-adrenergic blockade with phentolamine. Phentolamine significantly increased the slope of the relationship in each panel.

is due primarily to the small size and fragility of the superficial veins draining the right ventricle and to the absence of a common drainage path, such as the coronary sinus. A procedure developed in this laboratory enabled us to collect RC venous blood samples from conscious dogs at rest and during treadmill exercise (24). Measurements of RC venous PO_2 and RV MVO_2 were critical to this study. Any intervention, such as α-adrenergic blockade, that changes heart rate, blood pressure, or myocardial contractility also affects RV MVO_2. Since RV MVO_2 is a prime determinant of coronary blood flow and coronary venous PO_2, the independent contributions of other determinants, such as sympathetic vasoconstrictor tone, can be identified by plotting coronary response variables as functions of MVO_2 (1–4, 8, 9, 15, 16, 28–30). Plots of RC flow, RC conductance, and RC venous PO_2 as functions of RV MVO_2 all demonstrate that, in the normal state, sympathetic vasoconstrictor tone blunts RC metabolic dilation during moderate exercise. These effects were more evident as RV MVO_2 increased during exercise. This is consistent with a positive relationship between the intensity of sympathetic activation of RC α-adrenergic receptors and the intensity of exercise, as has been described for the left coronary circulation (15). Despite this increase in RC vasoconstrictor tone during exercise, RV O_2 balance is maintained by increased O_2 extraction, and anaerobic metabolism is avoided.

This approach can be further exploited to compare the roles of exercise-induced sympathetic vasoconstriction on O_2 balance in the RC and left coronary circulations. In Figure 4B, coronary venous PO_2 is plotted as a function of MVO_2 for each condition of this investigation; also plotted in Figure 4B are data from a comparable left coronary investigation by Gorman *et al.* (16). With sympathetic vasoconstrictor tone intact, increased MVO_2 caused a much steeper decline in RC venous PO_2 (slope = −1.50 mm Hg/ml O_2/min/100 g) than in left coronary venous PO_2 (slope = −0.22 mm Hg/ml O_2/min/100 g). This is consistent with our earlier report that RV myocardium initially mobilizes its O_2 extraction reserve during exercise (1), whereas the left ventricle is dependent on hyperemia to supply additional O_2 during exercise (2–5, 10). After phentolamine, coronary venous PO_2 fell less steeply in both the RC (slope = −0.46 mm Hg/ml O_2/min/100 g) and left coronary circulations (slope = −0.05 mm Hg/ml O_2/min/100 g). Importantly, α-adrenergic blockade-induced change in slope of the regression line for the RC circulation was 1.04 mm Hg/ml O_2/min/100 g, whereas the change in slope for the left coronary circulation was only 0.17 mm Hg/ml O_2/min/100 g. This greater effect on RC venous PO_2 is consistent with a large (+25%) increase in RC flow produced by α-adrenergic blockade in this investigation compared with smaller increases in left coronary flow reported by Huang and Feigl (6%; Ref. 6), Bache *et al.* (16%; Ref. 13), Heynadrickx *et al.* (14%; Ref. 19), and Strader *et al.* (21%; Ref. 21). Thus, during exercise, physiological modulation of coronary conductance by sympathetic vasoconstrictor tone and its effect on O_2 delivery by the coronary circulation appears to be more pronounced in the right ventricle. However, RV O_2 balance can still be maintained by utilizing the large RV O_2 extraction reserve.

α-Adrenergic blockade caused a large increase in RV MVO_2 at each exercise intensity. Since this change in RV MVO_2 could be taken into account as described above and as shown in Figures 3 and 4, it did not obscure the effects of α-adrenergic blockade on factors responsible for RV O_2 balance. However, this increase in RV MVO_2 merits further discussion. At least three factors could have increased RV MVO_2. First, sympathetic vasoconstriction in the left coronary circulation is mediated by both α_1- and α_2-adrenergic receptors (12, 14, 19–21, 33, 34). Thus, phentolamine, an agent that blocks both α_1- and α_2-adrenergic receptors, was used in this study. However, by blocking presynaptic α_2-adrenergic receptors, phentolamine interrupts the negative feedback control of norepinephrine release (25). It should also be noted that the selective α_1-adrenergic receptor antagonist, prazosin, has also been found to increase norepinephrine release (35, 36). The resulting increase in

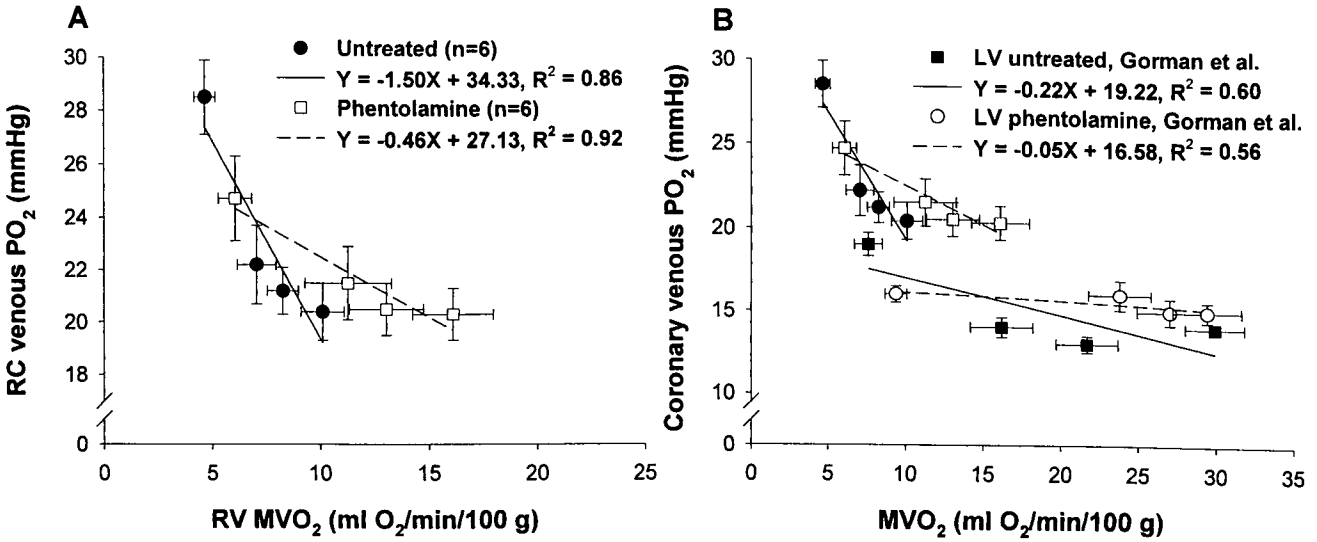

Figure 4. Panel A: RC venous PO_2 is plotted as a function of RV MVO_2 at rest and during graded treadmill exercise for the untreated condition, after α-adrenergic blockade (phentolamine, 1 mg/kg, iv, $n = 6$). Panel B: Effects of α-adrenergic blockade on right and left coronary venous PO_2 as functions of MVO_2 are compared. In panel B, RC venous PO_2 is replotted as a function of RV MVO_2 (note change of scale) at rest and during graded treadmill exercise before and after α-adrenergic blockade. Also plotted is left coronary venous PO_2 as a function of left ventricular (LV) MVO_2 at rest and during graded treadmill exercise before and after α-adrenergic blockade with phentolamine, as reported by Gorman *et al.* (16, data of Gorman *et al.* are replotted with permission of *J. Appl. Physiol.*). In the untreated state, the decline in the relationship between venous PO_2 and MVO_2 was significantly greater for the right ventricle. Phentolamine made the slope of this relationship significantly less negative for both ventricles.

β-adrenergic stimulation of RV myocardium would increase contractility and RV MVO_2. Second, peripheral vasodilation following systemic administration of phentolamine tended to decrease systemic arterial pressure, although systemic hypotension was apparently minimized by the baroreflex. The increases in heart rate and RV dP/dt_{max} observed after phentolamine (Table 1) are consistent with these two factors. Third, canine RV MVO_2 is highly flow dependent (Gregg phenomenon) so any intervention that increases RC blood flow also increases RV MVO_2 (37, 38). Increases in RC flow initiated by release of exercise-induced sympathetic vasoconstrictor tone may be amplified by release of NO, as has been reported for the left coronary circulation (31). Thus, the increase in RC blood flow and conductance during exercise after phentolamine could have been both a cause and a consequence of the greater increase in RV MVO_2—as well as removal of α-adrenergic coronary vasoconstriction. In any case, by examining response variables as functions of RV MVO_2, the presence of exercise-induced RC sympathetic vasoconstrictor tone was identified.

Plotting coronary response variables as functions of RV MVO_2 normalized for effects of increased β-adrenergic stimulation of RV myocardium and any resulting increase in myocardial O_2 demand. However, an additional effect of increased norepinephrine release after phentolamine is augmented feed-forward, β-adrenergic–mediated coronary vasodilation (16), which might have exaggerated the vasodilatory response following blockade of α-adrenergic coronary vasoconstriction. The greater RC venous PO_2 values at any RV MVO_2 observed after phentolamine is consistent with the notion that this β-mediated, feed-forward vasodilatory mechanism was opposed by an α-mediated vasoconstrictory mechanism in the untreated state. However, these data do not rule out the possibility that some of the effect of phentolamine on the RC venous PO_2 versus RV MVO_2 relationship was due to augmented β-mediated vasodilation added to the normal β-mediated component. As noted by Gorman *et al.* (16), experiments with adrenergic blockade can demonstrate the presence of α- and β-mediated responses, but such experiments cannot quantify these effects. It should be appreciated that both left and right coronary responses to α-adrenergic blockade shown in Figure 4B might be influenced by augmented β-adrenergic mediated coronary vasodilation. However, it seems unlikely that the marked differences between the right and left coronary responses to phentolamine could be due entirely to this mechanism.

Additional experiments with α-adrenergic blockade administered following β-adrenergic blockade might provide more information on sympathetic vasoconstriction in the RC circulation at rest and during exercise. Such experiments are beyond the scope of this investigation, and furthermore they would be unlikely to definitively quantify the α-adrenergic–mediated constriction. If α-adrenergic receptor-mediated vasoconstriction is present in the unblocked state, as indicated by the present study and by numerous studies of the left coronary circulation (12–22), then results from double blockade experiments will be confounded by the fact that circulating catecholamines will be abnormally elevated following β-adrenergic blockade alone during exercise (39). This effect would result in exaggerated α-adrenergic–mediated vasoconstriction in the

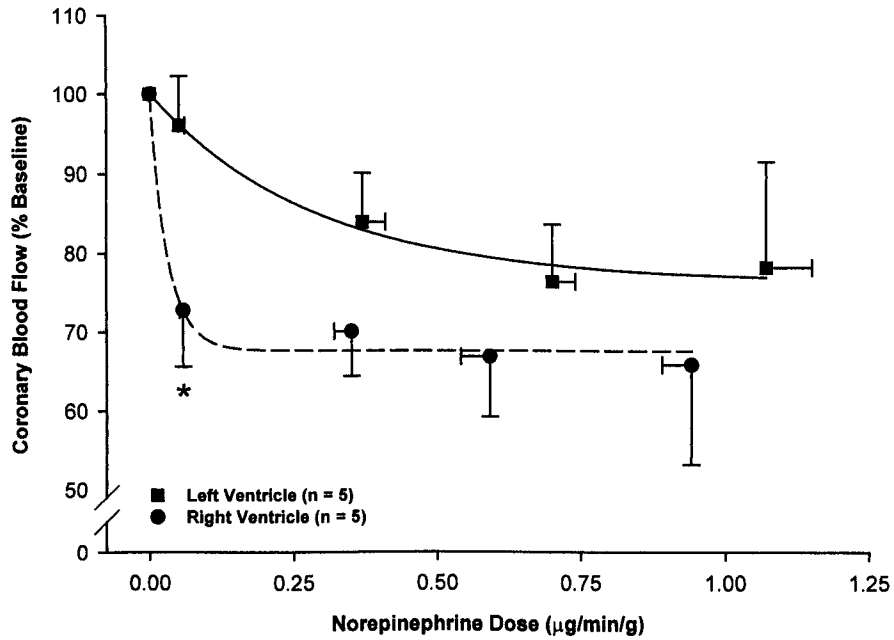

Figure 5. RC blood flow is plotted as % baseline to demonstrate the effects of graded intracoronary norepinephrine infusions in anesthetized, β-adrenergic–blocked dogs. Norepinephrine caused significant RC vasoconstriction that exceeded the response observed in similar left ventricular experiments. *Different from the left ventricle, same dose, $P < 0.05$.

β-blocked dogs, and thus the change in response variables after subsequent α-adrenergic blockade would not accurately reflect the extent of α-adrenergic–mediated vasoconstriction in the normal, unblocked state.

Since RV aerobic metabolic rate was affected by α-adrenergic blockade (as indicated by changes in computed values of RV MVO_2), it was necessary to take this effect of metabolic rate into account. Ideally, coronary response variables should be plotted against the independent variable, aerobic metabolic rate. In these experiments, aerobic metabolic rate was indexed by MVO_2, which was computed from the product of RC blood flow and arteriovenous O_2 content difference. Thus, in plots of RC flow, RC conductance, and RC venous PO_2 as functions of RV MVO_2, the *y*-axis variable was used also to compute the *x*-axis variable. We submit that the apparent lack of independence between the *x*- and *y*-axes variables does not invalidate this approach, since MVO_2 is clearly a valid index of aerobic metabolic rate and is a recognized determinant of coronary flow and venous PO_2. Such plots are informative, and they have been widely employed in coronary research (1–4, 8, 9, 15, 16, 28–30). An alternative, much less direct approach to estimate aerobic metabolic rate would be to use a cardiac function index, such as the rate pressure product. Since the data required for determination of RV MVO_2 were available from these experiments, coronary response variables were plotted as functions of RV MVO_2.

To further test the hypothesis that an α-adrenergic vasoconstrictor tone can limit RC blood flow during exercise and to argue against the notion that the increase in RC venous PO_2 at any exercise-induced increase in MVO_2 was due to augmented β-adrenergic–mediated RC vasodilation after administration of phentolamine, additional experiments were conducted in anesthetized, open-chest dogs. Propranolol inhibited β-adrenergic–mediated increases in heart rate, RV contractility, and RC vasodilation during graded RC infusions of norepinephrine. Under these experimental conditions, intracoronary infusion of norepinephrine produced significant RC vasoconstriction (Fig. 5). This should correspond to the RC response to sympathetic nerve release of norepinephrine or to increased circulating catecholamines during exercise (40) without activation of β-adrenergic mechanisms, and, importantly, activation of other competing metabolically mediated vasodilatory mechanisms. Furthermore, we found that the decrease in coronary blood flow due to norepinephrine was greater in the right ventricle compared with the left ventricle (Fig. 5). This finding is consistent with the results from exercising conscious dogs (Fig. 4B) and provides further support for the presence of pronounced α-adrenergic RC vasoconstriction during exercise.

Huang and Feigl (6) reported that α-adrenergic blockade in the LC region of the left ventricle decreased the ratio of subendocardial to subepicardial flow during exercise. They concluded that enhanced α-adrenergic coronary vasoconstriction is physiologically important for maintaining subendocardial flow during metabolic coronary dilation. However, in anesthetized dogs, Baumgart *et al.* (41) could detect this effect only when the coronary vasculature had been previously dilated maximally and the cardiac sympathetic nerves were stimulated. Morita *et al.* (42) demonstrated that α-adrenergic–mediated left coronary vasoconstriction reduced systolic retrograde coronary flow. Reduction of to-and-fro flow oscillations in arterial vessels that penetrate the left ventricular wall might result in more

Table 2. Regional Myocardial Blood Flow Before and After α-Adrenergic Blockade with Phentolamine

Region	Untreated		Phentolamine		α-Adrenergic blockade (*P* value)	Exercise (*P* value)	Interaction (*P* value)
	Rest	Exercise	Rest	Exercise			
RV subepi	48 ± 5	92 ± 12	60 ± 6	171 ± 17*	0.005	0.003	0.032
RV subendo	59 ± 3	107 ± 11	72 ± 6	192 ± 17*	0.002	0.003	0.032
RV ratio	1.26 ± 0.10	1.19 ± 0.05§	1.21 ± 0.05§	1.13 ± 0.03§	0.384	0.179	0.967
LAD subepi	115 ± 11	191 ± 13	137 ± 9	338 ± 43*	0.043	0.013	0.067
LAD subendo	149 ± 20	221 ± 33	141 ± 20	308 ± 64*	0.205	0.059	0.068
LAD ratio	1.29 ± 0.09§	1.14 ± 0.10	1.02 ± 0.09*	0.90 ± 0.10*	0.001	0.037	0.391
LC subepi	103 ± 6	169 ± 13	125 ± 13	282 ± 46*	0.062	0.017	0.093
LC subendo	149 ± 15	245 ± 34	165 ± 17	357 ± 62*	0.086	0.044	0.039
LC ratio	1.44 ± 0.07§	1.44 ± 0.11§	1.32 ± 0.02§	1.26 ± 0.03§	0.075	0.762	0.687

Values are mean ± SE; $n = 4$; Flow units are ml/min/100 g; subepi, subepicardial blood flow; subendo, subendocardial blood flow; ratio, subendocardial blood flow/subepicardial blood flow; exercise, 4 miles/hr, 10% incline; RV, right ventricular; LAD, left anterior descending; LC left circumflex; * $P < 0.05$ vs. untreated, same condition; § $P < 0.05$ vs. uniformity. All exercise flow values were significantly greater than respective rest values.

flow to the subendocardium during exercise. Our measurements of LAD flow support the idea that α-adrenergic coronary vasoconstriction helps maintain subendocardial flow, since α-adrenergic blockade caused the ratio of subendocardial to subepicardial flow to fall significantly in this region. In the left circumflex region, however, transmural flow ratios at rest or during exercise were not significantly decreased after α-adrenergic blockade, although there was a tendency toward decline (P [ANOVA, main effect of blockade] = 0.075). It is possible that these differences in left ventricular responses reflect regional heterogeneity of adrenergic activation as suggested by Baumgart *et al.* (41).

Whether sympathetic vasoconstriction is important for maintaining flow to the subendocardium of the right ventricle was tested by measuring the transmural distribution of RC flow (Table 2). Since α-adrenergic blockade did not alter either the resting or exercise flow distribution, we conclude that adequate RV subendocardial flow is not dependent on sympathetic vasoconstrictor tone. Since the RV wall is much thinner than the left ventricular wall, and the RC circulation is subjected to lesser myocardial tissue pressures than the left coronary circulation, to-and-fro flow oscillations of RC flow would be minimal, so vasoconstrictor tone is not essential to direct adequate blood flow to the RV subendocardium.

The dissection required for implantation of a blood flow transducer on the RC artery might have damaged sympathetic nerves to the right ventricle. Heusch *et al.* (43) reported that coronary dissection and implantation of flow transducers on the canine LAD coronary artery induced functionally important and morphologically demonstrable denervation of LAD-perfused myocardium. Interestingly, the same procedures applied to the left circumflex coronary artery did not produce denervation. This issue has not been investigated with regard to the right ventricle. However, the large increase in RV dP/dt_{max} observed during exercise (Table 1) indicates that the sympathetic innervation to the RV myocardium was intact. Likewise, the RC vasodilation observed following phentolamine is consistent with intact sympathetic innervation of the RC vasculature in the untreated condition. It is possible that some damage to RV sympathetic nerves did occur during the instrumentation, and this damage might have blunted RV and RC responses to exercise and subsequent α-adrenergic blockade. On the other hand, if adrenergic coronary vasoconstriction is produced by circulating catecholamines rather than by neurogenic release in the heart, as reported by Chilian *et al.* (40), the question of cardiac denervation is moot.

In conclusion, α-adrenergic vasoconstrictor tone does not restrict resting RC blood flow, but during exercise this tone transmurally blunts RC hyperemia and forces the right ventricle to mobilize its O_2 extraction reserve to maintain RV O_2 demand/supply balance. Exercise-induced α-adrenergic vasoconstrictor tone is more pronounced in the RC circulation than has been reported for the left coronary circulation.

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