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Myocardial Ischemia in a Canine Model of Pulmonary Hypertension and Right Coronary Artery Stenosis

*Hans-Joachim Priebe, M.D.**

This study was performed to study the effects of acute pulmonary embolization (injection of autologous muscle) on global and regional (ultrasonic dimension technique) right ventricular (RV) performance, coronary hemodynamics (electromagnetic flow probes), and gas exchange during underlying critical stenosis (cuff occluder) of the right coronary artery (RCA) in eight open-chest dogs. Resting coronary blood flow (CBF) and regional myocardial performance remained unaffected by the induction of RCA stenosis. Following embolization pulmonary artery (PA) pressure, pulmonary vascular resistance, end-diastolic dimensions and pressure increased, and PA flow, stroke volume (SV), and aortic pressure (AoP) decreased ($P < 0.05$). There was a marked decline (60%) in CBF accompanied by severe myocardial dysfunction suggestive of ischemia (akinesis, systolic lengthening, postsystolic shortening) in the area supplied by the stenosed RCA. Gas exchange, lung compliance, and *p*H worsened. Release of the RCA constriction led to a fourfold increase in CBF, return of PA flow, SV, and AoP to baseline values, and disappearance of regional myocardial dysfunction despite continued pulmonary hypertension. These data indicate that RV function may deteriorate in response to even small increases in afterload if coronary vascular reserve is absent and aortic pressure is allowed to decrease. (Key words: Circulation: pulmonary; right ventricle. Heart: coronary artery stenosis; coronary hemodynamics; regional myocardial performance; right ventricular performance. Pulmonary hypertension: experimental.)

DURING INCREASED right ventricular (RV) afterload RV performance critically depends on adequate augmentation of coronary perfusion.[1] Thus, RV systolic stress is expected to be poorly tolerated in the presence of severely reduced coronary vascular reserve even if resting coronary blood flow (CBF) should meet myocardial oxygen demands (MV_{O_2}) at rest. The clinical correlate would be the patient with severe right coronary artery (RCA) disease who is asymptomatic at rest and who subsequently experiences a sudden increase in RV afterload associated with pulmonary embolism, acute respiratory failure, or ventilation of the lungs with high levels of positive end-expiratory pressure (PEEP). Survival will depend to a large extent on the ability of the RV to sustain the acute increase in work load.[2] Accordingly, this study was performed to study the effects of moderate degrees of acute pulmonary hypertension (PH) and respiratory insufficiency (features of both pulmonary embolism and acute respiratory failure) during preexisting impaired RV perfusion on global and regional RV function, and on coronary hemodynamics. The identical experimental model of PH and respiratory insufficiency has previously been employed to investigate the response of RV myocardium and coronary circulation to an acute increase in RV afterload during unimpaired coronary blood supply.[3]

Methods

INSTRUMENTATION

Following approval from the local Ethics Committee on Animal Research, eight mongrel dogs received preanesthetic medication consisting of intramuscular fentanyl (0.04 mg/kg) and droperidol (2 mg/kg). Anesthesia was induced with small incremental doses of iv pentobarbital up to a maximum dose of 10 mg/kg and maintained by continuous iv infusions of pentobarbital ($1\ mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl ($20\ \mu g \cdot kg^{-1} \cdot h^{-1}$). Following tracheal intubation controlled ventilation with a constant volume ventilator (Servo Ventilator 900C, Siemens-Elema) at a fractional concentration of O_2 in inspired gas of 1.0 was facilitated by a continuous iv infusion of pancuronium ($0.04\ mg \cdot kg^{-1} \cdot h^{-1}$). Tidal volume, duration of inspiration, and of inspiratory pause were set at 15 ml/kg and at 25% and 10% of the total respiratory cycle time, respectively. Respiratory rates were adjusted to obtain an initial arterial carbon dioxide tension (Pa_{CO_2}) between 30 and 40 mmHg. The ventilatory pattern was kept unchanged throughout the experiment. PEEP (2 mmHg) was applied to prevent major airway collapse in the open-chest animals. Tidal volume, respiratory rate, PEEP, and plateau airway pressure were continuously monitored and displayed *via* sensor placed between endotracheal tube and ventilator (Lung Mechanics Calculator 940, Siemens-Elema). For determination of the fractional end-tidal CO_2 concentration (FET_{CO_2}) a small-bore catheter was placed close to the carina *via* the tracheal tube and connected to a precalibrated infrared gas analyzer (Beckman, Medical Gas Analyzer LB-2). Catheter-tip manometers (6F, Millar Instruments Inc) were inserted, advanced into the aortic root, and right (RV) and left ventricles (LV), and calibrated as previously described.[3]

All dogs were in the supine position and placed on a heating element. Body temperature was monitored con-

* Professor of Anesthesia.

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Address reprint requests to Dr. Priebe: Universitaetsklinik, Klinik fuer Anaesthesiologie, Hugstetter Strasse 55, D-7800 Freiburg, Federal Republic of Germany.

tinuously by a thermistor of a flow-directed thermodilution catheter (Edwards Laboratory, Model 93-132-5F) that had been advanced into the pulmonary artery (PA). All animals received 4–6 $ml \cdot kg^{-1} \cdot h^{-1}$ of normal saline. After an initial iv bolus dose (1 mEq/kg) sodium bicarbonate was administered by continuous iv infusion (0.5 $mEq \cdot kg^{-1} \cdot h^{-1}$) throughout the experiment.

The chest was entered through a median sternotomy. Except for small incisions required for the placement of flow probes and piezoelectric crystals, the pericardium was kept intact. Following placement of the monitoring devices, the incisions were closed loosely. Precalibrated electromagnetic flow probes (Stölzer Messtechnik, Waldkirch) of appropriate sizes to ensure a snug fit were placed around the main PA, the RCA approximately 1–2 cm distal to its origin, and around the left anterior descending coronary artery (LAD) distal to its first large diagonal branch. The flow probes were connected to flow meters with incorporated nonocclusive zero, which were rechecked repeatedly during the experiment.

Regional myocardial performance was evaluated by sonomicrometry.[4] Two pairs of piezoelectric crystals (5 MHz, 1.5–2.0 mm diameter) were inserted into the subendocardium of the inflow (longitudinal direction) and outflow tract (transverse direction) of the RV. Care was taken to place the crystals in the inflow tract within and those in the outflow tract outside the areas supplied by the RCA distal to the flow probe. This was done by transiently occluding the RCA at the site of the placement of the flow probe and observing the area of developing cyanosis. Myocardial segment lengths (SL) between each pair of crystals were determined at end-diastole (SL_{ed}), pulmonic valve opening (SL_{vo}), at times of maximum ($SL_s max$) and minimum SL during systole ($SL_s min$), at end-systole (SL_{es}), and at the time of minimum SL during diastole ($SL_d min$). End-diastole was defined as the beginning of the sharp upslope in the expanded RV pressure or the RV dP/dt tracings, pulmonic valve opening as the beginning of the upslope in the PA flow tracing, and end-systole as the moment the PA flow signal crossed the zero line following ejection. Percent segment shortening during systole (ΔSL_{ss}), (paradoxical) systolic lengthening (ΔSL_{sl}), and postsystolic shortening (ΔSL_{ps}) were derived from the following formulas:

$$\Delta SL_{ss}\,(\%) = (SL_{ed} - SL_s min)/SL_{ed} \cdot 100;$$

$$\Delta SL_{sl}\,(\%) = (SL_s max - SL_{vo})/SL_s max \cdot 100;$$

$$\Delta SL_{ps}\,(\%) = (SL_{es} - SL_d min)/SL_{es} \cdot 100.$$

For subsequent statistical analysis, negative values for ΔSL_{sl} and ΔSL_{ps} were listed as zero.

For subsequent pulmonary embolization approximately 20 g of autologous sartorius muscle was resected, freed of all visible fat and connective tissue, and finely chopped by hand until resembling a smooth paste with all particles of similar size.[3] This was then suspended in 100 ml of normal saline containing 2,000 units of heparin.

Critical Stenosis

Details regarding definition and induction of the critical stenosis of the RCA have been provided previously.[5] In brief, critical coronary artery stenosis was defined as the minimum constriction necessary to prevent an increase in resting CBF by more than 10% in response to an iv injection of the powerful coronary vasodilator acetate.[6,7] Numerous preliminary studies had shown that it consistently increased CBF threefold to fivefold, a response similar to that observed in this preparation following a 10-s occlusion of the RCA. When, during progressive constriction of the RCA, CBF failed to increase by more than 10% in response to acetate, it also failed to do so in response to a 10-s occlusion. The increase in CBF was not blunted after repeated injections of acetate, and CBF returned to baseline values within 1–2 min. Acetate was thus utilized as a convenient means of repeatedly stimulating coronary vasodilation, and this way avoiding potential mechanical damage to the coronary artery and/or residual regional myocardial dysfunction, possibly associated with numerous vascular occlusions.

A pneumatic, syringe-driven, high-pressure low-volume cuff occluder was placed around the RCA immediately distal to the flow probe. Intraluminal pressure was monitored continuously *via* three-way stopcock placed between cuff occluder and syringe using Statham transducers (P23 ID). While observing the maximally amplified mean and phasic RCA flow signals on the oscilloscope, the occluder was gradually inflated until dampening of the phasic flow signal and a tendency for the mean CBF to decline were observed. At this point 0.02 ml/kg body weight of a concentrated acetate solution (2.7 mM/ml) was injected intravenously. If the injection resulted in a greater than 10% increase in resting CBF, the occluder was inflated further and acetate was readministered. This procedure was continued until acetate failed to increase resting CBF by more than 10%. It required 2–4 injections of acetate to establish the critical RCA stenosis.

Cardiovascular and Respiratory Measurements

A multichannel recorder was used for the continuous recording of all hemodynamic and ultrasonic signals. RV dP/dt, systemic (SVR) and pulmonary vascular resistances (PVR), stroke volume (SV), and static lung compliance (C_L) were determined or derived as previously described.[3] Mean aortic (AoP_m), RV (RVEDP) and LV end-diastolic (LVEDP), and RV (RVSP) and LV systolic pressures (LVSP) were all determined by catheter-tip manometers,

and mean PA pressure (PAP_m) by flow-directed thermodilution catheter (Edwards Laboratory, Model 93-132-5F).

Experimental Protocol

After the sternotomy and the various cutdowns required for insertion of catheters, pentobarbital was discontinued, and no further pentobarbital was administered for approximately 2 h prior to the start of the experiment. Additional boli of fentanyl (10 μg/kg) were administered as indicated by increases in heart rate (HR) and blood pressure or movement of the animal. At the end of the surgical preparation, at least 30 min was allowed for stabilization. Hemodynamic, regional myocardial function and respiratory variables, body temperature (T), hematocrit (Hct; Microcentrifuge Compur, Model M 1100), arterial blood gases, and arterial *p*H (Instrumentation Laboratory, Model 613) were recorded at the end of each experimental period. In five animals the lungs were excised immediately postmortem for histologic examination.

After control readings had been obtained, critical stenosis (S) of the RCA was induced as described earlier. PH was then induced by repeatedly injecting small volumes (0.5–2 ml) of the muscle suspension through a femoral vein catheter until PAP_m had approximately doubled. Measurements were made 15 min after stabilization of PH (PH + S). Subsequently, the coronary artery stenosis was released, and measurements were repeated after CBF had stabilized following reactive hyperemia in response to the release of the stenosis (PH − S).

On average, 8 ml (range, 4–12 ml) of the muscle suspension and 35 min (range, 25–75 min) were required to establish a stable level of PH.

Statistical Analysis

The data were statistically analyzed by Friedman's statistic followed by Wilcoxon signed-rank test where appropriate (for comparisons between experimental periods) or by Mann-Whitney test (for comparisons within experimental periods). A P value of ≤ 0.05 was considered statistically significant.

Results

There were no significant differences between control values and those determined after induction of RCA stenosis (tables 1 and 2; figs. 1–4). The small (mean 8%) decrease in RCA blood flow (CBF_R) was not significant.

Embolization resulted in increases in PVR (fourfold), PAP_m, RVEDP, RVSP, RV dP/dt, and HR (35%) and decreases in PA flow (PAF; 18%), SV (38%), LVEDP, LVSP, AoP_m (17%), and SVR (table 1; fig. 1).

Total RV cardiac cycle time decreased by 27%, systolic time by 19%, and time spent in diastole by 33% (table 1). Hct and T did not change significantly (table 1).

All diastolic and systolic SL increased in RV inflow as well as in RV outflow tract (table 2; fig. 2). However, these increases were more pronounced in the inflow tract. Increases in SL_{vo} and SL_{es} were 12% *versus* 5% and 24% *versus* 9%, respectively, when comparing RV inflow with outflow tract ($P < 0.05$). In the inflow tract minimum systolic (SL_smin) and end-diastolic SL (SL_{ed}) were identical, maximum systolic SL (SL_smax) exceeded SL_{ed} and

TABLE 1. Cardiovascular, Respiratory, and General Homeostasis Parameters

Variable	Control	Stenosis	PH + S	PH − S
Global hemodynamics				
RVSP (mmHg)	24 ± 1	24 ± 1	30 ± 1*	30 ± 1*
RV dP/dt (mmHg/s)	369 ± 18	365 ± 21	450 ± 34*	476 ± 41*
LVEDP (mmHg)	6.4 ± 0.5	6.3 ± 0.4	5.6 ± 0.3*	5.6 ± 0.3*
LVSP (mmHg)	107 ± 5	106 ± 3	87 ± 6*	103 ± 3†
AoP_m (mmHg)	98 ± 4	95 ± 3	79 ± 6*	94 ± 2†
SVR (units)	64 ± 8	63 ± 8	55 ± 4*	59 ± 8
RV cardiac cycle times				
Total (ms)	529 ± 26	603 ± 36	443 ± 28*	499 ± 25*†
Systolic (ms)	278 ± 9	279 ± 11	227 ± 9*	250 ± 5
Diastolic (ms)	313 ± 27	324 ± 32	216 ± 22*	249 ± 23*†
Respiratory and acid–base status				
Pa_{O_2} (mmHg)	528 ± 14	520 ± 18	367 ± 45*	427 ± 47*
Pa_{CO_2} (mmHg)	33 ± 1	33 ± 1	41 ± 2*	40 ± 2*
Fet_{CO_2} (%)	3.7 ± 0.1	3.7 ± 0.1	3.2 ± 0.1*	3.5 ± 0.1
C_L (ml/mmHg)	90 ± 8	90 ± 9	58 ± 5*	55 ± 6*
*p*H	7.44 ± 0.01	7.44 ± 0.01	7.35 ± 0.02*	7.37 ± 0.01*†
General homeostasis				
Hct (%)	32 ± 2	32 ± 2	33 ± 1	34 ± 1
T (° C)	37.2 ± 0.3	37.2 ± 0.3	37.3 ± 0.3	37.4 ± 0.4

Values are mean ± SEM.
* $P < 0.05$, *versus* control.
† $P < 0.05$, *versus* PH + S.

TABLE 2. Regional RV Myocardial Segment Lengths

Variable	Control	Stenosis	PH + S	PH − S
RV inflow tract				
SL_{ed} (mm)	10.0 ± 0.4	10.0 ± 0.3	10.9 ± 0.4*	10.5 ± 0.4*†
SL_{vo} (mm)	9.8 ± 0.4	9.9 ± 0.4	11.1 ± 0.4*	10.4 ± 0.4*†
SL_smax (mm)	9.8 ± 0.4	9.9 ± 0.4	11.6 ± 0.5*	10.5 ± 0.4*†
SL_{es} (mm)	9.0 ± 0.4	8.9 ± 0.4	11.0 ± 0.5*	9.2 ± 0.4†
SL_dmin (mm)	9.0 ± 0.4	8.9 ± 0.4	10.4 ± 0.4*	9.2 ± 0.4†
RV outflow tract				
SL_{ed} (mm)	9.3 ± 0.4	9.4 ± 0.4	9.9 ± 0.4*	9.6 ± 0.4†
SL_{vo} (mm)	9.4 ± 0.4	9.5 ± 0.4	10.0 ± 0.5*	9.7 ± 0.4†
SL_smax (mm)	9.4 ± 0.4	9.5 ± 0.4	10.0 ± 0.5*	9.7 ± 0.4†
SL_{es} (mm)	8.0 ± 0.3	8.0 ± 0.3	8.7 ± 0.4*	8.3 ± 0.3†
SL_dmin (mm)	8.0 ± 0.3	8.0 ± 0.3	8.6 ± 0.3*	8.3 ± 0.3†

Values are mean ± SE.
* $P < 0.05$, *versus* control.
† $P < 0.05$, *versus* PH + S.

SL_{vo}, and minimum diastolic SL (SL_dmin) became less than SL_{es}. As a result of these marked differences in myocardial SL, in the inflow tract shortening during systole (ΔSL_{ss}) was practically abolished (whereas it decreased only in the outflow tract, NS), and significant systolic lengthening (ΔSL_{sl}) and postsystolic shortening (ΔSL_{ps}) developed (fig. 3). Some degree of ΔSL_{sl} (0.2 ± 0.2%) and ΔSL_{ps} (1.0 ± 0.4%) was observed in the RV outflow tract as well, but these values were not significantly different from those determined during stenosis and from zero.

Induction of PH caused a marked decline (58%) in CBF_R (fig. 4). LAD flow (CBF_{LAD}) did not decrease significantly when expressed in milliliters per minute, but it decreased when expressed in microliters per beat.

There were significant decreases in FET_{CO_2}, Pa_{O_2}, *p*H, and C_L and an increase in Pa_{CO_2} (table 1).

Following release of the RCA stenosis, PVR, PAP, and

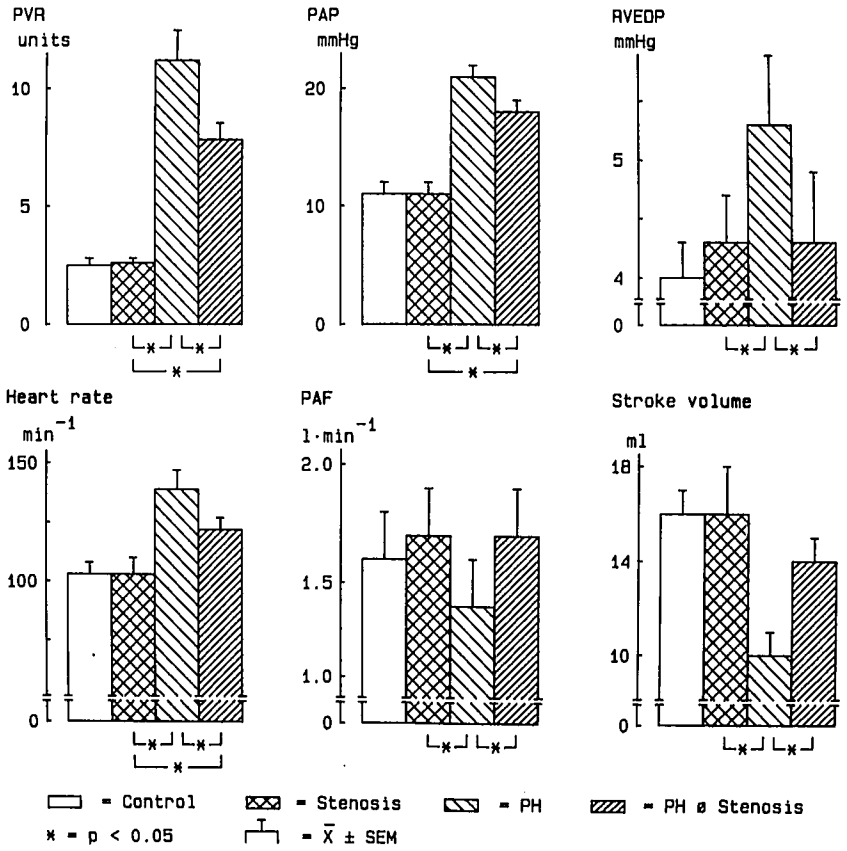

FIG. 1. Bars represent the mean values and SEM.

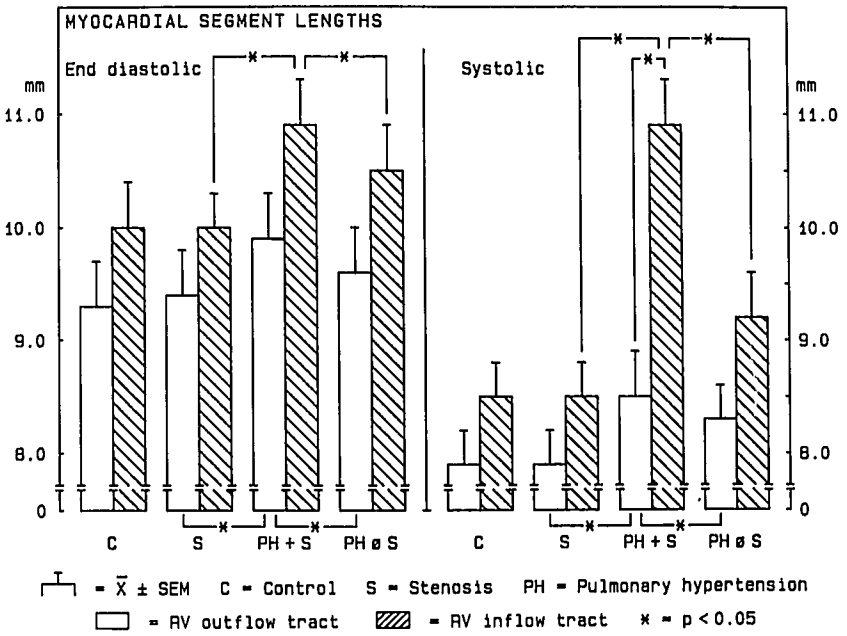

FIG. 2. End-diastolic and (minimum) systolic segment lengths.

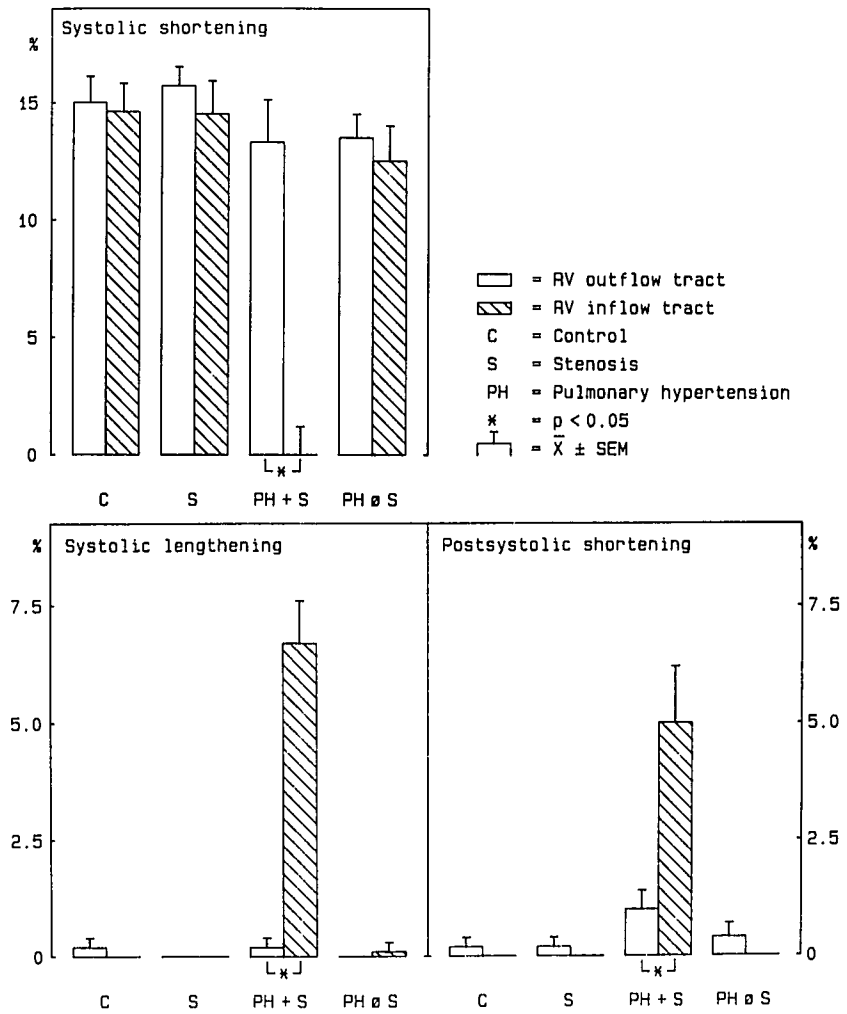

FIG. 3. Various parameters of regional RV myocardial performance. Values for systolic lengthening and postsystolic shortening in the RV inflow tract during PH + S are significantly different ($P < 0.05$) from preceding and following values.

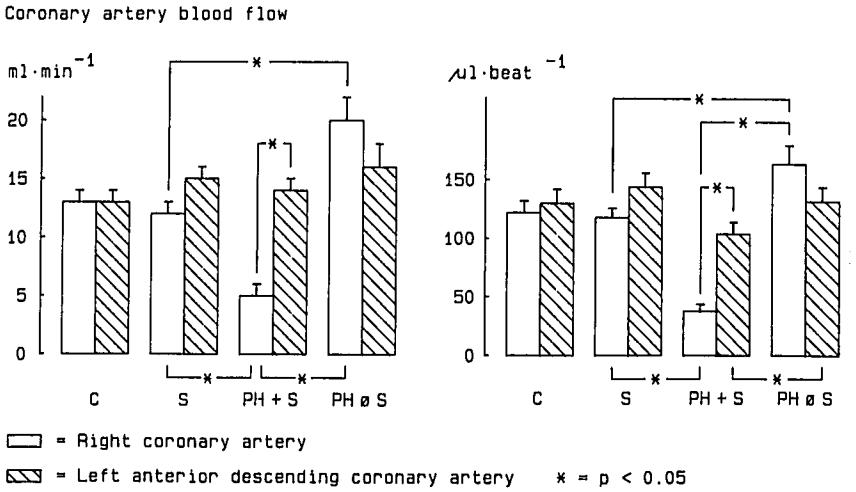

FIG. 4. Bars represent the mean values and SEM.

HR decreased, but they remained well above control values (fig. 1). RVEDP, PAF, SV, LVSP, and AoP_m returned to baseline values (fig. 1; table 1), and RVSP, RV dP/dt, and LVEDP remained unchanged (table 1).

All diastolic and systolic SL in RV inflow and outflow tract declined (table 2; fig. 2). Net systolic shortening returned in the inflow tract and systolic lengthening and postsystolic shortening disappeared (fig. 3). There were no quantitative or qualitative differences between inflow and outflow tract when compared directly with each other. However, when compared with their respective baseline values, SL in the inflow tract tended to remain elevated more so than in the outflow tract.

CBF_R increased by 300%, and it was higher by 50% when compared with the baseline value (fig. 4). CBF_{LAD} per heart beat also increased. FET_{CO_2}, Pa_{CO_2}, and C_L did not change significantly, *p*H increased, and Hct and T remained unchanged (table 1).

Histologic examination of the excised lungs of five dogs revealed moderate, at times pronounced perivascular edema, and striated muscle fibers located mostly in lobular and supralobular arteries.

Discussion

Characteristics of this canine model of acute pulmonary embolization and possible mechanisms involved in the production of PH and impairment of gas exchange have previously been discussed in detail.[3]

The degree of coronary artery stenosis aimed at has been termed "critical" in the literature.[8] Critical stenosis has been defined as the minimum constriction required "to prevent an increase in flow over resting values in response to increased myocardial oxygen demands."[8] Resting CBF should hardly be affected despite reductions in coronary artery diameter by as much as 75–93%.[8] In this study critical stenosis was defined as the minimum constriction necessary to prevent an increase in resting CBF by more than 10% in response to an iv injection of the powerful coronary vasodilator acetate.[6,7] Stenoses established this way resulted in reductions of resting CBF well within the range reported by other investigators.[8]

Constancy of coronary constriction is essential in this kind of investigation. For this purpose intraluminal cuff pressures were monitored continuously. Following induction of PH cuff pressures were allowed to decrease by an amount (5–35 mmHg) equivalent to the decrease in mean aortic pressure. This was done to maintain intraluminal distending pressures and, thus, prevent passive collapse of the stenotic segment and worsening of the severity of the stenoses. It is therefore likely that deterioration in CBF_R and, subsequently, in regional myocardial performance reflects the true consequences of the experimental intervention (PH) rather than a worsening of coronary artery stenosis. Nevertheless, hydraulic worsening of the coronary artery stenoses by the external occluder in response to a possible reduction in distal coronary artery pressure cannot entirely be ruled out.[9–11] However, the majority of human coronary stenoses are compliant and behave in a dynamic fashion[12–14]; consequently, transient dynamic variations in the severity of a stenosis must not be limited to the healthy experimental animal with externally compressed flexible coronary arteries, but they may also develop in eccentric lesions of human coronary arteries.

Regional myocardial function was evaluated by the ultrasonic dimension technique,[4] with which an excellent correlation between reduction in CBF[15] or perfusion pressure[16] and regional mechanical function has been demonstrated. Regional myocardial dysfunction and systolic paradox are changes characteristic of myocardial ischemia.[15]

Induction of the RCA stenosis did not cause any kind of myocardial dysfunction in the area supplied by the stenosed RCA. This was to be expected because resting CBF_R decreased little. The model thus simulates the clinical situation in which a patient with compromised coro-

nary vascular reserve is asymptomatic in the absence of increased MV_{O_2} or reduced myocardial O_2 supply. Subsequent pulmonary embolization resulted in an acute increase in RV afterload as indicated by a fourfold increase in PVR and a doubling of PAP. Despite increases in indices of contractility (RVSP, RV dP/dt) and preload (end-diastolic dimensions and pressures), RV pump function (PAF, SV) declined markedly. This is consistent with previous experimental data demonstrating an inverse relationship between RV afterload and SV[17] and impaired systolic performance during an acute increase in RV afterload unrelated to reductions in preload or contractility.[18] Decreases in RV output and SVR might have contributed to the small but significant decrease in LVEDP. Because LVEDP continued to exceed RVEDP, it is unlikely that the mechanism of ventricular interdependence[17] contributed to reduced cardiac output and systemic pressure.

Following the decrease in PAF it could have been expected that with preserved baroreceptor function contractility, HR and SVR would increase to maintain AoP. Indices of RV contractility (RVSP, RV dP/dt) and HR did increase. However, SVR decreased (12%), thus contributing to the decrease in AoP and coronary perfusion pressure. The mechanism for the decrease in SVR remains unclear. It is possible that humoral substances released from platelets or injured tissue at the sites of pulmonary embolization and the concomitant decrease in pH and increase in Pa_{CO_2} might have contributed to the decrease in SVR.

Pulmonary embolism-induced RV hypertension elicited akinesis, paradoxical systolic bulging, and postsystolic shortening in the area supplied by the stenosed RCA. Such manifestations of myocardial ischemia[15] were not observed in the RV outflow tract. These differences in regional myocardial function indicate that 1) this degree of PH is well tolerated in the presence of a presumed normal coronary circulation (RV outflow tract), and 2) the adverse effects on RV inflow tract performance were not due to the experimental model (open-chest) or due to interactions with the baseline anesthetic.

It is noteworthy that segment shortening in the RV outflow tract did not decrease significantly despite the acute increase in RV afterload. Several mechanisms might have been involved in maintaining regional contraction amplitude. First, coronary perfusion to the outflow tract remained basically unimpaired. Second, it is likely that preload (as reflected by end-diastolic SL and pressure) had increased. Third, inotropy might also have increased due to the increase in contraction frequency,[19] homeometric autoregulation,[20] or a reflex increase in cardiac sympathetic nerve activity secondary to the decrease in systemic pressure. And fourth, a compensatory increase in systolic shortening in nonischemic areas in response to acute ischemia elsewhere has been described.[21]

Development of regional myocardial ischemia was associated with a pronounced decrease in CBF_R (70% when expressed as flow per heart beat) at a time when indices of MV_{O_2} (preload, afterload, HR) were markedly elevated. The usual response to an acute increase in RV peak pressure is an increase in RV myocardial perfusion.[3,22] Several mechanisms are likely to have contributed to the decrease in CBF_R. First, there were substantial decreases in systolic (30%), mean (25%), and diastolic (20%) aortic-RV pressure gradients following induction of PH. Because the vasculature distal to a critically stenosed coronary artery becomes near maximally dilated and autoregulation is lost, flow across the stenosis becomes entirely pressure-dependent. Adequate diastolic perfusion pressure is of particular importance during RV hypertension because 1) the subendocardium is, in general, prone to hypoperfusion during RV hypertension,[23] 2) with rising RVSP RV myocardial perfusion occurs increasingly during diastole[24,25] (whereas RCA flow normally occurs during the entire cardiac cycle), and 3) during a critical coronary stenosis subendocardial flow reserve may be exhausted at a time when some dilator reserve is still present in the epicardium.[26] It has previously been shown that CBF and regional myocardial shortening will vary directly with changes in mean coronary perfusion pressure below 30 mmHg in the absence and below 45 mmHg in the presence of an elevated RV afterload.[16] Assuming a pressure gradient in the order of 45 mmHg across a coronary narrowing,[26] calculated mean coronary perfusion pressures (mean AoP − mean RV pressure − 45 mmHg) were approximately 35 and 15 mmHg during RCA stenosis and during PH, respectively. These calculations are consistent with findings of unchanged CBF and regional myocardial performance following induction of RCA stenosis and marked deterioration in flow and function during PH.

A second factor that is likely to have contributed to the decrease in CBF_R was the increase in HR that led to a decrease in absolute diastolic filling time (33%) and an increase in relative systolic time (22%). Considering the particular vulnerability of the subendocardium to hypoperfusion, a reduction in diastolic duration may well become the limiting factor in ensuring adequate RV perfusion at times of elevated intracavitary pressures and maximal coronary vasodilation (associated with a critical coronary stenosis). Tachycardia is particularly deleterious because it decreases myocardial O_2 supply at the same time it increases MV_{O_2}. Accordingly, tachycardia *per se* has been shown to worsen myocardial ischemia in the presence of a coronary stenosis.[27] It is therefore likely that the increase in HR significantly contributed to the development of regional myocardial ischemia independent of the concomitant rise in RV afterload.

Finally, myocardial perfusion was probably impeded throughout the cardiac cycle due to increased extravascular compressive forces during systole (elevated RVSP,

RV dP/dt, systolic SL, HR) and diastole (elevated end-diastolic SL and pressure). Thus, essential determinants of myocardial perfusion (perfusion pressure, intramyocardial pressure, vasomotor tone)[28] were all affected adversely by the combination of elevated RV afterload and critical coronary stenosis. With a likely concomitant increase in MV_{O_2}, regional balance between O_2 supply and demand was upset to an extent that resulted in myocardial ischemia.

As for the left coronary circulation, mean CBF_{LAD} remained unchanged due to the increase in HR. This is reflected by the decrease in CBF_{LAD} when expressed per heart beat. Such a decrease may be related to reductions in LVEDP, LVSP, AoP_m, and SVR resulting in a reduction of LV MV_{O_2}. Similar findings have been reported previously.[22]

The decreases in Pa_{O_2}, FET_{CO_2}, and C_L and the increase in Pa_{CO_2} are suggestive evidence for the development of ventilation–perfusion mismatch, increased dead space ventilation, an increase in intrapulmonary shunt, increased bronchomotor tone, and interstitial edema. Similar findings have been reported to occur in patients with acute respiratory failure[29] and pulmonary embolism.[30]

The effects of an acute increase in RV afterload on RV coronary hemodynamics and myocardial function in the absence of impaired coronary perfusion have previously been studied in the same experimental model with almost identical baseline cardiovascular dynamics.[3] Despite considerably greater increases in PAP (threefold *vs.* twofold) and RVSP (100 *vs.* 25%), PAF increased (35%), SV declined considerably less (15 *vs.* 35%), and RV end-diastolic dimensions and pressure and AoP_m did not change significantly, and there was no regional myocardial dysfunction suggestive of ischemia. In addition, induction of PH was accompanied by a doubling of CBF_R and a 60% decrease in coronary vascular resistance. These differences in cardiovascular response to an acute increase in RV afterload are in agreement with previous findings, which show that 1) during RV systolic stress overall cardiac performance becomes increasingly dependent on RV function, and 2) with RCA occlusion RV failure occurs at a much lower RVSP, emphasizing the utmost importance of adequate CBF in maintaining cardiac output during increased RV afterload.[1]

The importance of adequate coronary perfusion during elevated RV afterload is emphasized further by the findings of normalization of PAF, SV, AoP_m, and regional myocardial performance following release of the RCA constriction despite continued PH. The marked improvement in cardiovascular performance was accompanied by a fourfold increase in CBF. When compared with baseline values, CBF_R had risen by 50%. The decreases in PAP_m and PVR following release of the RCA constriction might reflect the tendency for some spontaneous improvement with time in this model.[3] Part of the decrease in PVR may have also been due to recruitment of pulmonary vasculature in response to the increase in PAF.[31]

Fundamental differences in coronary vascular distribution exist between canine and human hearts.[32] Unlike the human the canine has a dominant left coronary system. The RCA is small, supplying only one-half to two-thirds of the RV free wall.[33] Impaired RCA perfusion will therefore not disturb blood supply to the interventricular septum. Septal contraction, however, contributes to RV function nearly as much as does that of the RV free wall,[34] and it may be of particular importance during RV pressure overload.[35] Accordingly, it has been shown that in pigs with a dominant right coronary system (supplying a significant portion of the septum) the hemodynamic consequences of impaired RCA perfusion are more pronounced[36] than in the dog.[1] In the human with a coronary distribution similar to the pig more detrimental cardiovascular responses than in the dog thus have to be expected. In patients with coronary artery disease, RV diastolic dysfunction occurs at lower levels of afterload stress than it would with uncompromised myocardial perfusion.[37]

A clinical correlate to this experimental study could be a patient with coronary vasospasm and pulmonary hypertension. Although in this model RV function normalized upon release of the RCA occlusion, in the clinical setting some degree of RV dysfunction may persist following resolution of the coronary spasm due to "stunning" of the myocardium.[38] With brief periods of coronary artery occlusion (<20 min) followed by reperfusion, while no tissue necrosis occurs and mean CBF returns to control values, deficits in contractile function, depression of biochemical processes, and changes in ultrastructure of the postischemic myocardial segment may be present for hours to days.[39,40]

In summary, in this canine model acute pulmonary embolization during underlying critical stenosis of the RCA resulted in increases in indices of afterload (PAP, PVR) and preload (end-diastolic SL and pressure), in decreases of pump function (PAF, SV) and systemic pressure, and in regional myocardial dysfunction suggestive of severe ischemia (akinesis, systolic lengthening, postsystolic shortening). This was accompanied by a pronounced decrease in CBF_R. Abnormalities in respiratory function were consistent with increased ventilation–perfusion mismatch and increased dead space ventilation. Release of the RCA constriction led to a marked increase in CBF_R and improvement of global and regional myocardial performance despite continued PH. These data emphasize the importance of preserved RV perfusion and performance in maintaining global pump function during elevated RV afterload. They further suggest that patients with RCA disease, even though asymptomatic at rest, may experience severe regional myocardial ischemia when exposed acutely to only moderate degrees of elevated RV

afterload as may occur during acute respiratory failure, pulmonary embolism, or ventilation with PEEP. These effects may be magnified if aortic pressure decreases during pulmonary hypertension.

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