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Flow-mediated vasodilatation of the main pulmonary artery

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Abstract. This study compares the independent effects of flow ($\dot{Q}_{pa}$) and transmural pressure (P_{pa}) on the diameter (D) and length of a segment (L) of the main pulmonary artery (MPA) in anesthetized open-chested dogs. $\dot{Q}_{pa}$ was increased by a shunt from the left lower lobe pulmonary artery to an external jugular vein. P_{pa} was increased with positive end-expiratory pressure ($n = 5$), or with a femoral arteriovenous shunt ($n = 5$). Mean P_{pa}, $\dot{Q}_{pa}$, D and L were calculated by averaging over a single cardiac cycle selected at end expiration of successive breaths. The independent effects of P_{pa} and $\dot{Q}_{pa}$ on MPA dimensions were determined by multiple linear regression. The effects of P_{pa} ($\Delta D\%/\Delta P\% = 0.153 \pm 0.03$ SE) and $\dot{Q}_{pa}$ ($\Delta D\%/\Delta Q\% = 0.021 \pm 0.004$ SE) on D were similar in both groups of dogs. Changes of L ($\Delta L\%/\Delta P_{pa}\% = 0.168 \pm 0.042$ SE and $\Delta L\%/\Delta \dot{Q}_{pa}\% = 0.033 \pm 0.006$ SE, $n = 5$) were similar to the corresponding changes of D. We conclude that the effects of flow are small relative to pressure and that flow not only causes vasodilatation but also vasoelongation of the MPA.

Animals, dog; Blood flow, and geometry, pulmonary artery; Pressure, and geometry, pulmonary artery; Pulmonary artery, geometry dependent on pressure, flow

It is generally accepted that blood flow affects the caliber of large and medium sized systemic arteries independent of any changes in transmural pressure. This phenomenon has been studied in the hind limb of the dog (Ingbrigtsen and Leraand, 1970), in the canine (Holtz *et al.*, 1983) and human (Drexler, 1989) coronary circulation, in the rabbit cerebral circulation (Garcia-Rolden and Bevan, 1990), and in the human brachial artery (Sinoway, 1989), but not in the pulmonary circulation. In the pulmonary circulation, the arteries operate under a much lower transmural pressure and are more compliant than their counterparts in the systemic circulation. Therefore, flow-mediated vasomotion in the pulmonary circulation may differ substantially from the systemic circulation.

Recent experiments have shown that changes of characteristic impedance due to pulmonary vascular obstruction has an important influence on wave reflection (Fitzpatrick and Grant, 1990). Characteristic impedance is dependent primarily on the dimensions and elasticity of the proximal pulmonary arteries (Grant and Canty, 1989).

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We were interested whether flow-mediated vasomotion occurs in the main pulmonary artery (MPA) because it may act to control the dimensions of this vessel and therefore modulate characteristic impedance.

In the present study, our objective was to compare the independent effects of pressure and flow on the diameter of the MPA in the anesthetized dog. To calculate the separate effects of pressure and flow, it is necessary to avoid the close relation that normally exists between both. For this purpose, a shunt was established from the left lower lobe pulmonary artery to the right external jugular vein. This shunt increases flow through the MPA with minimal change of its transmural pressure. Two series of experiments were performed. In both series we used the pulmonary-jugular shunt to increase main pulmonary arterial flow and measured the transmural pressure and diameter of the MPA. In the first series of experiments, we used positive end expiratory pressure (PEEP) to increase the transmural pressure of the MPA. In the second series of experiments, we used a femoral arteriovenous shunt instead of PEEP for this purpose, and measured the length of a segment of MPA in addition to its diameter.

Methods

Experimental preparation. Anesthesia was induced in ten adult mongrel dogs of both sexes weighing 18–22 kg, with thiamylal (6 $mg \cdot kg^{-1}$) and α-chloralose (120 $mg \cdot kg^{-1}$), intravenously. Anesthesia was then maintained with a continuous infusion of α-chloralose (43 $mg \cdot kg^{-1} \cdot h^{-1}$). Animals were ventilated with a pump (Harvard Apparatus, South Natick, MA) through an endotracheal tube at a rate of approximately 12 breaths per min and tidal volume of 10–15 ml/kg. A microswitch attached to the ventilator produced a 5 V pulse to indicate end-expiration. Thoracotomy was performed at the fifth intercostal space. PEEP of 5 cmH_2O was used to avoid atelectasis. The pericardium was incised and the MPA, left lower lobe pulmonary artery and the ascending aorta were dissected from the surrounding tissues. A Tygon catheter (1/8 inch i.d., 1/4 inch o.d.) was inserted retrograde into the left lower lobe pulmonary artery so that its tip was positioned at the junction of the left main and left lower lobe pulmonary arteries. This catheter was connected to the inflow of a Masterflex roller pump (model 7523–00 with pump head model 7015–52 and size 15 tubing, Cole-Parmer, Barrington, IL). The outflow was directed into a flow-through electromagnetic flow probe (Gould-Statham SP7519–188–607, Oxnard, CA) via a Tygon catheter (1/8 inch i.d., 1/4 inch o.d.) to the right external jugular vein. Care was taken to avoid air embolism. The roller pump controlled flow through the pulmonary-jugular shunt ($\dot{Q}_s$). Blood flow in the ascending aorta ($\dot{Q}_a$) was measured using an electromagnetic flow probe (SP7515 series, Gould-Statham). Both flow probes were coupled to Statham 2202 flowmeters. Mean pulmonary arterial flow ($\dot{Q}_{pa}$) was calculated from the sum of $\dot{Q}_a$ and $\dot{Q}_s$ (fig. 1). A pair of 3 mm ultrasonic crystals mounted on Dacron were sutured to the adventitia of the MPA to measure its diameter by sonomicrometry (model 120–1000–12, Triton, San Diego, CA). The setup was checked to ensure that there was no electrical

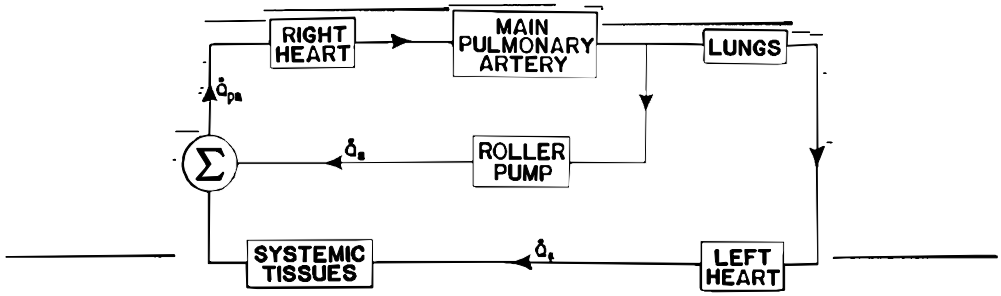

Fig. 1. Block diagram of the pulmonary-jugular shunt. Flow through the main pulmonary artery ($\dot{Q}_{pa}$) is calculated from the summation of aortic flow ($\dot{Q}_a$) and flow through the pulmonary-jugular shunt $\dot{Q}_s$).

interference between the electromagnetic flowmeters and the sonomicrometer. Pulmonary artery pressure (P_{pa}) and right ventricular pressure were measured continuously with separate micromanometer tipped catheters (model SPC-330, Millar, Houston, TX). These transducers were calibrated with zero referenced to atmospheric pressure. Airway pressure was monitored with a differential transducer (model MP45–1, Validyne, Northridge, CA); systemic arterial pressure was monitored in the left carotid artery with a single-ended pressure transducer (Spectromed P23XL) throughout the experiment. The ECG was sensed with an ECG/Biotach (Gould, Cleveland, OH) which produced a pulsed signal triggered by a QRS complex. Blood temperature was maintained at approximately 37°C.

The same experimental preparation was established in a second series of five dogs, but with two additional features. First, catheters were inserted into the right femoral artery and vein to form a femoral arteriovenous shunt. The catheters were connected to a second Masterflex roller pump with an identical configuration to that used for the pulmonary-jugular shunt. Second, another set of ultrasonic crystals were sutured on the MPA to measure the length of a segment of the main pulmonary artery (L) simultaneously with diameter. Those crystals were mounted orthogonally on a Dacron patch with a polystyrene support. Pulmonary arterial segment length was recorded instead of airway pressure.

Recording techniques. The analog signals of pulmonary arterial pressure, right ventricular pressure, aortic flow, pulmonary-jugular shunt flow, pulmonary arterial diameter, airway pressure, the QRS triggered pulse and the ventilator triggered pulse were passed directly to an AT compatible computer with an analog to digital conversion board (Data Translation 2801A, Malborough, MA) recording at a sampling rate of 50 Hz per channel. At end expiration, P_{pa}, D, aortic flow, pulmonary-jugular shunt flow, and either pulmonary arterial segment length or airway pressure were averaged over the next cardiac cycle which was identified by the QRS triggered pulse. Right ventricular end diastolic pressure (RVEDP) was identified from its relation to the QRS complex. The corresponding values were recorded on magnetic disk.

Protocols. Prior to data collection, we determined the maximum flow through the pulmonary-jugular shunt that could be achieved without causing collapse of the tubing in the roller pump to the approximately 0.7 $L \cdot min^{-1}$. Data collection was made for periods up to 20 min with changes in pressure and flow were made at approximately 3 min intervals. Data collection was started at zero time under control conditions which were defined as 5 cmH_2O PEEP and no flow through the pulmonary-jugular shunt. After 3 min, the pulmonary-jugular shunt flow was increased to maximum flow for 3 min and then returned to control conditions for 3 min. PEEP was then increased to 15 cmH_2O for 3 min prior to reinstituting the pulmonary-jugular shunt to maximum flow for 3 min. The shunt flow was discontinued and PEEP was maintained at 15 cmH_2O for 3 min before returning to control conditions for a further 3 min period.

This protocol was modified for a second series of experiments using a femoral arteriovenous shunt. The flow through the femoral arteriovenous shunt was limited only by the speed of the roller pump. After 3 min of control conditions, the pulmonary-jugular shunt was increased to maximum flow. Three min later, the femoral arteriovenous shunt was increased to maximum flow while the pulmonary-jugular shunt was continued. The pulmonary-jugular shunt flow was stopped 3 min later while the femoral arteriovenous shunt was continued for another 3 min before returning to control conditions. In two of the five experiments the sequence of pulmonary-jugular and femoral arteriovenous shunt flows was reversed. Data collection continued at 50 Hz per channel throughout the entire protocol.

Calculation of results. The average value of P_{pa}, $\dot{Q}_{pa}$, D and L of the entire ensemble from each experiment was subtracted for each value of P_{pa}, $\dot{Q}_{pa}$, D and L, respectively, in an attempt to avoid multicollinearity (Slinker and Glantz, 1985). The independent effects of pressure and flow on pulmonary arterial diameter and segment length were calculated in two stages. First, a multiple linear regression model was selected that best fit the data most efficiently in the statistical sense. Second, the coefficients are verified for lack of multicollinearity (Slinker and Glantz, 1985). It is apparent from fig. 1 that the pulmonary-jugular shunt not only increases flow through the main pulmonary artery, but also through the right ventricle. Therefore, it is conceivable that any dimensional change in the MPA could be related to changes in the right ventricular volume due to the increased flow. These changes maybe result from the right ventricle altering the geometry of the MPA, or by reflex effects via cardiac afferents. To test the possibility that the right ventricle participates in flow-mediated vasomotion, we also incorporated RVEDP as an indicator of altered right ventricular volume into the multiple linear regression.

Parameter estimation. Five different models were tested. The most efficient model represents a trade-off between reducing the residual sum of squares and increasing the number of parameters (coefficients) in the model.

$$\Delta D_{pa} = b_1 \Delta P_{pa} \qquad \text{(Model 1)}$$

$$\Delta D_{pa} = b_1\Delta P_{pa} + b_2\Delta P_{pa}^2 \quad \text{(Model 2)}$$

$$= b_1\Delta P_{pa} + b_3\Delta \dot{Q}_{pa} \quad \text{(Model 3)}$$

$$\Delta D_{pa} = b_1\Delta P_{pa} + b_4\Delta RVEDP \quad \text{(Model 4)}$$

$$= b_1\Delta P_{pa} + b_3\Delta \dot{Q}_{pa} + b_4\Delta RVEDP \quad \text{(Model 5)}$$

Because three of the models had the same number of parameters, the more commonly used *F* test was inappropriate and necessitated the use of other tests: the Akaike information criterion (Akaike, 1974) and the Schwarz criterion (Schwarz, 1978).

Selection of the best model does not ensure that the parameter estimation will yield meaningful results because of multicollinearity (Slinker and Glantz, 1985). Multicollinearity occurs when there is a close correlation between the predictor variables, for example between P and $\dot{Q}$, between P and RVEDP, or between RVEDP and $\dot{Q}$. To avoid harmful multicollinearity, four different criteria were used: (i) pairwise correlation coefficients between predictor variables less than 0.7 and greater than -0.7, (ii) variance inflation ratios less than 4, (iii) eigenvalues greater than 0.01, and (iv) condition indices less than 10 (Slinker and Glantz, 1985). All four criteria had to be fulfilled for the parameter estimate to be acceptable. The same procedure was followed for the estimation of the corresponding parameters for the effects of P_{pa}, $\dot{Q}_{pa}$ and RVEDP on L. The coefficients were expressed in the form of percent changes of D, L, P_{pa}, $\dot{Q}_{pa}$ and RVEDP from the corresponding average value of D, L, P_{pa}, $\dot{Q}_{pa}$ and RVEDP, respectively, in order to facilitate comparisons between effects of $P_{pa}$and $\dot{Q}_{pa}$ and between changes of D and L.

Statistical analysis. The coefficients for the effect of P_{pa} and $\dot{Q}_{pa}$ on D were assessed by the appropriate form of Student's *t*-test on the unweighted values. Analysis of variance with multiple factors was used to test the effects of PEEP, the pulmonary-jugular shunt and the femoral arteriovenous shunt on P_{pa}, $\dot{Q}_{pa}$, RVEDP, heart rate (HR), aortic flow ($\dot{Q}_a$). Statistical significance was accepted at the 5% level.

Results

Figure 2 shows an example of the sequential changes of mean P_{pa}, $\dot{Q}_{pa}$ and D obtained with the protocol used in the first series of experiments. For each successive breath, data has been averaged over one cardiac cycle selected at end expiration for a period of approximately 20 min. Flow through the pulmonary-jugular shunt resulted in an increase in $\dot{Q}_{pa}$ and a slight decrease in P_{pa}. It was not possible to achieve pure changes of $\dot{Q}_{pa}$ without concomitant changes of P_{pa}. Therefore, it was necessary to use the multiple linear regression analysis to separate the independent effects of pressure and flow. Nevertheless, it is apparent from this figure that D did not decrease despite this decrease

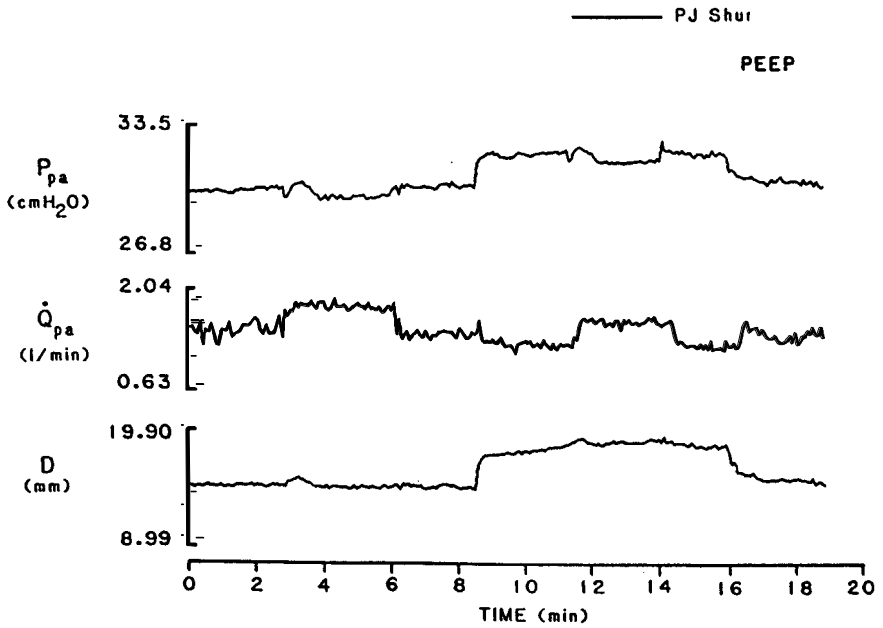

Fig. 2. Changes of pulmonary arterial transmural pressure (P_{pa}), flow ($\dot{Q}_{pa}$) and diameter (D) of the main pulmonary artery with time. PJ shunt indicates the period when there was flow through the pulmonary-jugular shunt. PEEP indicates the period when positive end-expiratory pressure was increased from 5 to 15 cmH_2O.

in P_{pa}. During the second period of the pulmonary-jugular shunt, a small increase of D is discernable. In this protocol, the level of PEEP was increased from 5 cmH_2O for control conditions to 15 cmH_2O to increase P_{pa}. Figure 3 shows the result of an experimental run obtained using the second protocol in which a femoral arteriovenous shunt was used to increase P_{pa} instead of PEEP which was held constant at 5 cmH_2O. Figure 3 shows the sequential changes that occur over a period of approximately 16 min plotted in a similar manner to fig. 2, but with an additional record showing sequential changes of the length of a segment of the MPA. Inspection of both figures indicates that the vast majority of the data is obtained under stable conditions; the transient states were brief.

The entire sequence of data obtained with these protocols were subjected to multiple linear regression to quantify the effects of changes of P_{pa}, $\dot{Q}_{pa}$ and RVEDP on D and L. The results for individual experiments are shown in table 1. In seven out of ten experiments model 5 provided the best fit, but on 3 of these occasions the coefficient for RVEDP could not be determined because of multicollinearity. Therefore, on these occasions model 3 was used to determine the coefficients for pressure and flow (C_p and C_q, respectively). Model 3 was the best fit in two experiments. In the remaining experiment, the nonlinear model (model 2) was tied with model 3 for being best fit. As a result of multicollinearity, for the coefficient C_{rv}, its magnitude could only be evaluated in 4 out of 10 occasions for diameter (mean value -0.046) and 2 out of 5 occasions

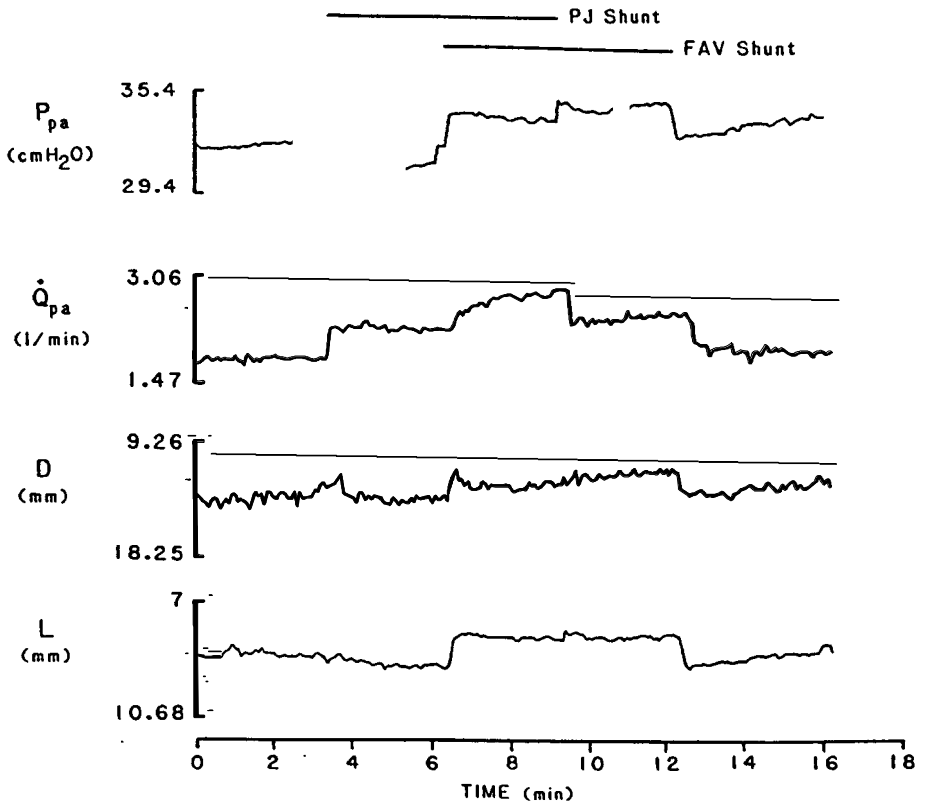

Fig. 3. Changes of pulmonary arterial transmural pressure (P_{pa}), flow ($\dot{Q}_{pa}$), diameter (D) and length of a segment of the main pulmonary artery with time. PJ shunt indicates the period when there was flow through the pulmonary-jugular shunt. FAV shunt indicates the period when there was flow through the femoral arteriovenous shunt.

for length (mean value −0.050). In all cases the coefficient C_{rv} had a negative sign suggesting that increases in RVEDP cause vasoconstriction. In contrast, C_q was positive in 9 out of 10 occasions for diameter and 5 out of 5 occasions for length, indicating that increases of flow causes vasodilatation and vasoelongation.

Figure 4 compares the coefficients for pressure and flow obtained in the first series with those obtained in the second series of experiments. No significant differences were found in C_p or C_q between the first and second series of experiments. In both series, C_p was on average 6 times greater than C_q. Therefore, a similar percent change of P_{pa} will cause 6 times greater change of diameter than the corresponding percent change of flow. Figure 5 shows results obtained with the second series of experiments. There were no significant differences between C_p and C_q for D, or between C_p and C_q for L.

Table 2 (series 1) shows mean P_{pa} and mean Q_{pa} averaged over the last minute of each period under the following conditions: (i) control conditions with 5 cmH_2O PEEP, (ii) increased pulmonary-jugular shunt flow, (iii) 15 cmH_2O PEEP and (iv) the combination of increased pulmonary-jugular shunt flow and PEEP. Analysis of variance with

TABLE 1

Effects of pressure and flow on main pulmonary arterial diameter and segment length.

Expt	Best fit	Diameter			Length			n
		C_p	C_q	C_{rv}	C_p	C_q	C_{rv}	
Series 1								
1	3	0.162 (0.002)	−0.006 (0.001)	0				270
2	5	0.056 (0.005)	0.033 (0.002)	−0.049 (0.002)				421
3	5	0.097 (0.007)	0.018 (0.001)	−0.060 (0.003)				316
4	5	0.288 (0.004)	0.019 (0.002)	0				277
5	5	0.065 (0.014)	0.048 (0.003)	0				253
Series 2								
6	5	0.301 (0.012)	0.021 (0.003)	−0.053 (0.002)	0.319 (0.009)	0.033 (0.002)	−0.028 (0.014)	207
7	5	0.246 (0.015)	0.030 (0.006)	0	0.032 (0.010)	0.025 (0.004)	0	209
8	3	0.133 (0.004)	0.021 (0.002)	0	0.165 (0.006)	0.035 (0.002)	0	201
9	2/3	0.053 (0.003)	0.003 (0.001)	0	0.122 (0.006)	0.013 (0.002)	0	215
10	5	0.128 (0.005)	0.023 (0.001)	−0.020 (0.002)	0.200 (0.002)	0.055 (0.002)	−0.072 (0.005)	206

Expt is the number of the experiment. Best fit refers to the multiple linear regression model number defined in Methods. C_p, C_q and C_{rv} are the coefficients of the regression equations for diameter and segment length; n is the number of data points in each data set. Coefficients are given as a dimensionless ratio (± 1 SE). 0 indicates that the coefficient could not be defined. The dash indicates that segment length was not measured in the first series of experiments.

multiple factors shows that pulmonary-jugular shunt increased $\dot{Q}_{pa}$ but there was no significant change of mean P_{pa}. PEEP increased mean P_{pa} but decreased $\dot{Q}_{pa}$. Table 2 (series 2) shows the pattern of changes of mean pulmonary artery pressure and flow that occur with pulmonary-jugular shunt and the femoral arteriovenous shunt with data analyzed in a similar manner. Pulmonary-jugular shunt again increased $\dot{Q}_{pa}$ but there was no significant change of mean P_{pa}. The femoral arteriovenous shunt flow significantly increased both mean $\dot{Q}_{pa}$ and P_{pa}. RVEDP increased with pulmonary-jugular shunt and PEEP, but there was no significant change in HR (table 2, series 1). $\dot{Q}_a$ decreased significantly with PEEP, but not with the pulmonary-jugular shunt. A similar pattern of results for RVEDP and HR occurred in the second series of experiments where flow was increased with a femoral arteriovenous shunt instead of increasing PEEP to elevate mean pulmonary artery pressure (table 2, series 2). Both types of shunt

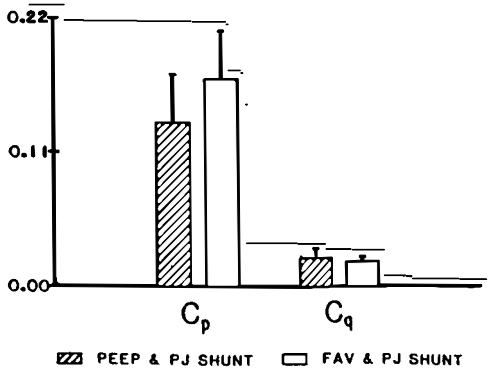

Fig. 4. The independent effects of pressure and flow on pulmonary arterial diameter. The effect of pressure is expressed as the percent change of diameter per percent change of pressure (C_p) and the effect of flow is expressed as the percent change of diameter per percent change of flow (C_q). Results are shown in the hatched bars for the first series of experiments in which both positive end expiratory pressure and the pulmonary jugular shunts were used (PEEP & PJ SHUNT), and in the open bars for the second series of experiments in which the pulmonary jugular and femoral arteriovenous shunts were used (FAV & PJ SHUNT). Data are shown as the mean and 1 SE.

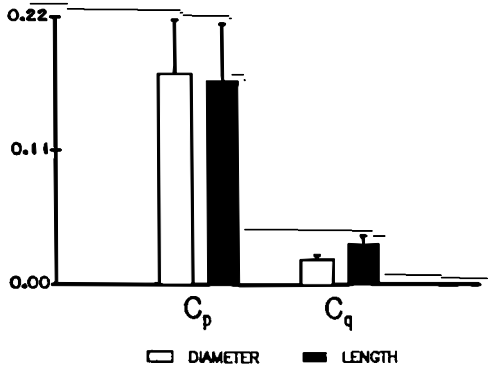

Fig. 5. The independent effects of pressure and flow on diameter compared with length of a segment of main pulmonary artery. Diameter changes are shown in the open bars and length changes are shown in the closed bars. The effect of pressure is expressed as the percent change of diameter (or length) per percent change of pressure (C_p) and the effect of flow is expressed as the percent change of diameter (or length) per percent change of flow (C_q). Data are shown as the mean and 1 SE.

increased RVEDP but did not affect HR. In contrast to PEEP, $\dot{Q}_a$ was increased by the femoral arteriovenous shunt but it was not affected significantly by the pulmonary-jugular shunt.

TABLE 2

Effects of positive end-expiratory pressure (PEEP), pulmonary-jugular (PJ) and femoral arteriovenous (FAV) shunts on hemodynamic variables.

Variables (units)	Conditions				Effects	
	Control	PJ	PEEP	PJ & PEEP	PJ	PEEP
Series 1						
P_{pa}	26.7	26.3	30.3	28.6	ns	
(cmH_2O)	(1.8)	(1.9)	(1.8)	(1.4)		
$\dot{Q}_{pa}$	1.67	2.10	1.24	1.73		
($L \cdot min^{-1}$)	(0.12)	(0.22)	(0.11)	(0.23)		
RVEDP	7.2	7.7	8.6	9.0		
(cmH_2O)	(0.7)	(1.1)	(0.7)	(1.1)		
HR	138	142	140	139	ns	ns
(min^{-1})	(6)	(10)	(7)	(11)		
$\dot{Q}_a$	1.67	1.50	1.24	1.13		
($L \cdot min^{-1}$)	(0.12)	(0.18)	(0.11)	(0.19)		
Series 2						
	Control	PJ	FAV	PJ & FAV	PJ	FAV
P_{pa}	27.4	26.6	29.8	29.3	ns	
(cmH_2O)	(3.0)	(3.2)	(3.1)	(3.1)		
$\dot{Q}_{pa}$	1.70	2.24	2.39	2.85		
($L \cdot min^{-1}$)	(0.27)	(0.29)	(0.36)	(0.37)		
RVEDP	9.6	10.1	10.2	10.8		
(cmH_2O)	(1.0)	(1.6)	(1.6)	(1.7)		
HR	139	139	146	146	ns	ns
(min^{-1})	(8)	(11)	(9)	(9)		
$\dot{Q}_a$	1.70	1.65	2.39	2.25	ns	
($L \cdot min^{-1}$)	(0.27)	(0.28)	(0.36)	(0.35)		

Variables: P_{pa} and $\dot{Q}_{pa}$ (pulmonary arterial pressure and flow, respectively), RVEDP (right ventricular end diastolic pressure), HR (heart rate), and $\dot{Q}_a$ (aortic flow) under four conditions. The statistical significance of the effects of PEEP, the PJ and FAV shunts are indicated as [a] ($P < 0.02$), [b] ($P < 0.005$), [c] ($P < 0.0001$) and ns (not significant). Data are shown as mean (± 1 SE).

Discussion

Limitations of methods. This paper describes a new experimental model for quantifying flow-mediated vasodilatation. It has the advantage of being able to make direct comparisons of the effects of flow with the effects of pressure on the MPA dimensions. In addition, the whole animal is used which avoids problems of simulating loading conditions of the vessel that is a problem with *in vitro* preparations. The problem of multicollinearity between pressure and flow was eliminated by the introduction of a

pulmonary-jugular shunt. This shunt increases flow through the MPA with only relatively small effects on transmural pulmonary arterial pressure and thereby avoided the close correlation between pressure and flow that is normally encountered under resting conditions. Although multicollinearity did not alter the ability to determine the independent effects of P_{pa} and $\dot{Q}_{pa}$, it did prove to be a problem in determining the independent effect of RVEDP in addition to P_{pa}, and $\dot{Q}_{pa}$. To determine the effects of RVEDP on D independent of the effects of P_{pa} and $\dot{Q}_{pa}$, additional experiments would have to be performed.

The first series of experiments were conducted with disparate methods for altering pressure and flow. The pulmonary-jugular shunt was used to increase $\dot{Q}_{pa}$ whereas PEEP was used to increase P_{pa}. PEEP is known to excite vagal reflexes (Cassidy *et al.*, 1979) although PEEP does not appear to have any significant vagally mediated effect on pulmonary arterial input impedance (Grant *et al.*, 1991). Increases in the level of PEEP could have altered the geometry of the MPA. Systematic differences could arise if the roller pump caused the release of vasoactive substances from the erythrocytes, leukocytes or platelets. To avoid these differences, a second series of experiments were conducted in which a femoral arteriovenous shunt was used instead of PEEP. Therefore, the same type of roller pump system was used to induce changes of both P_{pa} and $\dot{Q}_{pa}$. The results from both series of experiments were similar which suggests that these factors have little influence on the estimation of C_p or C_q. In both series of experiments, flow through the pulmonary-jugular shunt had no significant effect on heart rate or on $\dot{Q}_a$. This latter result is consistent with studies of the isolated heart: changes of left ventricular contraction affect right ventricular function but changes of right ventricular contraction do not influence left ventricular function (Elzinga *et al.*, 1980). Calculation of $\dot{Q}_{pa}$ as the sum of $\dot{Q}_a$ and $\dot{Q}_s$ neglects coronary blood flow. It is unlikely that changes of coronary blood flow had a substantial effect on our results because it accounts for less than 5% of left ventricular output (Cowley *et al.*, 1986).

All the protocols were conducted during anesthesia. Previous work suggests that chloralose anesthesia has no effect on cardiovascular function or vascular smooth muscle in dogs (Cox, 1972), nor does it alter flow-mediated vasodilatation in the large coronary arteries in dogs (Schwartz and Bache, 1987). The experimental design of the present study is limited to examining effects of mean pressure and mean flow on pulmonary arterial diameter and length. The effects of the oscillatory component of flow on pulmonary arterial diameter have yet to be determined. The methods and protocols used in this study were designed towards determining only the steady-state response. It is not possible from these data to determine a time course of flow-mediated vasodilatation because the transitionary periods were brief. To obtain information about the transient response, the protocols and data collection procedures would have to be altered substantially.

A systematic error in the measurement of the changes of transmural pressure could be attributed to changes of flow. The micromanometer is mounted on the side of the distal end of the catheter. Therefore, pressure is measured orthogonal to the direction of flow. This side pressure avoids any influence from kinetic energy changes that can

occur from direct impact of the stream on the micromanometer. The precise position of the catheter inside the vessel could not be monitored continuously and we cannot exclude the possibility of flow disturbances causing local pressure variations. Nevertheless, these events are more likely to cause random rather than systematic errors. The measurement of transmural pressure assumes that the extramural pressure is atmospheric. This assumption is reasonable because the chest was open and the MPA was dissected free from surrounding tissue.

A circular cross-sectional shape of the MPA is implicit in our analysis. Previous reports suggest that the MPA is elliptical in cross section but only with low pulmonary arterial pressures of less than 10 cmH_2O (Melbin and Noordergraf, 1971). Johnson *et al.* (1985) measured the degree of ellipticity in the anesthetized dogs with sonomicrometry. Their data indicates that the median ratio of the minor to major axes was 0.94 (range 0.59–1.0, $n = 9$). In addition, the changes of mean diameter in both axes were similar.

Mechanism of flow-mediated vasodilatation. In this preparation, flow-mediated vasodilatation could have originated from two sources: the right side of the heart or the MPA. Increased flow through the right ventricle could have distorted the anatomy of the MPA, or there may be a reflex effect on the MPA due to increased right ventricular pressure or volume mediated by cardiac afferents. In some experiments, RVEDP did exert an effect on pulmonary arterial diameter independent of pressure. In other experiments this effect could not be defined because of multicollinearity resulting from the direct relation between RVEDP and $\dot{Q}_{pa}$. Nevertheless, increased RVEDP was associated with vasoconstriction, therefore it could not account for flow-mediated vasodilatation.

The more likely possibility is that flow-mediated vasodilatation occurred due to mechanisms acting locally within the MPA. It is unlikely to be explained by a passive mechanical effect, therefore a humoral mechanism seems a more likely possibility. Flow may stimulate release of agents such as prostacyclin (Moncada and Vane, 1978), or nitric oxide (Palmer *et al.*, 1987). Nitric oxide is believed to be one of the endothelial derived relaxing factors (EDRF). There is some suggestion that EDRF is active in large pulmonary arteries of the isolated perfused canine lung. Acetylcholine-induced vasodilatation of large arteries can be blocked by methylene blue (Barman *et al.*, 1989). Although it is beyond the scope of the present study to distinguish between these possible mechanisms it does throw some light on the physiological significance of flow-mediated vasodilatation.

Significance of flow-mediated vasodilatation. Flow-mediated vasodilatation occurred in 9 of the 10 dogs studied. To our knowledge, this finding has not been reported previously in the pulmonary circulation. In addition, these experiments indicate that flow not only causes vasodilatation, but also vasoelongation. Flow-mediated vasoelongation had not been studied in the systemic vessels presumably because they are always considered to be strongly tethered by surrounding tissue. Nevertheless, the effect of flow-mediated

vasoelongation on resistance is small compared to flow-mediated vasodilatation because resistance is dependent upon the fourth power of diameter.

Although the effects of flow-mediated vasodilatation are small compared to those of pressure, this phenomenon may be of importance during exercise when large changes of flow in the MPA occur with relatively small changes of pressure. The fact that the MPA can respond to both pressure and flow suggests that a stretch receptor lying in the wall of the vessel could act to transduce changes of hydraulic power. Although baroreceptors have been demonstrated in the walls of proximal pulmonary arteries, it is unclear as to whether these receptors or others respond to stretch (Coleridge and Kidd, 1960).

It is unlikely that flow-mediated vasodilatation in the MPA has any significant effect on pulmonary vascular resistance because the main site of resistance seems to reside beyond the proximal pulmonary arteries (Dawson, 1984). Nevertheless, the diameter of the MPA may have an important influence on characteristic impedance and pulmonary arterial compliance (Grant and Canty, 1989). The major portion of pulmonary arterial compliance resides in the proximal pulmonary arteries, since the major portion of pulmonary arterial blood volume is located in those vessels (Dawson, 1984). Therefore, flow-mediated vasodilatation of the MPA may be of importance in modulating wave reflection through its effect on characteristic impedance (Fitzpatrick and Grant, 1990) or modulating right ventricular-vascular interaction through its effects on pulmonary arterial compliance (Piene and Sund, 1979).

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