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Research Article

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Abnormal Coronary Vascular Response to Exercise in Dogs with Severe Right Ventricular Hypertrophy

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ABSTRACT Measurements of right coronary artery blood flow, aortic and right ventricular (RV) pressures and heart rate were radiotelemetered during strenuous, spontaneous exercise in normal dogs and dogs with severe RV hypertrophy induced by chronic (5–6 mo) pulmonary artery stenosis. With fixed pulmonic stenosis, dogs with RV hypertrophy exhibited a decrease ($P < 0.01$) in arterial pressure during exercise. Under these conditions, exercise increased right coronary artery blood flow and decreased right coronary vascular resistance less ($P < 0.05$) in dogs with RV hypertrophy compared with normal. This attenuated response of right coronary artery blood flow of dogs with RV hypertrophy was not observed when arterial pressures remained at preexercise values during exercise. However, regardless of changes in arterial pressures during exercise, all dogs with RV hypertrophy demonstrated a striking postexercise coronary hyperemia ($P < 0.01$), suggesting a perfusion deficit of the hypertrophied right ventricle during exercise. These results imply a fundamental defect in the ability of the coronary circulation of the severely hypertrophied right ventricle to provide sufficient nutrient supply in the face of elevated metabolic demands of exercise.

INTRODUCTION

It is conceivable that the eventual decompensation of the hypertrophied ventricle to cardiac failure may be the result of inadequate compensatory adjustments of the coronary circulation supplying the increased cardiac mass. Pressure overload-induced right ventricular (RV)[1] hypertrophy is characterized by progressive, marked increases in blood flow per gram selectively to the right ventricle, without a significant change in the ratio of capillary number to muscle fiber number (1). These factors suggest that coronary vascular reserve of the hypertrophied right ventricle might be limited. Whereas this may not have significant consequences at rest, it could have serious implications during periods of elevated metabolic demand, as occur during severe exercise, when increases in oxygen delivery to the hypertrophied ventricle are primarily dependent on increases in coronary blood flow. The coronary vascular response to the cardiovascular stress of strenuous exercise has not been previously described in the presence of severe RV hypertrophy. The primary goal of the present study, therefore, was to characterize both hemodynamic and coronary vascular adjustments of dogs with severe RV hypertrophy to spontaneous, free-ranging exercise. Because the coronary vascular response of the normal right ventricle to this stress has not been previously characterized, it was also important to assess the responses to exercise in a separate series of normal dogs.

METHODS

Surgical preparation and induction of RV hypertrophy. 11 mongrel dogs of either sex (conditioned and free of microfilaria) were tranquilized with Tranvet-10 (Propiopromazine HCl; 0.1 mg/kg i.m.), intubated, artificially ventilated, and prepared for sterile surgery. The heart was exposed via a left thoracotomy in the fourth intercostal space. A heparin-filled Tygon catheter (Norton Co., Tallmadge, Ohio) was implanted in the right ventricle, and an inflatable hydraulic occluder (20–26 mm ID: Jones Co., Silver Springs, Md.) was placed around the main pulmonary artery. The distal ends of the catheter and occluder were exteriorized and positioned between the scapulae. All animals were placed on a 1-wk postsurgical regimen of antibiotics.

A minimum of 3 wk was allowed for recovery from the effects of this initial surgery. At this time, pressure-overload RV hypertrophy was produced by gradual, chronic inflation of the hydraulic occluder previously implanted around the main pulmonary artery (1). A stable, peak RV systolic pressure

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[1] *Abbreviations used in this paper*: RVH, right ventricular hypertrophy; RV, right ventricular.

of 50 mm Hg was achieved during the initial presentation of the pressure-overload. Over the succeeding 2 wk, inflation of the occluder was adjusted such that peak RV systolic pressure was at least 70 mm Hg, and RV pressure and heart rate were monitored on a biweekly basis thereafter. Subsequent changes in RV pressure and all other measured variables occurred spontaneously in the presence of a consistently applied stenosis of the pulmonary artery. The pressure overload was sustained over a 5–6-mo period.

4 mo after initial presentation of the pressure-overload, a second thoracotomy was performed through the fourth right intercostal space. A segment (~2 cm) of the right main coronary artery was dissected free of connective tissue and fat in a retrograde direction from the first major ventricular branch to its aortic origin, for placement of an inflatable hydraulic occluder (4 mm ID) and a proximal Doppler ultrasonic flow transducer. In four of the dogs, a solid-state pressure transducer (P22: Konigsberg Instruments, Inc., Pasadena, Calif.) was inserted into the RV cavity via a stab wound in the mid-anterior free wall. 3–4 wk later, an additional solid-state pressure transducer and a heparin-filled catheter were chronically implanted either in the descending thoracic aorta (four dogs) or abdominal aorta (seven dogs) through a 1-cm longitudinal incision, and secured with three to five sutures (4–0 silk, Ethicon Inc., Somerville, N. J.).

A separate group of 11 dogs with identical instrumentation, but not subjected to chronic pulmonary artery stenosis, served as the control group.

Experimental measurements. Right main coronary artery blood flow was measured with a CW Doppler ultrasonic flowmeter (2). The accuracy and reliability of this method of measuring coronary blood flow has been described previously in detail (3). At autopsy a catheter was inserted into the right main coronary artery via the ostium with its tip proximal to the implanted flow probe. Flow probe calibration was achieved *in situ* by perfusing blood through the catheter at known flow rates. Aortic and RV pressures were measured and telemetered from the implanted gauges (4, 5). These gauges were calibrated both in vitro and in vivo using the implanted aortic and RV catheters attached to a Statham P23 Db strain gauge manometer (Statham Instruments, Inc., Oxnard, Calif.), which in turn was calibrated against a mercury manometer.

Experimental protocol. A period of at least 3 wk was allowed for full recovery from the effects of anesthesia and surgery. At this time all the animals appeared healthy and vigorous. During the exercise period, instrumentation necessary for the continuous transmission of aortic pressure, RV pressure, and right main coronary artery blood flow signals by radiotelemetry (described in detail previously) were carried by each dog in a backpack (6, 7). The exercise regimen consisted of each dog running freely behind a mobile recording van over a hilly, 0.3-mile course. Speeds of 25–35 miles/h were achieved routinely by normal dogs during exercise. Whereas running speeds of dogs subjected to long term pulmonary artery stenosis were similar to normal dogs during the early phase of exercise, some of these dogs were unable to maintain peak speeds over the entire exercise course. However, it is important to emphasize that the dogs with RV hypertrophy exercised to their maximum capacity, as reflected by the near collapse of these dogs at the end of the exercise run.

At autopsy, abdominal ascites and hepatic congestion were not observed in those dogs with RV hypertrophy, indicating that these animals were not in congestive heart failure. After excising the heart, the atria, great vessels, valves, large surface vessels, and epicardial fat were separated from the heart and discarded. The free walls of the right and left ventricles were weighed separately, and the values for ventricular mass to body weight ratio were computed using the body weight of the dog at the time of the initial surgery. RV wall thickness was measured at a consistent site in the mid-free wall and included trabecular muscles.

Data analysis. The experimental data were recorded (Honeywell model 5600 B, Honeywell, Inc., Denver, Col.) and played back onto a multichannel, direct-writing oscillograph (Gould-Brush Inc., Measurement Systems Div., Cleveland, Ohio). A continuous record of RV derivative of pressure with respect to time (dP/dt) was derived from the pressure signal with an operational amplifier (National Semiconductor, Inc., Santa Clara, Calif.) connected as a differentiator. Mean aortic pressure and mean right coronary artery blood flow were derived using passive electronic filters with a 2-s time constant. Mean right coronary artery resistance was calculated as the quotient of mean aortic pressure minus RV end-diastolic pressure and mean right coronary artery blood flow. A cardiotachometer (Beckman type 9856, Beckman Instruments, Inc., Fullerton, Calif.) triggered by the electrical signal from the aortic pressure pulse, provided instantaneous and continuous records of heart rate.

The measured variables were evaluated for data analysis over a period of at least 15–30 s while the dogs were standing quietly just prior to exercise, at two separate points during the exercise run, corresponding to one-tenth and two-tenths of a mile of the exercise course, and at 1 and 5 min after the exercise period. The data were stored and statistically analyzed with a PDP 11/34 computer (Digital Equipment Corp., Maynard, Mass.). The area under the phasic right coronary artery blood flow signal was integrated utilizing the computer in order to evaluate the relative proportions of blood flow occurring during systole and diastole for each cardiac cycle. Stroke systolic right coronary artery blood flow was defined as the blood flow occurring between the initial upstroke of RV dP/dt and peak negative RV dP/dt. Blood flow throughout the remaining portion of the cardiac cycle represented stroke diastolic right coronary artery blood flow. In addition to the overall groups of normal dogs ($n = 11$) and dogs with RV hypertrophy and fixed pulmonic stenosis ($n = 9$), the response of the right coronary circulation to exercise was also assessed in subgroups of normal dogs ($n = 3$) and dogs with RV hypertrophy ($n = 4$) which did not change mean aortic pressure during exercise. The subgroup of four dogs with RV hypertrophy was composed of two dogs with RV hypertrophy and fixed pulmonic stenosis, and two dogs with RV hypertrophy in which the pulmonic stenosis was released 1 d prior to the exercise period. Differences between morphologic and hemodynamic characteristics of normal dogs and dogs with RV hypertrophy were analyzed by Student's t test for unpaired comparisons (8). Changes in the measured variables in response to exercise and differences in the measured variables during exercise among the different groups were analyzed by multivariate analysis of variance (8). Values presented represent mean±1 SEM.

RESULTS

Morphologic and hemodynamic characteristics of RV hypertrophy (Table I)

Chronic pulmonary artery stenosis of 5–6 mo duration resulted in substantial hypertrophy of the right ventricle as evidenced by significant increases ($P < 0.001$) in RV free wall weight to body weight ratio, RV wall thickness, and RV free wall weight to left

TABLE I
Morphology and Base-line Hemodynamics

	Normal	RVH	P*
	(n = 11)	(n = 9)	
RV weight/body weight, *g/kg*	1.69±0.14	2.59±0.15	<0.001
RV thickness, *mm*	6.77±0.74	11.4±0.82	<0.001
RV weight/LV weight	0.50±0.03	0.83±0.04	<0.0001
LV weight/body weight, *g/kg*	3.21±0.24	3.67±0.32	NS
RV systolic pressure, *mm Hg*	34±2	114±4	<0.0001
RV end-diastolic pressure, *mm Hg*	4.4±0.4	10.0±2.0	<0.05
RV *dP/dt*, *mm Hg/s*	946±55	1298±72	<0.005
Mean aortic pressure, *mm Hg*	110±5	111±5	NS
Diastolic aortic pressure, *mm Hg*	85±4	93±3	NS
Heart rate, *beats/min*	129±9	154±7	<0.05

* *P* value for comparison between normal dogs and dogs with RVH.

ventricular free wall weight ratio. Moreover, in the field prior to exercise, dogs with RV hypertrophy exhibited significantly elevated ($P < 0.05$) levels of RV systolic and end-diastolic pressures, RV *dP/dt* and heart rate compared to normal dogs, whereas values of aortic pressure were similar in the two groups.

Hemodynamic and coronary vascular responses to free-ranging exercise

NORMAL

Fig. 1 illustrates the response of a normal dog to spontaneous, free-ranging exercise. The summarized data are presented in Table II and Figs. 2 and 3.

Hemodynamic measurements (Table II). Exercise in normal dogs was associated with significant increases ($P < 0.05$) in mean aortic pressure, RV systolic and end-diastolic pressures, RV *dP/dt* and heart rate. With the exception of RV end-diastolic pressure, the values of these measured variables remained significantly elevated ($P < 0.05$) 1 min following cessation of exercise, although RV systolic pressure, RV *dP/dt* and heart rate had returned towards preexercise levels. Only heart rate remained significantly elevated ($P < 0.05$) 5 min after the end of the exercise period. Diastolic aortic pressure rose, but not significantly, with exercise.

Coronary vascular measurements (Figs. 2, 3). Mean right coronary artery blood flow increased ($P < 0.001$) rapidly and substantially from a preexercise level of 25±2 ml/min with the onset of exercise, and remained at this new steady-state level throughout the exercise period. With cessation of exercise right coronary artery blood flow decreased rapidly, such that by 1 min following the end of exercise, blood flow was only slightly higher (33±3 ml/min) than preexercise levels. Conversely, mean right coronary artery resistance decreased by 3.13±0.65 mm Hg/ml per min ($P < 0.01$) during exercise from a preexercise level of 5.51±0.93 mm Hg/ml per min, and remained depressed throughout the exercise period. 1 min after exercise, right coronary artery resistance had already returned to preexercise levels. Thus, both hemodynamic and coronary

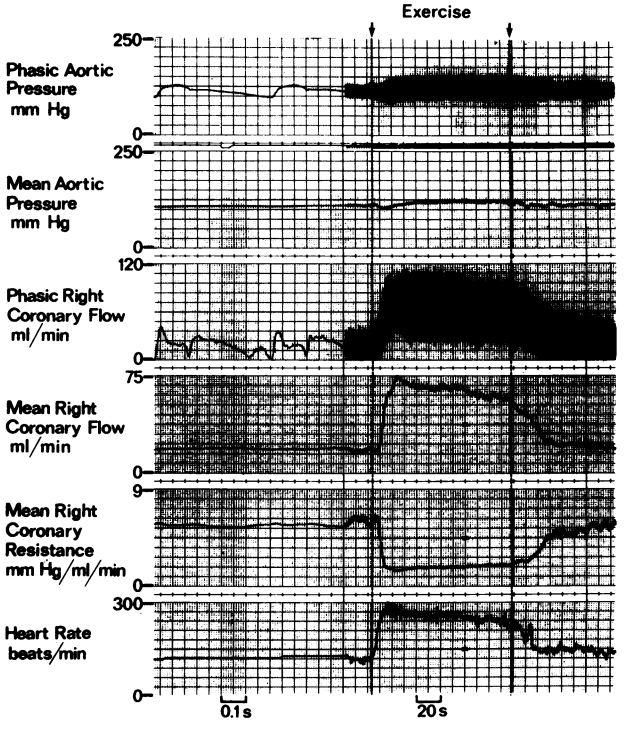

FIGURE 1 The effects of spontaneous, free-ranging exercise are shown on the radiotelemetered measurements of phasic and mean aortic pressure and right coronary blood flow, mean calculated right coronary resistance and heart rate in a normal dog. Note that right coronary blood flow and resistance increase and decrease, respectively, rapidly with the onset of exercise and return smoothly to preexercise levels following the exercise period.

TABLE II

Hemodynamic Changes during Exercise and 1 and 5 Min Postexercise

		Exercise*	+1 Min	+5 Min
ΔMean aortic pressure, *mm Hg*	Normal	22±5‡	22±6‡	6±6
	RVH	−25±6‡	13±5§	1±5
	P	<0.001	NS	NS
Δ Diastolic aortic pressure, *mm Hg*	Normal	7±3	9±2‡	−2±3
	RVH	−25±5‡	7±4	0±4
	P	<0.001	NS	NS
ΔRV systolic pressure, *mm Hg*	Normal	28±6‡	9±3§	−3±1
	RVH	−12±9	43±9‡	0±3
	P	<0.01	<0.02	NS
ΔRV end-diastolic pressure, *mm Hg*	Normal	3.0±1.4§	−1.1±0.7	−1.9±0.8
	RVH	7.9±1.4‡	7.5±2.2‡	−1.0±1.5
	P	NS	<0.01	NS
ΔRV *dP/dt, mm Hg/s*	Normal	2,111±347‡	778±234‡	93±63
	RVH	857±346	1960±447‡	160±48
	P	<0.05	<0.07	NS
ΔHeart rate, *beats/min*	Normal	163±11‡	61±7‡	27±9§
	RVH	101±13‡	52±11‡	8±6
	P	<0.01	NS	NS

P value for comparison between changes in normal and RVH groups in response to exercise.
* Changes in measured variables at 0.2 miles of exercise course.
Symbols represent significant change of measured variables from control levels in each group in response to exercise (‡$P < 0.001$; §$P < 0.05$).

vascular responses to exercise normally occurred rapidly with the onset of exercise, were sustained throughout the exercise period, and returned smoothly to preexercise levels soon after cessation of exercise.

RV HYPERTROPHY

The response of a dog with severe RV hypertrophy to spontaneous, free-ranging exercise is illustrated in Fig. 4. The summarized data are presented in Table II and Figs. 2 and 3.

Hemodynamic measurements (Table II). Whereas exercise was normally associated with an increase ($P < 0.001$) in mean aortic pressure, both mean and diastolic aortic pressures decreased ($P < 0.001$) in dogs with RV hypertrophy. However, 1 min after cessation of exercise, levels of mean aortic pressure were increased ($P < 0.05$) from preexercise values to a similar extent in both groups. In contrast to normal dogs, RV systolic pressure did not increase significantly during exercise. However, 1 min after exercise, RV systolic pressure was markedly increased ($P < 0.001$) by 43±9 mm Hg from preexercise levels, which was greater ($P < 0.02$) than the increment in normal dogs. RV end-diastolic pressure increased ($P < 0.001$) during exercise, but unlike normal dogs the increase ($P < 0.001$) was sus-

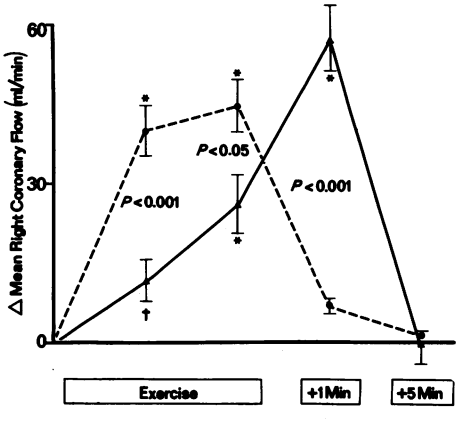

FIGURE 2 Changes (Mean±1 SEM) in mean right coronary blood flow are shown in response to exercise in normal dogs (●, - - -) (25±2 ml/min) and dogs with right ventricular hypertrophy (RVH) (▲, ——) (59±11 ml/min). The increase in blood flow during exercise is significantly attenuated in dogs with RVH compared with normal. In contrast, whereas blood flow is almost returned to preexercise levels 1 min after exercise in normal dogs, dogs with RVH exhibit a marked postexercise coronary hyperemia. Values in parentheses represent preexercise levels of mean right coronary blood flow for the respective groups. Symbols represent statistically significant changes (*$P < 0.001$; †$P < 0.02$) in blood flow from preexercise levels. *P* values represent comparisons between responses of normal dogs and dogs with RVH.

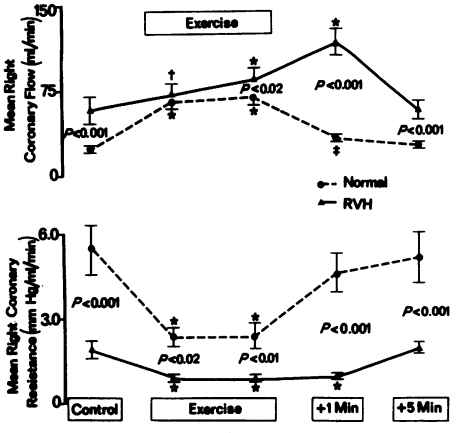

FIGURE 3 Absolute levels (Mean±1 SEM) of mean right coronary blood flow and mean right coronary resistance are shown for normal dogs and dogs with RVH at control, at two separate points during exercise corresponding to 0.1 and 0.2 miles of the exercise course, and 1 and 5 min following the end of the exercise period. Most striking is the existence of a marked coronary hyperemia in dogs with RVH following cessation of the exercise period. Symbols represent signficant changes of the measured variables from control levels for the two groups (*$P < 0.001$; ‡$P < 0.02$; †$P < 0.05$). P values represent comparisons between normal dogs and dogs with RVH.

tained 1 min after exercise. The increase in RV *dP/dt* during exercise was significantly attenuated ($P < 0.05$) in dogs with RV hypertrophy. Furthermore, dogs with RV hypertrophy exhibited their peak increase ($P < 0.001$) in this variable immediately following exercise, at a time when RV *dP/dt* in normal dogs was returning towards preexercise levels. Heart rate increased to similar peak levels as occurred in normal dogs during exercise, but the increment was less ($P < 0.01$) in dogs with RV hypertrophy due to a higher ($P < 0.05$) preexercise level. Heart rate returned normally towards control following the exercise period.

Coronary vascular measurements (Figs. 2 and 3). Preexercise levels of mean right coronary blood flow were elevated ($P < 0.001$) to 59±11 ml/min in dogs with RV hypertrophy. Note that the phasic waveform for right coronary artery blood flow (Fig. 4) exhibits a diminished proportion of blood flow during systole compared to normal (Fig. 1) and resembles the normal phasic waveform for left circumflex coronary artery blood flow (1). The preexercise stroke systolic diastolic flow ratio was reduced significantly ($P < 0.01$) in dogs with RV hypertrophy (49±4%) compared with normal (85±8%). During exercise mean right coronary blood flow increased only 26±6 ml/min in dogs with RV hypertrophy, which was significantly less ($P < 0.05$) than the increase of 45±5 ml/min in normal dogs. Moreover, whereas the stroke systolic/diastolic flow ratio increased ($P < 0.01$) in both groups during exercise, the ratio increased to a lower ($P < 0.01$) level in dogs with RV hypertrophy (93±12%) compared with normal (155±11%). 1 min after exercise, mean right coronary blood flow was only slightly greater than preexercise levels in normal dogs, whereas dogs with RV hypertrophy exhibited a profound coronary vasodilation, in that mean right coronary blood flow was increased ($P < 0.001$) by 57±6 ml/min from preexercise levels. At this time stroke systolic/diastolic flow ratios had returned to preexercise levels in normal dogs (100±12%) and dogs with RV hypertrophy (57±6%). It is important to note that the absolute levels to which blood flow increased were similar in the two groups during early exercise, slightly higher ($P < 0.02$) in dogs with RV hypertrophy during late exercise, and markedly higher ($P < 0.01$) in these dogs 1 min after exercise (Fig. 3).

Preexercise levels of mean right coronary artery resistance were significantly reduced ($P < 0.001$) in dogs with RV hypertrophy (1.95±0.28 mm Hg/ml per min) compared to normal. Right coronary resistance decreased less ($P < 0.01$), i.e., by 1.12±0.21 mm Hg/ml per min, but reached lower ($P < 0.02$) absolute levels (0.83±0.12 mm Hg/ml per min) during exercise compared to normal. Most striking, however, was the maintenance of a prolonged postexercise decrease ($P < 0.001$) in resistance in dogs with RV hypertrophy, in contrast to the rapid return of resistance to preexercise levels in the normal group.

PARADOXICAL CHANGES IN HEART RATE DURING EXERCISE IN DOGS WITH RV HYPERTROPHY

Heart rate increased significantly ($P < 0.001$) and to similar peak levels in both normal dogs and dogs with RV hypertrophy during exercise. However, as illustrated in Fig. 4, a subset of dogs ($n = 6$) with RV hypertrophy exhibited marked, paradoxical reductions in heart rate from peak levels during exercise. This response characteristically occurred in the mid-to-late portion of the exercise run, when heart rate decreased ($P < 0.001$) in this subset of dogs from 297±3 to 150 ±11 beats/min. When the exercise period was repeated on a subsequent day with four of these dogs following the preexercise administration of atropine sulfate, 0.1 mg/kg, i.v., the reduction in heart rate late in the exercise period from a peak level of 280±7 beats/min was not observed.

INFLUENCE OF PERFUSION PRESSURE ON CORONARY VASCULAR RESPONSE TO EXERCISE (TABLE III)

The extent to which the decrease in arterial pressure mediates the abnormal coronary vascular response to exercise in dogs with RV hypertrophy was assessed. The results are summarized in Table III. The coronary vascular response to exercise in a group

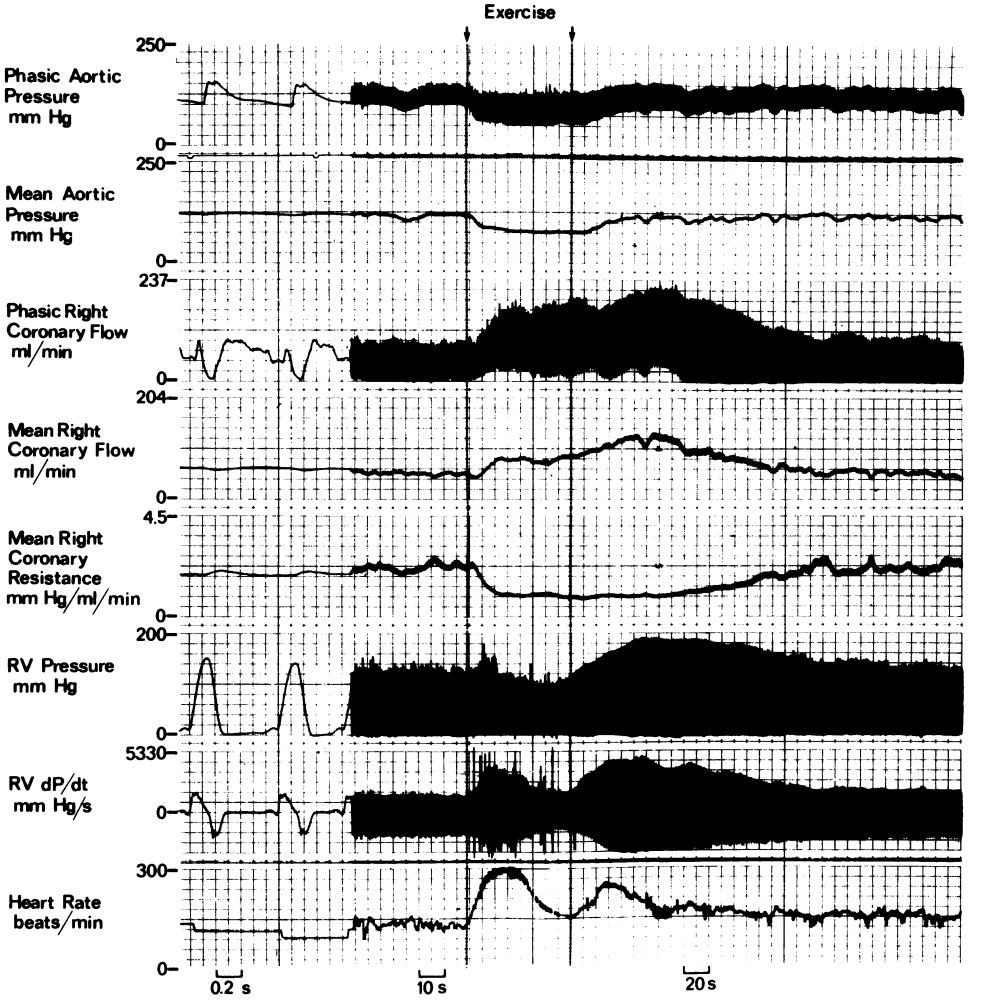

FIGURE 4 Effects of spontaneous, free-ranging exercise on the measured variables in a dog with severe RVH. In addition to the abnormal hemodynamic and coronary vascular adjustments to exercise that characterized the entire group of dogs with RVH, this is an example of one of a subset of dogs with severe RVH, which exhibited an abrupt, pronounced decrease in heart rate from peak levels during the exercise period. Note the profound postexercise increase in right coronary blood flow, as well as the prolonged return of right coronary resistance to preexercise levels following the end of the exercise period.

of dogs with RV hypertrophy ($n = 4$) in which mean and diastolic aortic pressures were unchanged during exercise was compared with: (*a*) the entire group of normal dogs ($n = 11$) in which mean aortic pressure increased ($P < 0.01$) and diastolic aortic pressure was unchanged during exercise; (*b*) a subgroup of these normal dogs ($n = 3$) in which mean and diastolic aortic pressures were unchanged during exercise; and (*c*) the entire group of dogs with RV hypertrophy ($n = 9$) in which mean and diastolic aortic pressures decreased ($P < 0.001$) during exercise. Preexercise levels of mean aortic pressure were similar among all groups. Preexercise levels of mean right coronary artery blood flow were elevated ($P < 0.001$), and levels of right coronary artery resistance were decreased ($P < 0.001$) in the two groups with RV hypertrophy compared to the two normal groups. Mean right coronary blood flow increased ($P < 0.01$) to a similar extent during exercise in both normal groups. The subset of normal dogs that did not increase arterial pressure during exercise failed to exhibit any degree of postexercise coronary hyperemia. As might be expected, the RV hypertrophy group which maintained arterial pressure during exercise exhibited increases in blood flow to significantly higher ($P < 0.01$) levels than the other three groups. However, despite this enhanced coronary perfusion during exercise, the postexercise increase in blood flow was clearly evident in this group, and actually rose to a higher ($P < 0.001$) level than that observed in those dogs with RV hypertrophy,

TABLE III

Influence of Perfusion Pressure on Coronary Vascular Response to Exercise

		Preexercise	Exercise*	+1 Min
Mean aortic pressure, *mm Hg*	Normal	110±5	132±8	130±10
	Normal subgroup‡	106±8	107±8	120±11
	RVH	111±5	87±8	125±7
	RVH subgroup§	111±4	112±10	127±7
	RVH subgroup:			
	vs. normal	NS	$P < 0.01$	NS
	vs. normal subgroup	NS	NS	NS
	vs. RVH	NS	$P < 0.001$	NS
Diastolic aortic pressure, *mm Hg*	Normal	85±4	92±4	92±4
	Normal subgroup	84±4	83±6	96±10
	RVH	93±3	68±6	100±5
	RVH subgroup	87±3	83±10	103±5
	RVH subgroup:			
	vs. normal	NS	NS	NS
	vs. normal subgroup	NS	NS	NS
	vs. RVH	NS	$P < 0.02$	NS
Mean right coronary flow, *ml/min*	Normal	25±2	70±6	33±3
	Normal subgroup	24±1	69±8	28±3
	RVH	59±11	85±12	116±11
	RVH subgroup	71±23	133±17	151±20
	RVH subgroup:			
	vs. normal	$P < 0.001$	$P < 0.001$	$P < 0.001$
	vs. normal subgroup	$P < 0.001$	$P < 0.001$	$P < 0.001$
	vs. RVH	NS	$P < 0.001$	$P < 0.001$
Mean right coronary resistance, *mm Hg/ml per min*	Normal	5.51±0.93	2.38±0.43	4.58±0.69
	Normal subgroup	4.47±0.42	1.57±0.07	4.32±0.19
	RVH	1.95±0.28	0.83±0.12	0.95±0.11
	RVH subgroup	1.82±0.45	0.77±0.12	0.77±0.09
	RVH subgroup:			
	vs. normal	$P < 0.001$	$P < 0.001$	$P < 0.001$
	vs. normal subgroup	$P < 0.001$	NS	$P < 0.001$
	vs. RVH	NS	NS	NS

* Values of the measured variables at 0.2 miles of exercise course.

‡ Normal subgroup comprised of three normal dogs where arterial pressure did not change during exercise.

§ RVH subgroup comprised of four RVH dogs where arterial pressure did not change during exercise.

which exhibited reductions in arterial pressure during exercise.

DISCUSSION

Results from this study provide the first compelling evidence that dogs with severe RV hypertrophy have a strikingly abnormal coronary vascular response to free-ranging exercise. The most distinguishing characteristic of this abnormal response to exercise is the appearance of a profound postexercise coronary hyperemia (Figs. 2–4). The postexercise coronary hyperemia is observed not only in dogs with RV hypertrophy that undergo decreases in arterial pressure during exercise, but is also noted in dogs with RV hypertrophy in which arterial pressure is maintained during exercise (Table III). This response is strongly indicative of a fundamental defect in the ability of the coronary circulation of the hypertrophied right ventricle to sufficiently compensate for the elevated metabolic demands of exercise.

The postexercise coronary hyperemia suggests that a perfusion deficit had been incurred by the hypertrophied right ventricle during exercise. An analogous phenomenon has been reported recently in skeletal muscle of anesthetized dogs (9, 10). These investigators observed a "prolonged vasodilation" following cessation of electrical stimulation of *in situ* skeletal muscle when arterial inflow was restricted to the contracting muscle. It is also of interest that following brief periods

of myocardial ischemia induced by coronary artery occlusion, the resultant reactive hyperemia is associated with a transient overshoot in myocardial function above preischemic levels in the region rendered ischemic (11). This overshoot in function was prevented by inhibiting the reactive hyperemia by gradually releasing the coronary occlusion (11). Moreover, a postexercise augmentation of left ventricular function associated with coronary hyperemia was observed in a prior study conducted in this laboratory, in which the normal increase in left main coronary inflow was restricted during exercise (12). These prior studies (9–12) lend support to the hypothesis that the postexercise coronary hyperemia observed in the present study was most likely mediated by the accumulation of myocardial metabolites secondary to inadequate oxygen supply during exercise. However, an alternative explanation could be that the coronary hyperemia is due to an increase in oxygen demand consequent to elevated levels of RV systolic and end-diastolic pressures and *dP/dt* that were observed immediately following exercise in dogs with RV hypertrophy. This is a less likely explanation, since there was no obvious need for RV pressure and *dP/dt* to rise following, as opposed to during, exercise. Furthermore, the increases in pressure and *dP/dt* occurred at a time when heart rate was falling rapidly back to preexercise control levels.

The mechanism(s) responsible for the apparent accumulated perfusion deficit of the hypertrophied right ventricle during exercise are likely multifactorial. In part, the attenuated right coronary vascular response during exercise (Fig. 2) could be related to the elevated preexercise levels of right coronary blood flow, or could be secondarily related to the smaller increments in heart rate and RV *dP/dt* in dogs with RV hypertrophy during exercise (Table II). Increased extravascular compression of the coronary vasculature supplying the hypertrophied right ventricle could serve to limit the extent of the increase in blood flow during exercise. The lower level to which stroke systolic/diastolic flow ratio increased during exercise in these dogs would appear to support this possibility. Additionally, the decrease in coronary perfusion pressure during exercise in dogs with RV hypertrophy with a fixed pulmonic stenosis almost certainly attenuated the magnitude of the increase in right coronary artery blood flow during exercise. This is supported by the observation that right coronary artery blood flow increased to significantly higher levels during exercise in dogs with RV hypertrophy in which arterial pressure was sustained during the exercise period (Table III). However, a decrease in coronary perfusion pressure cannot be entirely responsible for the abnormal coronary vascular response to exercise, because the most prominent feature of this response (i.e., the postexercise coronary hyperemia) was also observed in those dogs with RV hypertrophy that did not exhibit reductions in either mean or diastolic arterial pressures during exercise (Table III). Previous studies from this laboratory (13, 14) have demonstrated that dogs in chronic right heart failure exhibit augmented alpha adrenergic constriction of peripheral vascular beds during free-ranging exercise. Moreover, alpha adrenergic activation during exercise can attenuate the normal coronary vascular response to exercise (7). Thus, it could be postulated that an enhancement of coronary alpha adrenoceptor activation may limit the extent of the increase in right coronary artery blood flow during exercise in these dogs with RV hypertrophy. But perhaps the most likely mechanism for the abnormal coronary vascular response to exercise is that coronary vasodilator capacity of the hypertrophied right ventricle is significantly reduced. A recent study from our laboratory provides supportive evidence for this hypothesis (15). In that investigation (15) maximal coronary vasodilator capacity (response to adenosine infusion) of the hypertrophied right ventricle was found to be reduced significantly. This reduction was most prominent in the endocardial layer of the hypertrophied right ventricle. This diminution in maximal coronary vasodilator capacity likely limits the ability of the coronary vasculature supplying the hypertrophied ventricle to sufficiently increase nutrient supply in the face of markedly elevated levels of metabolic demand, which are associated with the cardiovascular stress of free-ranging exercise.

Whereas RV hypertrophy is characterized by a marked increase in blood flow per gram of ventricle at rest (1), blood flow to the hypertrophied left ventricle has been shown to be either modestly reduced (16–19), unchanged (20–24), or only slightly increased (25). Moreover, in contrast to the results of the present study, coronary vascular adjustments to exercise of the hypertrophied left ventricle appear to be largely normal (21, 22, 26–28). Although slight degrees of relative endocardial underperfusion during exercise have been reported (21, 22, 28), similar changes were observed in the non-hypertrophied control group (22, 28). One possible explanation for the divergent results between these studies and the present study is the difference in the ventricle being subjected to the chronic pressure overload. It should also be noted, however, that those studies concerned with the coronary vascular response of the hypertrophied left ventricle measured discrete changes in myocardial blood flow (radioactive microsphere technique) during less strenuous treadmill exercise, whereas the present investigation involved continuous measurements of right coronary artery blood flow (Doppler ultrasonic technique) during spontaneous, severe, free-ranging exercise.

There are several aspects of the methodology and the interpretation of results that require discussion. First, it should be noted that measurements of right coronary artery blood flow do not reflect the total perfusion of either the normal or hypertrophied right ventricle. Whereas the right coronary artery provides substantial blood supply to the central core of the RV free wall, up to 37% of total perfusion of the normal right ventricle, primarily the blood flow to peripheral margins, originates from the left coronary artery (29). It could be argued that the attenuated increase in right coronary artery blood flow during exercise in dogs with RV hypertrophy is the result of enhanced perfusion of the hypertrophied right ventricle from the left coronary artery. However, this is not a likely explanation for several reasons. First, the fractional contribution of the right coronary artery to total perfusion of the right ventricle is greatly enhanced following the development of RV hypertrophy (29). Second, in the presence of right main coronary artery occlusion, absolute levels of perfusion of normal and hypertrophied right ventricles originating from the left coronary artery are similar (29). Moreover, if perfusion of the hypertrophied right ventricle had been sufficiently augmented by blood flow from the left coronary artery, then the postexercise right coronary hyperemia would not have been observed.

It is also important to note that measurements of right coronary artery blood flow do not permit an assessment of possible transmural variations in blood flow during exercise to the hypertrophied right ventricle. However, it must be emphasized that the flow measuring technique utilized in this study has permitted continuous measurements of right coronary artery blood flow in the field by radiotelemetry techniques at a time when the dogs were exercising at maximum levels of capacity. It is under these conditions of severe cardiovascular stress that a markedly abnormal response to exercise has been detected in dogs with RV hypertrophy.

It is recognized that there is a fine line between animals with severe RV hypertrophy alone, and those with hypertrophy and failure in combination. These dogs did not exhibit the more apparent signs of right heart failure, i.e., abdominal ascites, liver congestion, peripheral edema, or markedly elevated levels of RV end-diastolic pressure at rest. However, these dogs did demonstrate significant hemodynamic abnormalities (decreases in aortic and RV systolic pressures and an increase in RV end-diastolic pressure) during exercise, and it is, therefore, possible that the cardiovascular stress of exercise was sufficient to precipitate acute cardiac failure.

An additional point of interest was the marked, slowing of heart rate from peak exercise levels prior to cessation of exercise observed in some of the dogs with RV hypertrophy. This abrupt slowing of heart rate was blocked by atropine, indicating that the efferent limb of this response can be ascribed to activation of the parasympathetic nervous system. This is a paradoxical response, because exercise is normally associated with a withdrawal of parasympathetic activity. Although speculative, it is possible that a perfusion deficit of the hypertrophied right ventricle during exercise results in the production of a myocardial metabolite, which in turn could activate ventricular mechanoreceptors or peripheral arterial or cardiac chemoreceptors during exercise. In this regard, it is interesting that a recent preliminary study (30) has reported that the intracoronary injection of prostaglandins induces hypotension and reflex bradycardia, instead of the expected tachycardia mediated by arterial baroreceptors. A cardio-coronary reflex parasympathetic coronary vasodilation elicited by chemical stimulation of cardiac receptors (i.e., the Bezold-Jarisch reflex) has also previously been reported (31), and may contribute a component of the postexercise coronary hyperemia observed in some of these dogs with RV hypertrophy.

In conclusion, results of this study provide evidence that coronary vascular adaptations to the stress of spontaneous, free-ranging exercise are markedly abnormal in dogs with severe RV hypertrophy. These findings support the concept that compensatory adjustments of the coronary circulation of the severely hypertrophied right ventricle may be insufficient to supply adequate levels of nutrient supply during periods of elevated metabolic demand of the hypertrophied right ventricle. This inadequate coronary vascular response is most likely responsible for the state of near collapse observed in the dogs with hypertrophy immediately postexercise and may be causally related to the pathogenesis of congestive right heart failure.

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REFERENCES

1. Murray, P. A., H. Baig, M. C. Fishbein, and S. F. Vatner. 1979. Effects of experimental right ventricular hypertrophy on myocardial blood flow in conscious dogs. *J. Clin. Invest.* **64**: 421–427.
2. Franklin, D., N. W. Watson, K. E. Pierson, and R. L. Van Citters. 1966. Technique for radiotelemetry of blood flow velocity from unrestrained animals. *Am. J. Med. Electron.* **5**: 24–28.
3. Vatner, S. F., D. Franklin, and R. L. Van Citters. 1970. Simultaneous comparison and calibration of the Doppler and electromagnetic flowmeters. *J. Appl. Physiol.* **29**: 907–910.

4. Patrick, T. A., S. F. Vatner, W. S. Kemper, and D. Franklin. 1974. Telemetry of left ventricular diameter and pressure measurements in unrestrained animals. *J. Appl. Physiol.* **37**: 276–281.
5. Baig, H., T. A. Patrick, and S. F. Vatner. 1977. Implantable pressure gauges for use in chronic animals. *In* Indwelling and Implantable Pressure Transducers. D. G. Fleming, W. H. Ko, and M. R. Neuman, editors. CRC Press, Inc., Boca Raton, Fla. 25–43.
6. Vatner, S. F., C. B. Higgins, S. White, T. Patrick, and D. Franklin. 1971. The peripheral vascular response to severe exercise in untethered dogs before and after complete heart block. *J. Clin. Invest.* **50**: 1950–1960.
7. Murray, P. A., and S. F. Vatner. 1979. α-adrenoceptor attenuation of the coronary vascular response to severe exercise in the conscious dog. *Circ. Res.* **45**: 654–660.
8. Armitage, P. 1974. *In* Statistical Methods in Medical Research. Blackwell Scientific Publications, Oxford, England. 3rd printing. 189–198.
9. Morganroth, M. L., E. W. Young, and H. V. Sparks. 1977. Prostaglandin and histaminergic mediation of prolonged vasodilation after exercise. *Am. J. Physiol.* **233**(1): H27–H33.
10. Belloni, F. L., R. D. Phair, and H. V. Sparks. 1979. The role of adenosine in prolonged vasodilation following flow restricted exercise of canine skeletal muscle. *Circ. Res.* **44**: 759–766.
11. Pagani, M., S. F. Vatner, H. Baig, and E. Braunwald. 1978. Initial myocardial adjustments to brief periods of ischemia and reperfusion in the conscious dog. *Circ. Res.* **43**: 83–92.
12. Vatner, S. F., R. J. McRitchie, P. R. Maroko, T. A. Patrick, and E. Braunwald. 1974. Effects of catecholamines, exercise, and nitroglycerin on the normal and ischemic myocardium in conscious dogs. *J. Clin. Invest.* **54**: 563–575.
13. Higgins, C. B., S. F. Vatner, D. Franklin, and E. Braunwald. 1972. Effects of experimentally produced heart failure on the peripheral vascular response to severe exercise in conscious dogs. *Circ. Res.* **31**: 186–194.
14. Millard, R. W., C. B. Higgins, D. Franklin, and S. F. Vatner. 1972. Regulation of the renal circulation during severe exercise in normal dogs and dogs with experimental heart failure. *Circ. Res.* **31**: 881–888.
15. Murray, P. A., and S. F. Vatner. 1981. Reduction of maximal coronary vasodilator capacity in conscious dogs with severe right ventricular hypertrophy. *Circ. Res.* **48**: 25–31.
16. Gamble, W. J., C. Phornphutkul, A. E. Kumar, G. L. Sanders, F. J. Manasek, and R. G. Monroe. 1973. Ventricular performance, coronary flow, and MVO_2 in aortic coarctation hypertrophy. *Am. J. Physiol.* **224**: 877–883.
17. Malik, A. B., T. Abe, H. O'Kane, and A. S. Geha. 1973. Cardiac function, coronary flow, and oxygen consumption in stable left ventricular hypertrophy. *Am. J. Physiol.* **225**: 186–191.
18. Pyle, R. L., H. S. Lowensohn, E. M. Khouri, D. E. Gregg, and D. F. Patterson. 1973. Left circumflex coronary artery hemodynamics in conscious dogs with congenital subaortic stenosis. *Circ. Res.* **33**: 34–38.
19. Johnson, L. L., R. R. Sciacca, K. Ellis, M. B. Weiss, and P. J. Cannon. 1978. Reduced left ventricular myocardial blood flow per unit mass in aortic stenosis. *Circulation.* **57**: 582–590.
20. West, J. W., H. Marcker, H. Wendel, and E. L. Foltz. 1959. Effects of renal hypertension on coronary blood flow, cardiac oxygen consumption and related circulatory dynamics of the dog. *Circ. Res.* **7**: 476–485.
21. Holtz, J., W. Restorff, P. Bard, and E. Bassenge. 1977. Transmural distribution of myocardial blood flow and of coronary reserve in canine left ventricular hypertrophy. *Basic Res. Cardiol.* **72**: 286–292.
22. White, R., M. Sanders, T. Peterson, and C. Bloor. 1977. Regional myocardial blood flow in developing cardiac hypertrophy. *Circulation* **55–56**(Suppl. III, III-36): 132. (Abstr.)
23. Mueller, T. M., M. L. Marcus, R. D. Kerber, J. A. Young, R. W. Barnes, and F. M. Abboud. 1978. Effect of renal hypertension and left ventricular hypertrophy on the coronary circulation in dogs. *Circ. Res.* **42**: 543–549.
24. O'Keefe, D. D., J. I. E. Hoffman, R. Cheitlin, M. J. O'Neill, J. R. Allard, and E. Shapkin. 1978. Coronary blood flow in experimental canine left ventricular hypertrophy. *Circ. Res.* **43**: 43–51.
25. Rembert, J. C., L. H. Kleinman, J. M. Fedor, A. S. Wechsler, and J. C. Greenfield, Jr. 1978. Myocardial blood flow distribution in concentric left ventricular hypertrophy. *J. Clin. Invest.* **62**: 379–386.
26. Vrobel, T. R., W. S. Ring, R. W. Anderson, R. W. Emory, and R. J. Bache. 1978. Myocardial blood flow in the exercising dog with chronic left ventricular hypertrophy. *Circulation.* **57–58**(Suppl. II, II-56): 212. (Abstr.)
27. Bache, R. J., and T. R. Vrobel. 1979. Effects of exercise on blood flow in the hypertrophied heart. *Am. J. Cardiol.* **44**: 1029–1033.
28. Mueller, T. M., M. L. Marcus, C. L. Eastham, and C. M. Tipton. 1979. Effects of treadmill exercise in dogs with pressure-induced left ventricular hypertrophy. *Fed. Proc.* **38**: 955 (Abstr.)
29. Murray, P. A., and S. F. Vatner. 1980. Fractional contributions of the right and left coronary arteries to perfusion of normal and hypertrophied right ventricles of conscious dogs. *Circ. Res.* **47**: 190–200.
30. Hintze, T. H., M. J. Panzenbeck, A. Baez, E. J. Messina, and G. Kaley. 1979. Ventricular receptors perfused by the circumflex coronary artery are activated by prostaglandins to cause a Bezold-Jarisch like response in the dog. *Circulation.* **59–60**(Suppl. II, II-80): 308. (Abstr.)
31. Feigl, E. O. 1975. Reflex parasympathetic coronary vasodilation elicited from cardiac receptors in the dog. *Circ. Res.* **37**: 175–182.