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Effects of Vasodilators on Gas Exchange in Acute Canine Embolic Pulmonary Hypertension

Marion Delcroix, M.D., Christian Mélot, M.D., Ph.D.,† Philippe Lejeune, M.D.,† Marc Leeman, M.D.,† Robert Naeije, M.D., Ph.D.‡*

Pulmonary vascular tone was investigated by the construction of pulmonary arterial pressure (PAP)/cardiac output ($\dot{Q}$) plots, and gas exchange, by the multiple inert gas elimination technique, in 24 anesthetized dogs before and after pulmonary embolization of autologous clots. Three PAP/$\dot{Q}$ plots were obtained by a manipulation of venous return at baseline and 60 min and 110 min after embolization. Before the third PAP/$\dot{Q}$ plot, the dogs were randomly allocated to one of the following iv treatments: 1) placebo (n = 6); 2) prostaglandin E_1 (PGE_1) 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 6); 3) hydralazine 2 mg/kg (n = 6); and 4) nitroprusside 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n = 6). These vasodilators decreased systemic arterial pressure by a mean of 44%. Ventilation–perfusion ($\dot{V}_A/\dot{Q}$) distributions were determined at the same $\dot{Q}$ (2.4 ± 0.1 $l \cdot min^{-1} \cdot m^{-2}$, mean ± SE) of each PAP/$\dot{Q}$ plot. Embolization increased the intercept and the slope of the PAP/$\dot{Q}$ plots ($P < 0.001$). Distributions of $\dot{V}_A/\dot{Q}$ were only moderately impaired, with an increased dispersion of both $\dot{V}_A$ and $\dot{Q}$ and a shift of $\dot{V}_A$ distributions to higher $\dot{V}_A/\dot{Q}$. Pa_{O_2} changed from 208 ± 5 to 172 ± 8 mmHg ($P < 0.01$) (fraction of inspired O_2 was 0.4). None of the treatments had any effect on $\dot{V}_A/\dot{Q}$ distributions. Placebo and PGE_1 had no effect on PAP/$\dot{Q}$ plots. Hydralazine and nitroprusside reduced the slope of the PAP/$\dot{Q}$ plots. Thus, in this canine model of acute pulmonary embolism: 1) $\dot{V}_A/\dot{Q}$ distributions were moderately impaired accounting for only slight hypoxemia, and 2) pulmonary hypertension was partially reversible by hydralazine and by nitroprusside without associated non–flow-dependent change in $\dot{V}_A/\dot{Q}$ distributions and arterial oxygenation. (Key words: Embolism: pulmonary. Lung: pulmonary hypertension; pulmonary arterial pressure–flow relationships; ventilation–perfusion distributions. Lung, pharmacology: hydralazine, nitroprusside, prostaglandin E_1.)

EMBOLIC PULMONARY HYPERTENSION is caused by a direct mechanical obstruction of the pulmonary vessels but also in part by an active pulmonary vasoconstriction.[1,2] This observation has been the justification for attempts at pharmacologic pulmonary vasodilation in these patients when right ventricular failure occurs.[3] The ideal vasodilator for such a purpose would decrease pulmonary arterial pressures with minimal systemic hypotension and no adverse effect on pulmonary gas exchange.

* Research Fellow.

† Staff Intensivist; Assistant Professor of Medicine.

‡ Staff Intensivist; Professor of Medicine.

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Address reprint requests to Dr. Delcroix: Department of Intensive Care, Erasme University Hospital, Route de Lennik, 808, B-1070, Brussels, Belgium.

Pulmonary vascular pressure–flow relationships in embolic pulmonary hypertension have become better understood in recent years. Ducas *et al.*[4–6] showed that injection of autologous clots in dogs shifted pulmonary arterial pressure (PAP)/cardiac output ($\dot{Q}$) plots in an essentially parallel manner toward higher pressures, and suggested that pulmonary embolism-induced hypertension would be due more to an increase in closing pressures (Pc) of the pulmonary vessels (*i.e.*, the extrapolated pressure intercepts of PAP/$\dot{Q}$ plots) than to an increase in vascular resistance upstream to the site of vascular closure (*i.e.*, the slopes of PAP/$\dot{Q}$ plots). The same authors reported that the effects of potent vasodilators on PAP/$\dot{Q}$ plots in embolic pulmonary hypertension could be a reduction either in slopes (after isoproterenol)[4] or in extrapolated pressure intercepts (after hydralazine)[6] or no change (after prostaglandin E_1).[5]

Systemic arterial hypoxemia of variable severity is a characteristic finding in pulmonary embolism.[1] This hypoxemia has been accounted for by several mechanisms: right-to-left intrapulmonary and/or extrapulmonary shunting, diffusion impairment, ventilation–perfusion ($\dot{V}_A/\dot{Q}$) inequality, and reduced mixed venous P_{O_2}.[7–10] Vasodilators have been reported to impair pulmonary gas exchange in various types of pulmonary hypertension, such as obliterative vascular disease,[11] secondary to chronic obstructive pulmonary disease[12] and secondary to the adult respiratory distress syndrome.[13] How gas exchange might be affected by isolated changes in extrapolated pressure intercepts or in slopes of PAP/$\dot{Q}$ plots after administration of vasodilators in embolic pulmonary hypertension has not been documented.

The aim of the present investigation was to characterize abnormal pulmonary gas exchange using the multiple inert gas elimination technique in a canine model of acute pulmonary embolism with autologous blood clots at fixed ventilation and cardiac output, and to examine the combined effects on PAP/$\dot{Q}$ plots and on gas exchange of three potent vasodilators, nitroprusside, hydralazine and PGE_1.

Materials and Methods

Twenty-four mongrel dogs (21–30 kg, mean 26 kg) were anesthetized with sodium pentobarbital (25 mg/kg iv) and paralyzed with pancuronium bromide (0.2 mg/kg iv). Their lungs were ventilated with a servoventilator

Elema 900 B (Siemens Elema, Solna, Sweden) *via* a cuffed endotracheal tube. The inspired fraction of O_2 was 0.4, the respiratory rate 12 breaths/min and the tidal volume 15–20 ml/kg was adjusted to maintain an arterial P_{CO_2} between 30 and 35 mmHg. Pentobarbital (2 mg/kg) and pancuronium (0.2 mg/kg) were repeated hourly to maintain anesthesia and to prevent spontaneous respiratory efforts. Sodium bicarbonate was given as required to maintain arterial *p*H above 7.25. Temperature was maintained at 37–38° C by use of an electrical heating blanket. The experiments were performed in accordance with the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiological Society.

A thermistor-tipped pulmonary artery catheter (Model 93A-131-7F, Edwards Laboratories, Santa Ana, California) was inserted *via* the right external jugular vein and positioned by means of pressure monitoring in a branch of the pulmonary artery for measurements of PAP, pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and for mixed venous blood sampling. A polyethylene catheter was inserted in the abdominal aorta *via* the right femoral artery for systemic blood pressure (SBP) measurements and arterial blood sampling. A balloon catheter (Pericor 45, Datascope, Paramus, New Jersey) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a titratable decrease in cardiac output by reducing venous return. A large-bore polyethylene cannula was inserted into the left femoral artery and vein to act as an arteriovenous fistula. Closing this fistula resulted in a decrease in cardiac output by an average of 0.4 $l \cdot min^{-1} \cdot m^{-2}$. Thrombus formation along the catheters was prevented by 100 U/kg iv of sodium heparin just before the insertion.

Pulmonary and systemic arterial pressures were measured using Bentley transducers and the HERES computer system (ACEC, Charleroi, Belgium) and recorded on a 4-channel Gould recorder (model 2400S, Gould Inc, Instruments Division, Cleveland, Ohio). The pressure transducers were zero referenced at midchest and vascular pressures measured at end expiration. Heart rate (HR) was determined from a continuously monitored electrocardiographic lead. Cardiac output ($\dot{Q}$) was measured by thermodilution using injections of 10 ml of 0.9% sodium chloride at 0° C, a computer (9520-A, Edwards Laboratories), and an automated pneumatic pump electronically synchronized on the ventilatory cycle and was calculated as the mean of three determinations. Arterial and mixed venous blood gases were measured immediately after drawing the samples by a automated analyzer (ABL 2, Radiometer, Copenhagen, Denmark) and corrected for temperature. End-expiratory P_{CO_2} was measured with an infrared capnometer (Model 47217, Hewlett-Packard, Palo Alto, California). The inspiratory and expiratory circuits of the ventilator were separated using an electromagnetic valve electronically synchronized with the respiratory cycle. Minute ventilation was measured on the expiratory circuit through a Wright respirometer.

Body surface area was calculated as $0.112 \times \text{weight (kg)}^{2/3}$. Venous admixture was calculated as capillary O_2 content minus arterial O_2 content divided by capillary O_2 content minus mixed venous O_2 content. Capillary O_2 content was estimated using the calculated alveolar P_{O_2} and O_2 saturations determined from the nomogram of Rossing and Cain.[14]

The continuous $\dot{V}_A/\dot{Q}$ distributions were determined by the multiple inert gas elimination technique.[15] A mixture of six inert gases, sulfur hexafluoride (SF_6), ethane, cyclopropane, halothane, diethylether, and acetone dissolved in 5% dextrose in water solution, was infused in the left external jugular vein at a rate of 5 ml/min using an electronic infusion pump for at least 20 min prior to collecting 10-ml samples of mixed venous and arterial blood and a 50-ml sample of mixed expired gas through a heated collecting box, which was inserted in the expiratory circuit just behind the electromagnetic valve. The blood samples were equilibrated with 40 ml of nitrogen in a heated shaking bath for 45 min. The equilibrated gases and the mixed expired gas were then analyzed for SF_6 by an electron capture detector and for the other five gases by a flame ionization detector (Hewlett-Packard gas chromatograph 5890). In addition, a blood sample from each dog was used to measure the solubility of each gas.

From the measured solubilities of the six gases and their concentrations in arterial and mixed venous blood and mixed expired gas, two relationships were developed: the ratio of arterial to mixed venous concentrations (retention) and the ratio of mixed expired to mixed venous concentrations (excretion) were plotted against the solubility for each gas to derive retention – solubility curves. The representative distributions for blood flow and ventilation were then derived from these curves using the least-square analysis with enforced smoothing to minimize the effects of random experimental error.[16] The $\dot{V}_A/\dot{Q}$ distributions were combined with the mixed venous blood gases, cardiac output, minute ventilation in a lung model described by West and Wagner[17] to predict arterial P_{O_2} and P_{CO_2} assuming complete alveolar end-capillary equilibrium in each lung unit.

After ensuring steady state conditions for 20 min (stable HR, SBP, and PAP), a first 5-point PAP/$\dot{Q}$ plot was generated from hemodynamic determinations with open arteriovenous fistula (1 point), after closing the fistula (1 point), and then after stepwise inflations of the inferior vena cava balloon with occluded fistula (3 points). The average time to generate a PAP/$\dot{Q}$ plot was 30 min. A 200-ml sample of blood, collected before the baseline

measurements, was allowed to clot in a beaker and later cut into small pieces for infusion *via* the left external jugular vein. Embolization was carried out progressively during 30 min until mean PAP reached 40 mmHg. This pulmonary hypertension stabilized between 20 and 30 mmHg during a subsequent 30-min period, after which a second PAP/$\dot{Q}$ plot was constructed. Thereafter, the dogs received in a randomized order either no drug (placebo group, n = 6), PGE_1 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv (n = 6), nitroprusside 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv (n = 6), or hydralazine 2.0 mg/kg (n = 6). These doses were selected as to reduce mean SBP by no more than 40%. A third PAP/$\dot{Q}$ plot was then constructed 20 min later.

Blood gases were measured together with a determination of $\dot{V}_A/\dot{Q}$ distribution during the construction of each PAP/$\dot{Q}$ plot at an intermediate $\dot{Q}$ as close as possible of values between 2 and 2.5 $l \cdot min^{-1} \cdot m^{-2}$, which was always lower than the natural $\dot{Q}$ before embolization. The aim was to determine $\dot{V}_A/\dot{Q}$ distributions at unchanged ventilation (which was controlled) and unchanged $\dot{Q}$ (chosen during construction of the PAP/$\dot{Q}$ plots), so that only the effects of embolism and of drugs would be observed.

Inspection of the individual PAP/$\dot{Q}$ plots showed them to be essentially rectilinear; thus, a least-squares regression analysis was used to compute slopes and extrapolated pressure intercepts for each of them. A two-way analysis of variance with repeated measures was used to assess the effects of 1) embolization and drugs on the regression parameters derived from PAP/$\dot{Q}$ plots, and 2) embolization and drugs on hemodynamics and gas exchange at an intermediate $\dot{Q}$. Modified *t* tests were used when the *F* ratio of the analysis of variance reached a $P < 0.05$ critical level to compare slopes, intercepts, and PAP at a given level of flow of different subgroups.[18]

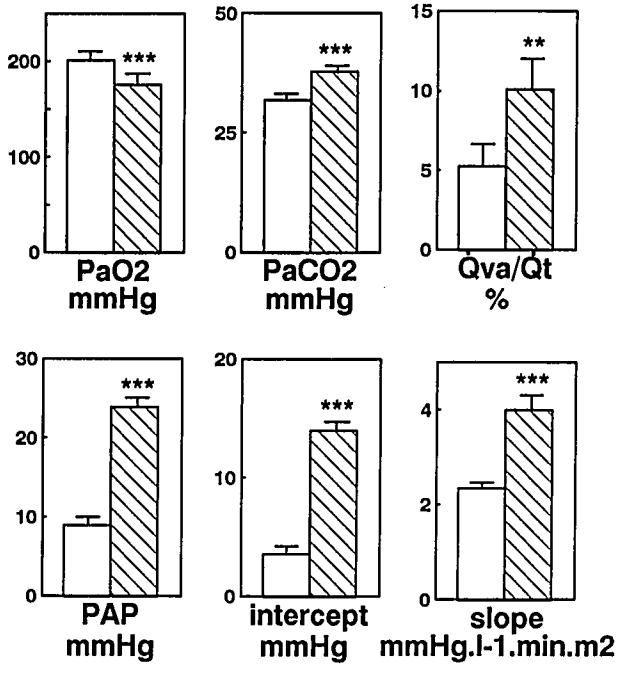

FIG. 1. Mean ± SE values of arterial P_{O_2} (Pa_{O_2}), arterial P_{CO_2} (Pa_{CO_2}), venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$), mean pulmonary arterial pressure (PAP), and intercepts and slopes of PAP/$\dot{Q}$ plots at baseline (empty columns) and 60 min after embolization (hatched columns) in 24 dogs (*$P < 0.5$, **$P < 0.05$, ***$P < 0.001$).

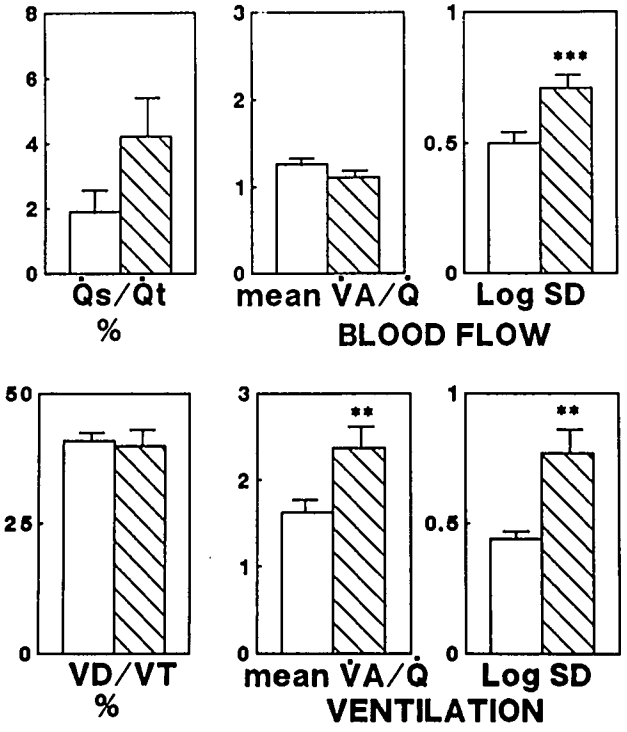

FIG. 2. Mean ± SE values of shunt ($\dot{Q}_s/\dot{Q}_t$), mean $\dot{V}_A/\dot{Q}$, and log SD of blood flow distribution, dead space (V_D/V_T), mean $\dot{V}_A/\dot{Q}$, and log SD of ventilation distribution at baseline (empty columns) and 60 min after embolization (hatched columns) in 24 dogs (*$P < 0.5$, **$P < 0.05$, ***$P < 0.001$).

Results

The PAP/$\dot{Q}$ plots were linear in all the experimental conditions with correlation coefficients ranging from 0.93 to 0.99.

The blood gases, hemodynamic and inert gas values shown in figures 1–3 and in tables 1–4 all were measured at an intermediate $\dot{Q}$ around 2 $l \cdot min^{-1} \cdot m^{-2}$. This $\dot{Q}$ was not significantly different from one experimental condition to another nor from one group to another.

Embolization

In the group of 24 dogs as a whole, embolization with autologous clots slightly decreased arterial P_{O_2} and in-

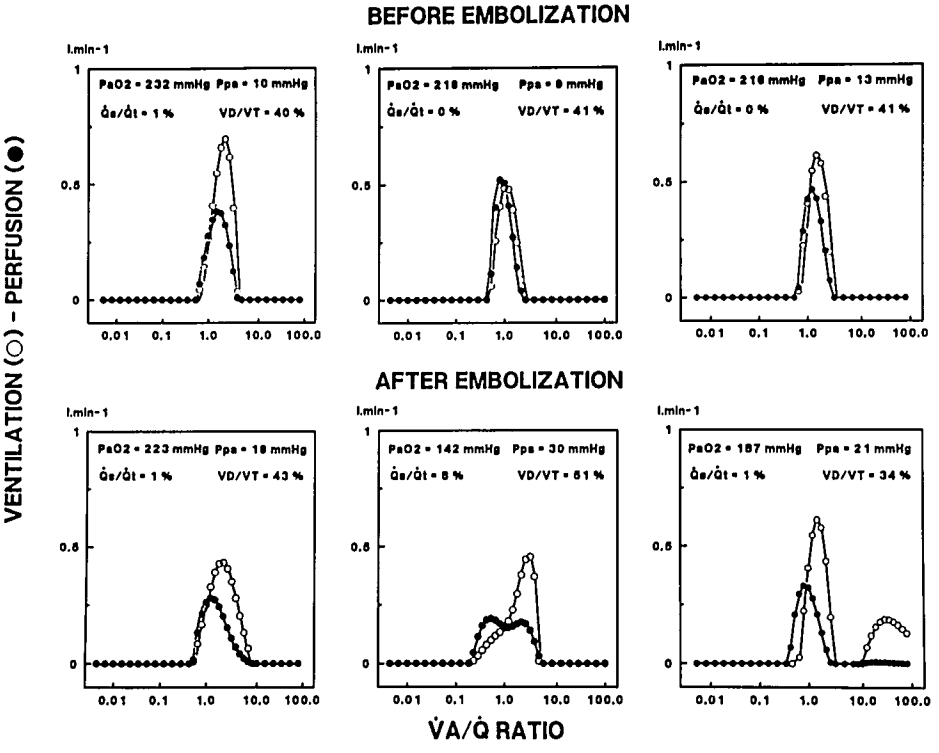

FIG. 3. $\dot{V}_A/\dot{Q}$ distributions before and after pulmonary embolism. Three patterns were obtained after embolization: a normal unimodal pattern (left panel), a broad unimodal pattern (middle panel), and a bimodal pattern with high $\dot{V}_A/\dot{Q}$ (right panel).

creased arterial P_{CO_2} and venous admixture, and induced pulmonary hypertension due to increases in both extrapolated pressure intercepts and slopes of PAP/$\dot{Q}$ plots (fig. 1). True shunt, dead space, and mean $\dot{V}_A/\dot{Q}$ of blood flow distribution were unchanged, whereas mean $\dot{V}_A/\dot{Q}$ of ventilation and the dispersion (log SD) of both distributions of blood flow and ventilation increased (fig. 2). The pattern of the $\dot{V}_A/\dot{Q}$ distributions was unimodal in all the dogs before embolization and became bimodal with high $\dot{V}_A/\dot{Q}$ units in 5 dogs, broad unimodal in 7, and was unchanged in 12 after embolization (fig. 3).

The correlation between measured Pa_{O_2}, corrected for electrode alinearity by tonometry, and predicted Pa_{O_2} was excellent (predicted P_{O_2} = 1.02 measured P_{O_2} + 13.32, r = 0.90), not significantly different from the identity line, neither for the slope nor for the intercept, and not affected by embolization.

After embolization slope and intercept of PAP/$\dot{Q}$ plots, blood gases, inert gases, and other hemodynamic variables remained stable during the time needed to generate two consecutive PAP/$\dot{Q}$ plots (table 1).

VASODILATORS

PGE_1 decreased pH and increased arterial P_{CO_2}, and decreased SBP but otherwise had no effect on hemodynamics, blood gases, and inert gas indices of gas exchange. The slope and intercept of the PAP/$\dot{Q}$ plots remained unchanged (table 2). Hydralazine decreased SBP, PCWP, and the slope but not the extrapolated pressure intercept of PAP/$\dot{Q}$ plots. Gas exchange was unaltered after hydralazine (table 3). Nitroprusside decreased SBP and the slope but not the extrapolated pressure intercept of PAP/$\dot{Q}$ plots. Gas exchange was unaltered after nitroprusside (table 4). The three vasodilators tested decreased SBP to the same extent by an average of 44%.

Discussion

The present results show that gas exchange is only moderately impaired in acute embolic pulmonary hypertension when studied at fixed ventilation and cardiac output and that this well-maintained gas exchange is not attributable to active pulmonary vasoconstriction.

Arterial hypoxemia is a characteristic finding in patients with pulmonary embolism.[1] Studies using the inert gas elimination technique have shown that gas exchange in these patients is abnormal because of a combination of increased intrapulmonary shunting, $\dot{V}_A/\dot{Q}$ inequality[8-10] and possibly a diffusion impairment.[9] A low mixed venous P_{O_2} has also been recognized as an extrapulmonary contributor to arterial hypoxemia.[9,10] In the canine model of acute pulmonary embolism by autologous clots, the distribution of $\dot{V}_A/\dot{Q}$ has been reported to be altered, with lung units that were either overperfused and underventilated or underperfused and overventilated, without

however a shunt or an increased dead space.[7] In keeping with that study, our dogs presented an increased dispersion of both ventilation and perfusion distributions, a shift of ventilation distributions to lung units with higher $\dot{V}_A/\dot{Q}$ and (in five of 24 animals) a true bimodal distribution, also without shunt or an increase in dead space. Our data do not indicate a diffusion impairment because measured and predicted P_{O_2} were not significantly different. Predicted P_{O_2} tended to be higher than measured P_{O_2} before as well as after embolization, probably explained by the 1–2% shunt due to the bronchial and thebesian circulations unmeasurable by the inert gases technique. In the controlled flow conditions of our experiments mixed venous P_{O_2} was not decreased. The abnormalities in the distributions of ventilation and perfusion were marked in our dogs but accounted for an only mild arterial hypoxemia because the amount of blood flow delivered to units with a lower than normal $\dot{V}_A/\dot{Q}$ was small.

Pulmonary hypertension in acute pulmonary embolism is due to mechanical obstruction of the pulmonary vasculature but also, to a certain extent, to active pulmonary vasoconstriction.[1,2] In the same experimental animal model of acute pulmonary embolism by autologous clots as in the present study, Ducas *et al.*[4–6] showed that PAP/$\dot{Q}$ plots were displaced in a parallel manner toward higher pressures, suggesting that pulmonary hypertension would be due more to an increase in the closing pressure of the pulmonary vessels than to their true vascular resistance. In our dogs both extrapolated pressure intercepts and

TABLE 1. Blood Gases, Hemodynamic, Inert Gas Variables, and PAP/$\dot{Q}$ Regression Parameters at Baseline, after Embolization, and during a Saline Infusion in Six Dogs at Fixed Flow

	Baseline	Embolism	Placebo
Arterial *p*H	7.34 ± 0.03	7.31 ± 0.03	7.34 ± 0.02
Arterial P_{O_2} (mmHg)	215 ± 5	185 ± 16*	192 ± 13
Arterial P_{CO_2} (mmHg)	32 ± 2	35 ± 3	35 ± 2
Mixed venous P_{O_2} (mmHg)	45 ± 1	46 ± 2	43 ± 2
Alveolar-arterial P_{O_2} gradient (mmHg)	38 ± 5	65 ± 16	58 ± 14
Venous admixture (% of total blood flow)	3 ± 1	7 ± 2	5 ± 2
Minute ventilation (l_{BTPS}/min)	5.2 ± 0.4	5.7 ± 0.4*	5.5 ± 0.4
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.37 ± 0.10	2.30 ± 0.14	2.23 ± 0.13
Heart rate (beats/min)	177 ± 14	188 ± 15	183 ± 14
Mean systemic arterial pressure (mmHg)	109 ± 4	116 ± 5	100 ± 9
Right atrial mean pressure (mmHg)	3 ± 1	3 ± 1	4 ± 1
Pulmonary artery mean pressure (mmHg)	9 ± 1	21 ± 3†	19 ± 2
Pulmonary artery wedge pressure (mmHg)	5 ± 1	4 ± 1	4 ± 1
Dead space$_{inert\ gas}$ (% of tidal volume)	43 ± 3	43 ± 6	42 ± 5
Shunt$_{inert\ gas}$ (% of total blood flow)	2 ± 2	3 ± 2	5 ± 3
Mean $\dot{V}_A/\dot{Q}$ of blood flow distribution	1.18 ± 0.08	1.14 ± 0.08	1.29 ± 0.12
Log SD of blood flow distribution	0.45 ± 0.06	0.70 ± 0.09*	0.61 ± 0.05
Mean $\dot{V}_A/\dot{Q}$ of ventilation distribution	1.47 ± 0.13	1.94 ± 0.18	1.87 ± 0.17
Log SD of ventilation distribution	0.43 ± 0.05	0.66 ± 0.08	0.60 ± 0.03
Slope ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	2.3 ± 0.2	3.3 ± 0.5	2.5 ± 0.5
Intercept (mmHg)	3.3 ± 0.7	12.3 ± 1.4†	12.4 ± 1.8
Correlation coefficient	0.97	0.96	0.96

Values are expressed as mean ± SE.
* $P < 0.05$, *versus* baseline.
† $P < 0.0001$, *versus* baseline.

TABLE 2. Blood Gases, Hemodynamic, Inert Gas Variables, and PAP/$\dot{Q}$ Regression Parameters at Baseline, after Embolization, and during a PGE_1 Infusion in Six Dogs at Fixed Flow

	Baseline	Embolism	PGE_1
Arterial *p*H	7.35 ± 0.02	7.32 ± 0.01	7.26 ± 0.02†
Arterial P_{O_2} (mmHg)	198 ± 12	156 ± 15*	137 ± 15
Arterial P_{CO_2} (mmHg)	33 ± 1	38 ± 2†	44 ± 2†
Mixed venous P_{O_2} (mmHg)	43 ± 1	47 ± 2	46 ± 3
Alveolar-arterial P_{O_2} gradient (mmHg)	57 ± 12	93 ± 15†	107 ± 16
Venous admixture (% of total blood flow)	5 ± 1	11 ± 4†	14 ± 4
Minute ventilation (l_{BTPS}/min)	5.2 ± 0.3	5.5 ± 0.1	5.7 ± 0.1
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.18 ± 0.08	2.16 ± 0.10	1.99 ± 0.07
Heart rate (beats/min)	150 ± 12	166 ± 12	163 ± 10
Mean systemic arterial pressure (mmHg)	101 ± 9	106 ± 9	63 ± 11‡
Right atrial mean pressure (mmHg)	5 ± 1	5 ± 1	5 ± 1
Pulmonary artery mean pressure (mmHg)	11 ± 1	24 ± 1‡	21 ± 1
Pulmonary artery wedge pressure (mmHg)	6 ± 1	7 ± 1	7 ± 1
Dead space$_{inert\ gas}$ (% of tidal volume)	45 ± 1	38 ± 8	45 ± 3
Shunt$_{inert\ gas}$ (% of total blood flow)	3 ± 2	4 ± 3	7 ± 4
Mean $\dot{V}_A/\dot{Q}$ of blood flow distribution	1.17 ± 0.08	0.99 ± 0.08	1.04 ± 0.09
Log SD of blood flow distribution	0.47 ± 0.09	0.76 ± 0.11*	0.84 ± 0.10
Mean $\dot{V}_A/\dot{Q}$ of ventilation distribution	1.46 ± 0.08	2.61 ± 0.61†	2.95 ± 0.35
Log SD of ventilation distribution	0.41 ± 0.05	0.95 ± 0.25*	1.09 ± 0.12
Slope ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	2.6 ± 0.4	3.7 ± 0.3†	3.1 ± 0.3
Intercept (mmHg)	5.1 ± 0.9	15.1 ± 1.3‡	15.0 ± 1.2
Correlation coefficient	0.95	0.96	0.98

Values are expressed as mean ± SE.
* $P < 0.005$, † $P < 0.05$, ‡ $P < 0.0005$, *versus* previous column.

TABLE 3. Blood Gases, Hemodynamic, Inert Gas Variables, and PAP/$\dot{Q}$ Regression Parameters at Baseline, after Embolization, and after Hydralazine in Six Dogs at Fixed Flow

	Baseline	Embolism	Hydralazine
Arterial *p*H	7.39 ± 0.01	7.36 ± 0.02	7.35 ± 0.02
Arterial P_{O_2} (mmHg)	199 ± 12	165 ± 20*	177 ± 18
Arterial P_{CO_2} (mmHg)	34 ± 1	42 ± 3†	39 ± 3
Mixed venous P_{O_2} (mmHg)	46 ± 1	49 ± 1	52 ± 3
Alveolar-arterial P_{O_2} gradient (mmHg)	51 ± 11	78 ± 19	68 ± 19
Venous admixture (% of total blood flow)	5 ± 1	10 ± 4*	8 ± 3
Minute ventilation (l_{BTPS}/min)	4.7 ± 0.3	4.9 ± 0.40	5.2 ± 0.5
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.59 ± 0.14	2.44 ± 0.18	2.41 ± 0.11
Heart rate (beats/min)	181 ± 12	198 ± 9*	191 ± 3
Mean systemic arterial pressure (mmHg)	101 ± 12	123 ± 7*	65 ± 5‡
Right atrial mean pressure (mmHg)	2 ± 1	2 ± 1	3 ± 1
Pulmonary artery mean pressure (mmHg)	8 ± 1	25 ± 3‡	20 ± 2*
Pulmonary artery wedge pressure (mmHg)	3 ± 1	6 ± 1†	4 ± 1*
Dead $space_{inert\ gas}$ (% of tidal volume)	38 ± 3	41 ± 4	41 ± 4
$Shunt_{inert\ gas}$ (% of total blood flow)	2 ± 1	6 ± 3	6 ± 3
Mean $\dot{V}_A/\dot{Q}$ of blood flow distribution	1.08 ± 0.06	1.05 ± 0.15	1.05 ± 0.13
Log SD of blood flow distribution	0.44 ± 0.05	0.62 ± 0.11	0.71 ± 0.15
Mean $\dot{V}_A/\dot{Q}$ of ventilation distribution	1.35 ± 0.11	2.12 ± 0.58	2.02 ± 0.40
Log SD of ventilation distribution	0.44 ± 0.05	0.69 ± 0.18	0.68 ± 0.09
Slope ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	2.4 ± 0.1	4.5 ± 0.8†	2.3 ± 0.2‡
Intercept (mmHg)	1.3 ± 0.9	13.9 ± 2.0‡	14.2 ± 1.5
Correlation coefficient	0.98	0.99	0.98

Values are expressed as mean ± SE.
* $P < 0.05$, † $P < 0.005$, ‡ $P < 0.0005$, *versus* previous column.

slopes of PAP/$\dot{Q}$ plots were increased. Ducas *et al.* also suggested that in acute canine embolic pulmonary hypertension vasodilators could act at different vascular sites because in their experiments hydralazine reduced extrapolated pressure intercepts without effect on slopes and isoproterenol reduced slopes without effect on pressure intercepts of PAP/$\dot{Q}$ plots.[4,6] In our dogs both hydralazine and nitroprusside reduced slopes without effect on pressure intercepts of PAP/$\dot{Q}$ plots.

It is well recognized that left atrial pressure or PCWP is not the correct outflow pressure of the pulmonary circulation in most types of pulmonary hypertension and that pulmonary vascular tone is therefore better evaluated by measurements of pulmonary vascular pressures at several levels of flow than by isolated pulmonary vascular resistance calculations.[19] If the pulmonary circulation is modeled as a recruiting system of parallel branches with fixed resistance and a distribution of closing pressures, the PAP/$\dot{Q}$ relationship, which is curvilinear at low flow, becomes linear at pressures above the highest closing pressure.[20] The extrapolation of the linear part of the PAP/$\dot{Q}$ relationship will intercept the pressure axis at a mean closing pressure that is the effective outflow pressure of the pulmonary circulation.[20] However, there may be several problems in transposing these concepts derived from experiments on isolated lung lobes to PAP/$\dot{Q}$ plots in intact animals. Passing from a high to a low $\dot{Q}$ can affect pulmonary vascular tone by a decrease in mixed venous P_{O_2},[21] a decrease in vascular pressures,[22] and a change in autonomic nervous system tone.[23] Associated changes in left atrial pressure can also affect PAP/$\dot{Q}$ plots.[24] Thus, PAP/$\dot{Q}$ plots are an integrated response

TABLE 4. Blood Gases, Hemodynamic, Inert Gas Variables, and PAP/$\dot{Q}$ Regression Parameters at Baseline, after Embolization, and during a Nitroprusside Infusion in Six Dogs at Fixed Flow

	Baseline	Embolism	Nitroprusside
Arterial *p*H	7.42 ± 0.02	7.37 ± 0.02*	7.34 ± 0.02
Arterial P_{O_2} (mmHg)	217 ± 8	184 ± 17*	176 ± 15
Arterial P_{CO_2} (mmHg)	29 ± 1	35 ± 1*	37 ± 2
Mixed venous P_{O_2} (mmHg)	44 ± 2	48 ± 1	48 ± 1
Alveolar-arterial P_{O_2} gradient (mmHg)	38 ± 8	66 ± 17*	72 ± 16
Venous admixture (% of total blood flow)	3 ± 1	7 ± 3	8 ± 3
Minute ventilation (l_{BTPS}/min)	5.6 ± 0.3	5.7 ± 0.3	5.7 ± 0.3
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.39 ± 0.17	2.37 ± 0.15	2.41 ± 0.16
Heart rate (beats/min)	170 ± 13	177 ± 14	181 ± 11
Mean systemic arterial pressure (mmHg)	101 ± 7	125 ± 7*	69 ± 6†
Right atrial mean pressure (mmHg)	3 ± 1	2 ± 1	3 ± 1
Pulmonary artery mean pressure (mmHg)	11 ± 1	28 ± 2†	23 ± 2*
Pulmonary artery wedge pressure (mmHg)	4 ± 1	6 ± 1*	6 ± 1
Dead $space_{inert\ gas}$ (% of tidal volume)	38 ± 2	40 ± 6	40 ± 6
$Shunt_{inert\ gas}$ (% of total blood flow)	1 ± 1	4 ± 3	5 ± 3
Mean $\dot{V}_A/\dot{Q}$ of blood flow distribution	1.35 ± 0.08	1.19 ± 0.16	1.18 ± 0.13
Log SD of blood flow distribution	0.51 ± 0.05	0.69 ± 0.09	0.67 ± 0.08
Mean $\dot{V}_A/\dot{Q}$ of ventilation distribution	1.78 ± 0.13	2.21 ± 0.30	2.06 ± 0.25
Log SD of ventilation distribution	0.52 ± 0.05	0.74 ± 0.13	0.73 ± 0.12
Slope ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	2.3 ± 0.2	4.4 ± 0.6‡	3.1 ± 0.4*
Intercept (mmHg)	4.6 ± 0.8	16.6 ± 1.1†	15.5 ± 1.3
Correlation coefficient	0.96	0.98	0.97

Values are expressed as mean ± SE.
* $P < 0.05$, † $P < 0.0005$, ‡ $P < 0.005$, *versus* previous column.

of all these stimuli instead of being purely passive before embolism and thereafter only affected by the mechanical and humoral effects of the injected clots. In addition, the recruitment model of the pulmonary circulation with its interpretation of pressure intercepts of PAP/$\dot{Q}$ plots as closing pressures remains unproved.[20] Parallel shifts of PAP/$\dot{Q}$ curves can be explained as well by a viscoelasticity model elaborated by Zhuang *et al.* on the basis of feline morphometric data.[25] Thus, the proposal by Ducas *et al.* that an increase in closing pressures is a major mechanism of acute embolic pulmonary hypertension[4-6] might be excessively speculative. We therefore used slopes and extrapolated pressure intercepts of PAP/$\dot{Q}$ curves to describe pulmonary hemodynamic changes without inference to specific mechanisms at any locus of the pulmonary vasculature.

Prostaglandin E_1 is a potent pulmonary vasodilator that has been shown effective in pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD),[26] to clinical[27] and experimental adult respiratory distress syndrome (ARDS),[28] to mitral valve disease,[29] to severe left heart failure,[30] in primary pulmonary hypertension,[31] and in experimental pulmonary hypertension induced by the infusion of a thromboxane A_2 analog.[32] PGE_1 does not inhibit hypoxic pulmonary vasoconstriction (HPV) at the maximum doses tolerated in healthy subjects (around 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[26] At doses ten times higher in dogs, as in the present study, PGE_1 inhibits HPV partially.§ We confirm that PGE_1 somewhat surprisingly does not reduce pulmonary hypertension resulting from acute pulmonary embolism.[5]

Hydralazine is an effective pulmonary vasodilator in pulmonary hypertension secondary to chronic obstructive or interstitial pulmonary diseases[33] but does not inhibit HPV[34] and is poorly effective in pulmonary hypertension induced by a thromboxane A_2 analog.[32] We confirm that hydralazine reduces PAP over a wide range of $\dot{Q}$ in acute canine embolic pulmonary hypertension.[6]

Nitroprusside inhibits HPV[35] and has been shown to be an effective pulmonary vasodilator in numerous clinical or experimental condition tested, except probably in experimental ARDS.[28] In the present study nitroprusside, similar to hydralazine, reduced PAP more at high than at low $\dot{Q}$.

A pharmacologic reduction in pulmonary vascular tone has been shown to impair $\dot{V}_A/\dot{Q}$ matching in primary pulmonary hypertension,[11] and in pulmonary hypertension secondary to COPD[12] and to ARDS.[13] In the present experiments a pulmonary vasodilation by hydralazine and by nitroprusside had no effect on $\dot{V}_A/\dot{Q}$ distributions. This may be related to the fact that after embolism only a small part of blood flow was distributed to lung units with a $\dot{V}_A/\dot{Q}$ lower than normal, without active pulmonary vasoconstriction being responsible for this.

It has to be emphasized that clinical extrapolations of the present findings should be restricted by the fact that we prevented changes in cardiac output secondary to pulmonary embolism or to pharmacologic interventions. Thus, our conclusions are limited to non–flow-dependent effects on $\dot{V}_A/\dot{Q}$ distributions and on pulmonary arterial pressures.

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References

1. Sharma GVRK, McIntyre KM, Sharma S, Sasahara AA: Clinical and hemodynamic correlates in pulmonary embolism. Clin Chest Med 5:421–437, 1984
2. McIntyre KM, Sasahara AA: The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 28:288–294, 1971
3. Bates ER, Crevey BJ, Remington Sprague F, Pitt B: Oral hydralazine therapy for acute pulmonary embolism and low output state. Arch Intern Med 141:1537–1538, 1981
4. Ducas J, Duval D, Dasilva H, Boiteau P, Prewitt RM: Treatment of canine pulmonary hypertension: Effects of norepinephrine and isoproterenol on pulmonary vascular pressure–flow characteristics. Circulation 75:235–242, 1987
5. Ducas J, Light RB, Girling L, Schick U, Prewitt RM: Effects of prostaglandin E_1 on the pulmonary vascular pressure–flow relationship in canine pulmonary hypertension. J Crit Care 3:24–31, 1988
6. Ducas J, Girling L, Schick U, Prewitt RM: Pulmonary vascular effects of hydralazine in a canine preparation of pulmonary thromboembolism. Circulation 73:1050–1057, 1986
7. Dantzker DR, Wagner PD, Tornabene VW, Alazraki NP, West JB: Gas exchange after pulmonary thromboembolization in dogs. Circ Res 42:92–103, 1978
8. D'Alonzo GE, Bower JS, DeHart P, Dantzker DR: The mechanisms of abnormal gas exchange in acute massive pulmonary embolism. Am Rev Respir Dis 128:170–172, 1983
9. Manier G, Castaing Y, Guenard H: Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. Am Rev Respir Dis 132:332–338, 1985
10. Huet Y, Lemaire F, Brun-Buisson C, Knaus WA, Teisseire B, Payen D, Mathieu D: Hypoxemia in acute pulmonary embolism. Chest 88:829–836, 1985
11. Dantzker DR, Bower JS: Pulmonary vascular tone improves $\dot{V}_A/\dot{Q}$ matching in obliterative pulmonary hypertension. J Appl Physiol 51:607–613, 1981
12. Mélot C, Hallemans R, Naeije R, Mols P, Lejeune P: Deleterious effect of nifedipine on pulmonary gas exchange in chronic obstructive pulmonary disease. Am Rev Respir Dis 130:612–616, 1984
13. Mélot C, Naeije R, Mols P, Hallemans R, Lejeune P, Jaspar N: Pulmonary vascular tone improves pulmonary gas exchange in the adult respiratory distress syndrome. Am Rev Respir Dis 136:1232–1236, 1987
14. Rossing RG, Cain SM: A nomogram relating P_{O_2}, *p*H, temper-

§ Leeman M, Lejeune P, Mélot C, Naeije R: Pulmonary artery pressure–flow plots in hyperoxic and in hypoxic dogs. Eur Respir J 1:711–715, 1988

ature, and hemoglobin saturation in the dog. J Appl Physiol 21: 195–201, 1966
15. Wagner PD, Saltzman HA, West JB: Measurement of continuous distributions of ventilation–perfusion ratios: Theory. J Appl Physiol 36:588–589, 1974
16. Evans JW, Wagner PD: Limits on $\dot{V}_A/\dot{Q}$ distributions from analysis of experimental inert gas elimination. J Appl Physiol 42:889–898, 1977
17. West JB, Wagner PD: Pulmonary gas exchange, Bioengineering Aspects of the Lung. Vol. 3. Edited by West JB. New York, Marcel Dekker, 1977, pp 361–458
18. Winer BJ: Statistical Principles in Experimental Design. New York, McGraw-Hill, 1971
19. McGregor M, Sniderman A: On pulmonary vascular resistance: The need for more precise definition. Am J Cardiol 55:217–221, 1985
20. Mitzner W: Resistance of the pulmonary circulation. Clin Chest Med 4:127–137, 1983
21. Hughes JD, Rubin LJ: Relation between mixed venous oxygen tension and pulmonary vascular tone during normoxic, hyperoxic and hypoxic ventilation in dogs. Am J Cardiol 54:1118–1123, 1984
22. Benumof JL, Wahrenbrock EA: Blunted hypoxic pulmonary vasoconstriction by increased lung vascular pressures. J Appl Physiol 38:846–850, 1975
23. Murray PA, Lodato RF, Michael JR: Neural antagonists modulate pulmonary vascular pressure–flow plots in conscious dogs. J Appl Physiol 60:1900–1907, 1986
24. Ducas J, Schick U, Girling L, Prewitt RM: Effects of altered left atrial pressure on pulmonary vascular pressure–flow relationships. Am J Physiol 255(Heart Circ Physiol 24):H19–H25, 1988
25. Zhuang FY, Fung YC, Yen RT: Analysis of blood flow in cat's lung with detailed anatomical and elasticity data. J Appl Physiol 55:1341–1348, 1983
26. Naeije R, Mélot C, Mols P, Hallemans R: Reduction in pulmonary hypertension by prostaglandin E_1 in decompensated chronic obstructive pulmonary disease. Am Rev Respir Dis 125:1–5, 1982
27. Mélot C, Lejeune P, Leeman M, Moraine JJ, Naeije R: Prostaglandin E_1 in the adult respiratory distress syndrome: Benefit for pulmonary hypertension and cost for pulmonary gas exchange. Am Rev Respir Dis 139:106–110, 1989
28. Leeman M, Lejeune P, Mélot C, Naeije R: Pulmonary vascular pressure–flow plots in canine oleic acid pulmonary edema. Effects of prostaglandin E_1 and nitroprusside. Am Rev Respir Dis 138:362–367, 1988
29. Szczeklik J, Dubiel JS, Mysik M, Pyzik Z, Krol R, Horzela T: Effects of prostaglandin E_1 on pulmonary circulation in patients with pulmonary hypertension. Br Heart J 40:1397–1401, 1978
30. Jacobs P, Naeije R, Renard M, Mélot C, Mols P, Hallemans R: Effects of prostaglandin E_1 on hemodynamics and blood gases in severe left heart failure. J Cardiovasc Pharmacol 5:170–171, 1983
31. Halpern SM, Shah PK, Lehrman S, Goldberg HS, Jasper AC, Koerner SK: Prostaglandin E_1 as a screening vasodilator in primary pulmonary hypertension. Chest 92:686–691, 1987
32. Prielipp RC, Rosenthal MH, Pearl RG: Vasodilator therapy in vasoconstrictor-induced pulmonary hypertension in sheep. ANESTHESIOLOGY 68:552–558, 1988
33. Rubin LJ, Peter RH: Hemodynamics at rest and during exercise after oral hydralazine in patients with cor pulmonale. Am J Cardiol 47:116–122, 1981
34. Bishop MJ, Kennard S, Artman LD, Cheney FW: Hydralazine does not inhibit canine hypoxic pulmonary vasoconstriction. Am Rev Respir Dis 128:998–1001, 1983
35. Naeije R, Lejeune P, Leeman M, Mélot C, Deloof T: Pulmonary arterial pressure–flow plots in dogs: Effects of isoflurane and nitroprusside. J Appl Physiol 63:969–977, 1987