

## Effects of Left Atrial Pressure on Pulmonary Shunt and the Dead Space/Tidal Volume Ratio

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The effects of changes in mean left atrial pressure ( $\overline{LAP}$ ) on pulmonary shunt ( $\dot{Q}_s/\dot{Q}_t$ ), dead space/tidal volume ratio ( $V_D/V_T$ ), respiratory rate ( $f$ ), and minute ventilation ( $\dot{V}$ ) were studied in 16 spontaneously breathing calves with artificial hearts for 4-24 days. Cardiac output and mean aortic, pulmonary arterial, and right atrial pressures were also measured. Pressure measurements were made from high-pressure tubing connected to taps in the chambers in the artificial hearts.  $\overline{LAP}$  was electively altered by changing heart rate from 50 to 150 beats/min or increasing or decreasing left ventricular air driving pressure and, thus, left ventricular contractility.  $\dot{Q}_s/\dot{Q}_t$  and  $V_D/V_T$  were determined via standard equations and cardiac output with the Fick technique while the calves breathed pure oxygen.  $\overline{LAP}$  in the range of 4-12 torr, whether produced by changing left ventricular air driving pressure or by changing heart rate, minimized  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ ,  $f$ , and  $\dot{V}$ . Alterations in  $\overline{LAP}$  within this "ideal" range did not influence  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ ,  $f$ , or  $\dot{V}$ , but changed cardiac output and pulmonary arterial, right atrial, and aortic pressures. Increases or decreases in  $\overline{LAP}$  out of the ideal range resulted in marked increases in  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ ,  $f$ , and  $\dot{V}$ . Correlation of  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ ,  $f$ , and  $\dot{V}$  with changes in  $\overline{LAP}$  from the ideal range were high,  $r = .71-.96$ . These data indicate that there exists an ideal range of  $\overline{LAP}$  that optimizes the matching of ventilation and perfusion in the lung, and that  $\overline{LAP}$  outside of this range may be associated with marked increases in respiratory rate, minute ventilation, venous admixture, and dead space ventilation. (Key words: Lung; blood flow; intravascular pressures; shunting; dead space. Ventilation: dead space; perfusion; shunting. Heart: artificial; vascular pressures.)

RECENT ADVANCES in the development of an artificial heart to replace the natural heart of the patient who has uncorrectable or untreatable heart disease have made available a unique animal model for study of complex cardiopulmonary interactions.<sup>1</sup> This model, the healthy unanesthetized calf with its natural heart removed and replaced with a pneumatic artificial heart, allows complete, non-pharmacologic control of cardiac function with the turn of one or more dials on the extrathoracic control module. Thus, the model

allows study of the effects of specific elements of cardiac function on the lung in an animal that is unanesthetized and has intact central nervous and peripheral vascular systems. In this study the bovine artificial heart model was used to determine the effects of changes in mean left atrial pressure ( $\overline{LAP}$ ) on the matching of ventilation and perfusion ( $\dot{V}/\dot{Q}$ ) in the lung as measured by pulmonary shunting ( $\dot{Q}_s/\dot{Q}_t$ ) and dead space/tidal volume ratios ( $V_D/V_T$ ).

### Methods

The experimental subjects were 16 83-91-kg Holstein bull calves trained to stand in response to the audible stimulus of a hand clap. Each calf was anesthetized with sodium methohexital, 3-5 mg/kg, intravenously, the trachea intubated, and the anesthesia maintained with halothane, 1-2 per cent. After excision of the natural heart, artificial heart implantation using a silicone rubber or polyurethane elliptical type of artificial heart was accomplished through a right lateral thoracotomy as previously described.<sup>2</sup> Mean right atrial ( $\overline{RAP}$ ), left atrial ( $\overline{LAP}$ ), pulmonary arterial ( $\overline{PAP}$ ), and aortic blood pressures and blood samples are obtained from high-pressure tubing connected to taps on the artificial atria and vascular grafts attaching the artificial ventricles to the natural pulmonary artery and aorta.

The system of artificial heart control used in these experiments, based on the maintenance of normal atrial pressures, has been described.<sup>3</sup> The control system is capable of independent frequency and percentage systole regulation with the turn of two dials on the control module. During this study, the artificial hearts were operated at heart rates that ranged from 50 to 150 beats/min with systole maintained at 30-40 per cent of the cardiac cycle. The control module also has independent right and left air drive line pressure dials, which change the rate of increase of the air drive line pressure and, thus, ventricular air pressures. The rate of increase of air pressure in the ventricle or the maximum rate of air pressure development ( $dP/dt_{max}$ ) in the ventricle during the isovolemic period of ventricular ejection is a measure of artificial heart ventricular contractility. Ventricular air driving pressures are measured in the air drive lines at the latter's exit from the control module with differential pressure transducers (Sanborn, model #267A) and are re-

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corded on an eight-channel Hewlett-Packard recorder. There is insignificant pressure drop between air drive line pressure at the control module and pressures in the ventricles, and values of air pressure  $dP/dt_{max}$  in the drive lines are the same as those in the ventricles.

Study procedures were initiated 4–24 days after artificial heart implantation, when arterial carbon dioxide tension ( $P_{aCO_2}$ ) had been 40 torr or less and arterial oxygen tension ( $P_{aO_2}$ ) had been 70 torr or more for six or more hours during breathing of room air. The calves were placed in a specially designed calf cage and had their right and left ventricle air drive line pressures set at 1.5 and 5.0, psi respectively. These pressures produced right ventricular  $dP/dt_{max}$  values between 675 and 815 torr/sec and left ventricular  $dP/dt_{max}$  between 2,859 and 3,146 torr/sec.<sup>†</sup> Heart rate was adjusted to 90 beats/min. Following this, the animals breathed oxygen through a specially designed airtight calf face mask. Inspiratory and expiratory “J” valves (Collins model #P-304) were attached to the mask portals; the inspiratory valve was connected to a source of oxygen and the expiratory valve to a Douglas bag for collection of mixed expired gas. After 20 min of breathing oxygen, pulmonary arterial and aortic blood samples were obtained (for oxygen content determination), mixed expired gas was analyzed for carbon dioxide tension and heart rate, and PAP, LAP, RAP, and mean aortic pressures were recorded. Oxygen uptake (corrected to STPD), respiratory rate ( $f$ ), tidal ( $V_T$ ) and minute volume ( $\dot{V}$ ) were then measured over a 3-min period by removing both “J” valves from the mask portals, attaching one of the portals to a standard 9-l, oxygen-filled Collins closed-circuit spirometer equipped with water and  $CO_2$ , absorbers and plugging the other portal of the face mask.

Cardiac output ( $\dot{Q}_t$ ) in l/min was calculated using the Fick equation.  $V_D/V_T$  was determined using the modified Bohr equation and  $\dot{Q}_s/\dot{Q}_t$  was measured utilizing either the standard or the modified shunt equation.  $P_{aCO_2}$  was measured with a Severinghaus electrode,  $pH$  with a Radiometer glass electrode, and  $P_{aO_2}$  with a modified Clark electrode. All electrodes were maintained at 39 C\*\* and frequently recalibrated with standard solutions and gases of known concentration and tension. Oxygen saturation was determined with an American Optical Company oximeter and hemoglobin with a Fisher Hemophotometer. Rectal temperature was monitored with a Yellow springs temperature probe and recording module. It was assumed that 1 g of fully oxygenated calf blood

<sup>†</sup> These are considered normal right and left ventricular  $dP/dt_{max}$  values in calves of this age.

\*\* Normal temperature for a calf.

combined with 1.39 ml of oxygen. Blood oxygen content in volumes per cent was calculated from hemoglobin capacity, oxygen saturation, and dissolved oxygen according to the following equation:

$$\text{Oxygen content} = (1.39 \times \text{g Hb}/100 \text{ ml blood}) \\ \times (\% \text{ Hb saturation}) + 0.0031 \times P_{aO_2}$$

Following collection of control data, the calves were disconnected from the spirometer and reconnected to the source of oxygen. LAP was then electively altered by increasing or decreasing left ventricular air driving pressure (thus changing left ventricular  $dP/dt_{max}$ ) in increments of 0.25 psi from 5 to 6.5 psi and 5 to 3 psi.<sup>††</sup> An equilibration period of 15 min was allowed after each change in air drive line pressure before left ventricular  $dP/dt_{max}$  and PAP, RAP, LAP, and mean aortic blood pressures were remeasured; mixed expired gas and pulmonary arterial and aortic blood samples were again collected. The animals were then reconnected to the spirometer and all values were redetermined.

LAP was also altered in each animal via elective changes in heart rate in increments of 10 beats/min from 90 to 150 and from 90 to 50 beats/min.<sup>‡‡</sup> As with changes in the left ventricular air driving pressure, an equilibration period of 15 min was allowed after each change in rate before pressure and spirometric measurements were made, blood samples were collected and analyzed, and cardiac output, shunt and dead space/tidal volume ratios calculated. Effects of changes in left ventricular air driving pressure and heart rate were measured in duplicate in each animal studied. All data were examined for significance utilizing Student's *t* test for paired data.

## Results

Increases and decreases in left ventricular air driving pressure from the control level (5 psi) produced no significant change in arterial or mixed venous blood gas or  $pH$  values in the range of 3.75–5.75 psi, but caused significant increases in mixed venous blood  $P_{O_2}$  and decreases in  $P_{aO_2}$  in the range of 6–6.5 psi (table 1). Mixed venous blood  $P_{CO_2}$  was increased and arterial and mixed venous blood  $P_{O_2}$  and  $pH$  decreased in the range of 3–3.5 psi. Extremes

<sup>††</sup> In half of the calves air driving pressure and heart rate were gradually increased or decreased from control values and in the other half increased or decreased to maximal or minimal values and then gradually returned to control values. Since data obtained were similar irrespective of the sequence of air driving pressure or heart rate changes, all data were combined.

<sup>‡‡</sup> Heart rate-induced changes in LAP were studied on the same day or the day after air driving pressure-induced changes were studied.

TABLE 1. Effects of Changes in Left Ventricular Air Driving Pressure and Heart Rate on Arterial and Mixed Venous Blood Gases and pH (Mean  $\pm$  SD)

| Myocardial Function                         | Unit Interval | Arterial Blood             |                             |                 | Mixed Venous Blood         |                             |                 |
|---|---------------|----------------------------|-----------------------------|-----------------|----------------------------|-----------------------------|-----------------|
|   |               | P <sub>O<sub>2</sub></sub> | P <sub>CO<sub>2</sub></sub> | pH              | P <sub>O<sub>2</sub></sub> | P <sub>CO<sub>2</sub></sub> | pH              |
| Left ventricular air driving pressure (psi) | 6.00-6.50     | 271 $\pm$ 25*              | 29 $\pm$ 5                  | 7.44 $\pm$ .03  | 49 $\pm$ 3*                | 34 $\pm$ 4                  | 7.42 $\pm$ .03  |
|   | 5.25-5.75     | 310 $\pm$ 31               | 34 $\pm$ 4                  | 7.43 $\pm$ .03  | 43 $\pm$ 4                 | 38 $\pm$ 3                  | 7.40 $\pm$ .03  |
|   | 4.50-5.00     | 353 $\pm$ 23               | 34 $\pm$ 3                  | 7.41 $\pm$ .03  | 39 $\pm$ 4                 | 38 $\pm$ 4                  | 7.38 $\pm$ .03  |
|   | 3.75-4.25     | 312 $\pm$ 28               | 36 $\pm$ 3                  | 7.39 $\pm$ .03  | 34 $\pm$ 3                 | 39 $\pm$ 3                  | 7.37 $\pm$ .03  |
|   | 3.00-3.50     | 61 $\pm$ 37                | 30 $\pm$ 3                  | 7.34 $\pm$ .05* | 31 $\pm$ 5*                | 43 $\pm$ 4*                 | 7.29 $\pm$ .04* |
| Heart rate (beats/min)                      | 140-150       | 109 $\pm$ 49*              | 29 $\pm$ 4                  | 7.34 $\pm$ .04* | 34 $\pm$ 5*                | 45 $\pm$ 3*                 | 7.29 $\pm$ .03* |
|   | 120-130       | 298 $\pm$ 26*              | 35 $\pm$ 3                  | 7.39 $\pm$ .03  | 39 $\pm$ 3                 | 39 $\pm$ 4                  | 7.35 $\pm$ .04  |
|   | 70-110        | 364 $\pm$ 23               | 30 $\pm$ 3                  | 7.42 $\pm$ .03  | 43 $\pm$ 4                 | 35 $\pm$ 3                  | 7.39 $\pm$ .03  |
|   | 50-60         | 122 $\pm$ 53*              | 28 $\pm$ 5                  | 7.33 $\pm$ .04* | 35 $\pm$ 5*                | 46 $\pm$ 4*                 | 7.29 $\pm$ .03* |

\*  $P < .05$ , Student's  $t$  test for paired data, compared with 4.50-5.00 psi air driving pressure or 70-110 beats/min heart rate.

of heart rate produced significant decreases in Pa<sub>O<sub>2</sub></sub> and mixed venous blood P<sub>O<sub>2</sub></sub> and pH and increases in mixed venous blood P<sub>CO<sub>2</sub></sub>.

Alterations in left ventricular air driving pressure from control (5 psi) resulted in marked and positively correlated changes in aortic blood pressure and cardiac output and negatively correlated changes in LAP, RAP, and PAP (table 2). Heart rate manipulations also produced significant changes in all of the above-mentioned variables (table 3), but the correlations were more complex. Heart rate manipulations produced little change in cardiac output within the range of 70-100 beats/min and in LAP, in the range of 70-120 beats/min. In contrast, heart rates of 50 and 60 and 130-150 beats/min produced marked decreases in cardiac output and increases in LAP.

Mean aortic pressure was inversely and highly correlated ( $r = .91$ ) with LAP values over the entire range of LAP produced in these experiments. Alterations in cardiac output produced by changes in left ventricular air driving pressure were also inversely and highly correlated ( $r = .90$ ) with LAP values. Correlation of LAP and  $\dot{Q}_t$  values during heart rate manipulations was less close ( $r = .71$ ). An important reason for the latter was the difficulty in producing low atrial pressures with high heart rates in an artificial heart with four artificial valves. Changes in LAP values of less than 8 torr resulted in little change in PAP and RAP whether the changes in LAP were obtained via heart rate or left ventricular air drive line pressure manipulations. Changes in LAP greater than 8 torr were directly related to increases in PAP and RAP.

Within the range of 4-12 torr, LAP was associated with  $\dot{Q}_t/\dot{Q}_i$  values that averaged 10 per cent (normal for a calf) irrespective of whether they were the result of changes in left ventricular air driving pressure or changes in heart rate (Fig. 1). On the other hand, LAP values between 16 and 20 and 0-2 torr

were associated with significantly higher  $\dot{Q}_t/\dot{Q}_i$ , and LAP values greater than 20 torr and less than 0 torr with markedly increased pulmonary shunts. LAP values outside the 4-12 torr range also produced increases in  $V_D/V_T$ ,  $\dot{V}$ ,  $f$ , and  $V_T$ , which became more marked at LAP values greater than 20 and less than 0 torr and were directly related to the difference in LAP from the "ideal" range (figs. 2-5). Correlation of  $\dot{Q}_t/\dot{Q}_i$ ,  $V_D/V_T$ ,  $f$ ,  $V_T$  and  $\dot{V}$  values with LAP at LAP values greater than 8 torr were high,  $r = +.88$ ,  $r = +.71$ ,  $r = +.92$ ,  $r = -.90$  and  $r = +.91$ , respectively, and with LAP values less than 8 torr also high,  $r = +.92$ ,  $r = +.96$ ,  $r = +.92$ ,  $r = -.84$  and  $r = +.89$ . Correlation of  $\dot{Q}_t/\dot{Q}_i$ ,  $V_D/V_T$ ,  $f$ ,  $V_T$  and  $\dot{V}$  values with cardiac output was equally good at LAP values greater than 8 torr, but much less close ( $r = +.61$ ,  $r = +.63$ ,  $r = +.59$ ,  $r = -.51$  and  $r = +.60$ , respectively) at LAP values less than 8 torr. PAP was also reasonably well correlated with  $\dot{Q}_t/\dot{Q}_i$ ,  $V_D/V_T$ ,  $f$ ,  $V_T$ , and  $\dot{V}$  values at LAP values greater than 8 torr but poorly correlated at LAP values less than 8 torr.

## Discussion

Although it is well known that alterations in the cardiovascular system may be associated with marked changes in pulmonary dynamics, pulmonary mechanics, and ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) relationships,<sup>4-12</sup> the effects of changes in specific modalities of cardiac function on the lung have not been carefully studied. Furthermore, what studies that have been performed have produced conflicting results. Thus, while some<sup>5</sup> have found that hemorrhage-induced decreases in cardiac output increase  $\dot{Q}_t/\dot{Q}_i$ , others<sup>7,8</sup> have shown just the opposite. Explanations for the differences in results have included: the presence or absence of pulmonary atelectasis or edema, the effects of various mixed venous oxygen tensions and pH values on hypoxic pulmonary vasoconstriction, the influences of a variety of alveolar

TABLE 2. Effects of Changes in Left Ventricular Air Driving Pressure on Cardiovascular Dynamics in 16 Calves with Artificial Hearts (Mean  $\pm$  SD)

| Left Ventricular Air Driving Pressure (psi) | LAP (torr)  | Mean Aortic Pressure (torr) | FAP (torr)  | RAP (torr)  | Cardiac Output (l/min) |
|---|-------------|-----------------------------|-------------|-------------|------------------------|
| 6.50  | -2 $\pm$ 3* | 130 $\pm$ 7*                | 12 $\pm$ 2  | 0 $\pm$ 2   | 13.2 $\pm$ 0.7*        |
| 6.25  | 0 $\pm$ 2*  | 125 $\pm$ 8*                | 12 $\pm$ 2  | 0 $\pm$ 2   | 12.1 $\pm$ 0.6*        |
| 6.00  | 1 $\pm$ 2*  | 120 $\pm$ 7*                | 12 $\pm$ 2  | 1 $\pm$ 2   | 11.9 $\pm$ 0.8*        |
| 5.75  | 2 $\pm$ 2   | 113 $\pm$ 5                 | 12 $\pm$ 2  | 1 $\pm$ 2   | 11.0 $\pm$ 0.7*        |
| 5.50  | 3 $\pm$ 3   | 110 $\pm$ 5                 | 12 $\pm$ 3  | 2 $\pm$ 2   | 10.5 $\pm$ 0.8*        |
| 5.25  | 4 $\pm$ 2   | 109 $\pm$ 6                 | 12 $\pm$ 2  | 2 $\pm$ 2   | 9.8 $\pm$ 0.6          |
| 5.00  | 4 $\pm$ 2   | 108 $\pm$ 5                 | 12 $\pm$ 2  | 3 $\pm$ 2   | 9.3 $\pm$ 0.6          |
| 4.75  | 5 $\pm$ 2   | 107 $\pm$ 5                 | 13 $\pm$ 2  | 3 $\pm$ 2   | 8.5 $\pm$ 0.6          |
| 4.50  | 7 $\pm$ 2   | 105 $\pm$ 5                 | 13 $\pm$ 2  | 3 $\pm$ 2   | 7.7 $\pm$ 0.5          |
| 4.25  | 8 $\pm$ 2*  | 103 $\pm$ 5                 | 15 $\pm$ 2  | 3 $\pm$ 2   | 7.3 $\pm$ 0.6          |
| 4.00  | 12 $\pm$ 2* | 98 $\pm$ 5*                 | 17 $\pm$ 2* | 4 $\pm$ 3   | 6.8 $\pm$ 0.6*         |
| 3.75  | 15 $\pm$ 2* | 95 $\pm$ 5*                 | 18 $\pm$ 3* | 7 $\pm$ 2*  | 6.2 $\pm$ 0.5*         |
| 3.50  | 17 $\pm$ 3* | 92 $\pm$ 5*                 | 20 $\pm$ 3* | 9 $\pm$ 3*  | 4.5 $\pm$ 0.4*         |
| 3.25  | 24 $\pm$ 4* | 86 $\pm$ 6*                 | 29 $\pm$ 4* | 14 $\pm$ 3* | 3.5 $\pm$ 0.4*         |
| 3.00  | 29 $\pm$ 4* | 82 $\pm$ 5*                 | 35 $\pm$ 4* | 17 $\pm$ 4* | 3.1 $\pm$ 0.5*         |

\*  $P < .05$ , Student's *t* test for paired data, compared with values obtained with left ventricular air driving pressure at 5.0 psi.

TABLE 3. Effects of Changes in Heart Rate on Cardiovascular Dynamics in 16 Calves with Artificial Hearts (Mean  $\pm$  SD)

| Heart Rate (Beats/Min) | LAP (torr)  | Mean Aortic Pressure (torr) | FAP (torr)  | RAP (torr)  | Cardiac Output (l/min) |
|------------------------|-------------|-----------------------------|-------------|-------------|------------------------|
| 150                    | 22 $\pm$ 4* | 91 $\pm$ 7*                 | 28 $\pm$ 4* | 10 $\pm$ 3* | 4.1 $\pm$ 0.6*         |
| 140                    | 16 $\pm$ 3* | 94 $\pm$ 6*                 | 20 $\pm$ 3* | 7 $\pm$ 3   | 4.5 $\pm$ 0.5*         |
| 130                    | 12 $\pm$ 3* | 94 $\pm$ 6*                 | 18 $\pm$ 2* | 6 $\pm$ 3   | 6.0 $\pm$ 0.6*         |
| 120                    | 7 $\pm$ 3   | 101 $\pm$ 6                 | 14 $\pm$ 2  | 4 $\pm$ 3   | 10.9 $\pm$ 0.6*        |
| 110                    | 6 $\pm$ 3   | 115 $\pm$ 7                 | 14 $\pm$ 4  | 5 $\pm$ 2   | 13.2 $\pm$ 0.8*        |
| 100                    | 5 $\pm$ 2   | 113 $\pm$ 6                 | 13 $\pm$ 3  | 5 $\pm$ 2   | 10.5 $\pm$ 0.8         |
| 90                     | 6 $\pm$ 2   | 109 $\pm$ 6                 | 13 $\pm$ 2  | 4 $\pm$ 2   | 9.9 $\pm$ 0.9          |
| 80                     | 7 $\pm$ 2   | 108 $\pm$ 6                 | 13 $\pm$ 2  | 6 $\pm$ 2   | 9.4 $\pm$ 0.8          |
| 70                     | 7 $\pm$ 3   | 107 $\pm$ 6                 | 14 $\pm$ 2  | 5 $\pm$ 3   | 8.6 $\pm$ 0.9          |
| 60                     | 12 $\pm$ 3* | 96 $\pm$ 6*                 | 16 $\pm$ 3  | 7 $\pm$ 2   | 7.0 $\pm$ 0.5*         |
| 50                     | 21 $\pm$ 3* | 89 $\pm$ 7*                 | 25 $\pm$ 4* | 8 $\pm$ 3   | 4.0 $\pm$ 0.5*         |

\*  $P < .05$ , Student's *t* test for paired data, compared with values obtained with heart rate at 90 beats/min.

oxygen tensions on pulmonary vascular resistance, and differences in intrapleural pressures, as generated by controlled versus spontaneous ventilation, on the distribution of pulmonary blood flow within the lung.

In two recent reports,<sup>1,13</sup> we demonstrated that in unanesthetized, spontaneously breathing calves changes in cardiac output could produce increases, decreases, or no change in  $\dot{Q}_s/\dot{Q}_t$  or  $V_D/V_T$ , depending on the direction and magnitude of the changes. Our data suggested that such calves have an "ideal" range of cardiac output in which  $\dot{Q}_s/\dot{Q}_t$  and  $V_D/V_T$  are optimal, and this ideal range is altered by position, exercise and metabolic state. Changes in cardiac output within the ideal range did not influence  $\dot{Q}_s/\dot{Q}_t$  or  $V_D/V_T$ , although increases or decreases outside the ideal cardiac output range produced marked increases and in both  $\dot{V}/\dot{Q}$  variables, as well as significant alterations in respiratory rate and tidal and minute respiratory volumes. In subsequent study,<sup>14</sup> we found that the ratio of right ventricular contractility to

left ventricular contractility (as measured by right ventricular/left ventricular  $dP/dt_{max}$ ) also influenced pulmonary performance. Results of the latter investigation indicated that there is an ideal range of ventricular  $dP/dt_{max}$  ratios for standing animals so that pulmonary compliance is maximal and absolute  $\dot{V}/\dot{Q}$  mismatching and minute ventilation are minimal. This ideal range of contractility ratios differed in different animals and also differed in the same animal in altered positions, *i.e.*, lying down versus standing.

None of the above-mentioned investigations provided evidence to show whether the primary cardiovascular factor altering  $\dot{Q}_s/\dot{Q}_t$  and  $V_D/V_T$  was blood flow through lungs or a change in peripulmonary (pulmonary arterial or left atrial) pressure. As a result, it was difficult even to speculate about the mechanism(s) producing the observed changes in  $\dot{V}/\dot{Q}$  matching. The results of this study document the relationship of cardiac output to  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ , and  $\dot{V}$  seen in our previous investigations, but suggest that LAP plays a much more influential role in altering all of these vari-

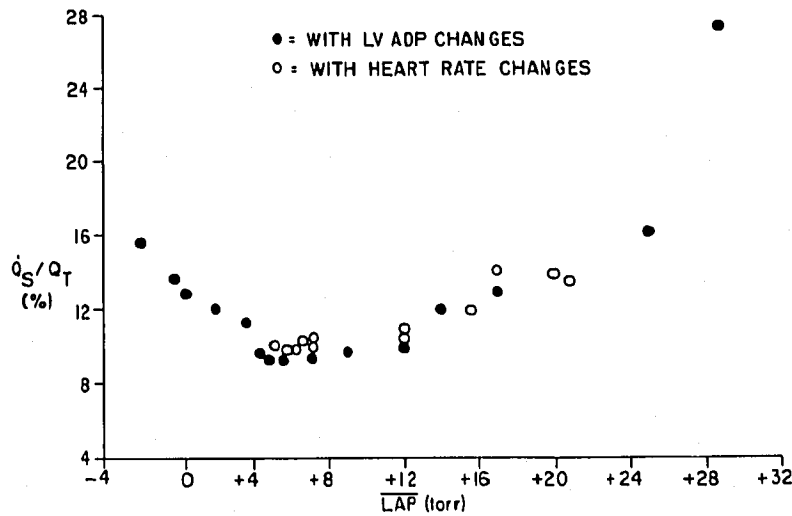


FIG. 1. Changes in mean left atrial pressure versus pulmonary shunt with manipulations of heart rate and left ventricular air driving pressure. Each symbol represents the mean of data for 16 calves.

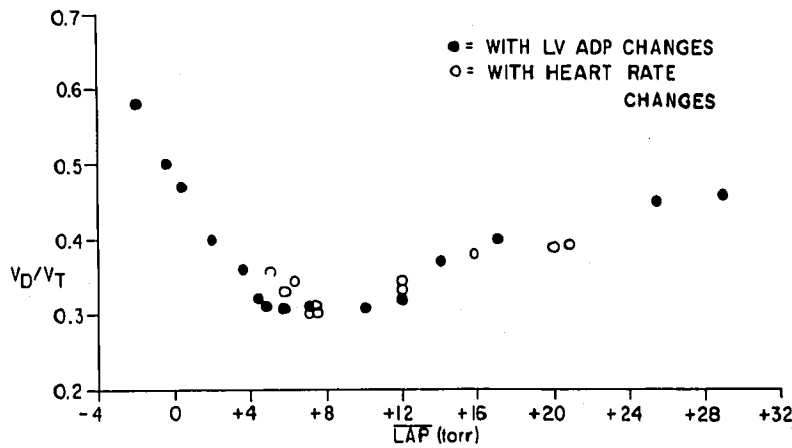


FIG. 2. Changes in mean left atrial pressure versus dead space/total tidal volume with manipulations of heart rate and left ventricular air driving pressure. Each symbol represents the mean of data for 16 calves.

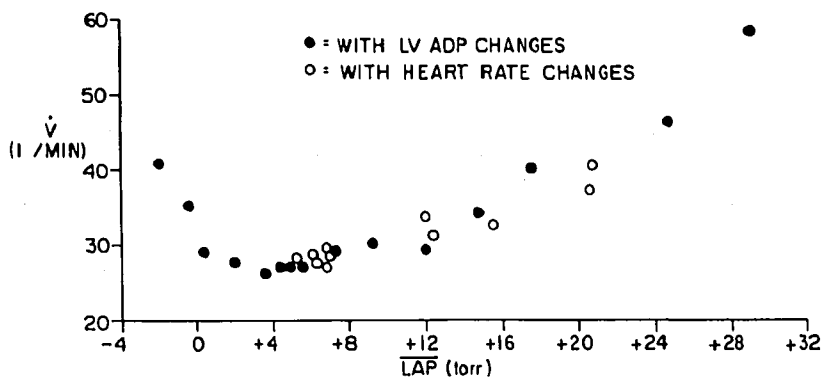


FIG. 3. Changes in mean left atrial pressure versus minute ventilatory volume with manipulations of heart rate and left ventricular air driving pressure. Each symbol represents the mean of data for 16 calves.

ables. This is probably best appreciated by comparing  $\dot{Q}_S/\dot{Q}_T$ ,  $V_D/V_T$ ,  $\overline{LAP}$ , and cardiac output changes produced by left ventricular air driving pressure manipulations with those resulting from alterations in heart rate. Examination of tables 2 and 3 and figures 1 and 2 demonstrates that changes in left ventricular air driving pressure produced an ideal range of

cardiac output (6–9 l/min) $\S\S$  at  $\overline{LAP}$  4–12 torr, which minimizes  $\dot{Q}_S/\dot{Q}_T$  and  $V_D/V_T$ . Cardiac output values outside the ideal range resulted in increases of both  $\dot{V}/\dot{Q}$  variables, as well as significantly higher or lower  $\overline{LAP}$  values. The results were somewhat different

$\S\S$  Normal for calves of this age and weight.

FIG. 4. Changes in mean left atrial pressure versus respiratory rate with manipulations of heart rate and left ventricular air driving pressure. Each symbol represents the mean of data for 16 calves.

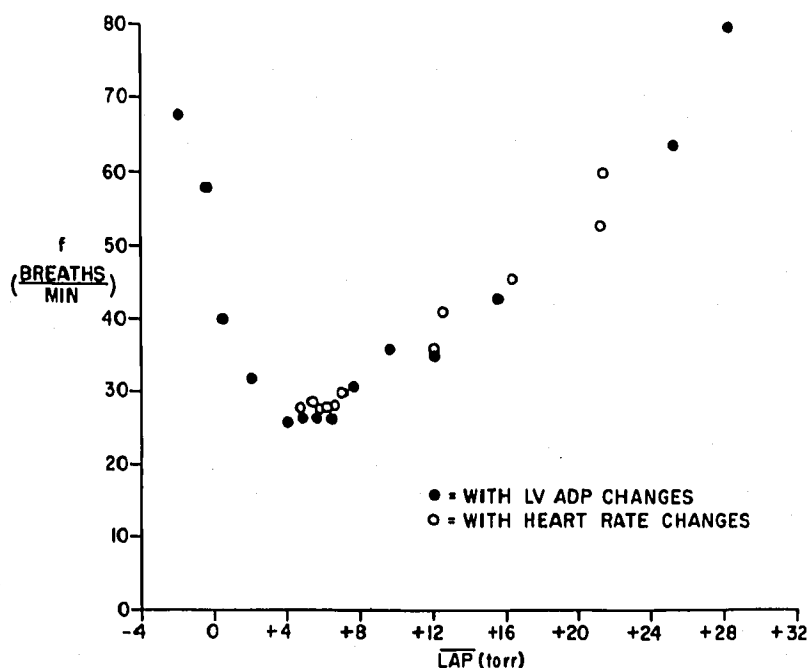
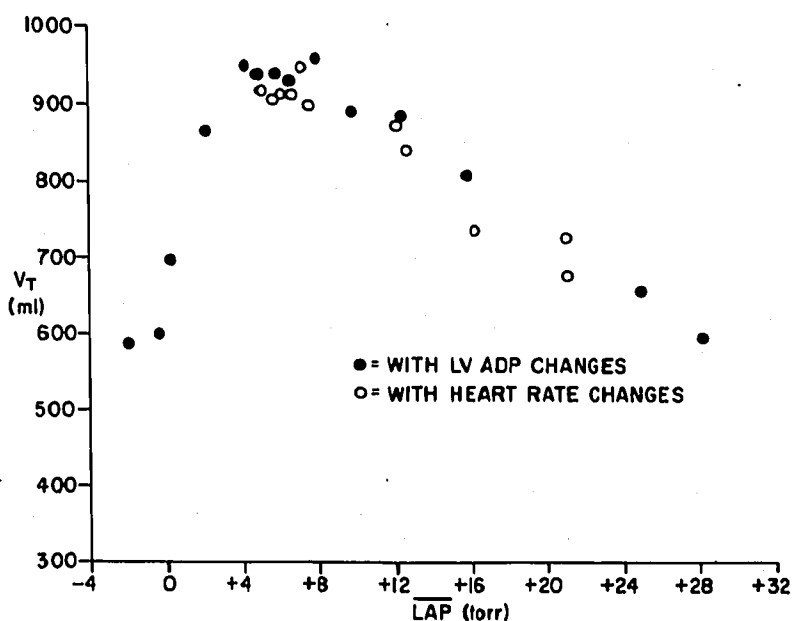


FIG. 5. Changes in mean left atrial pressure versus tidal volume with manipulations of heart rate and left ventricular air driving pressure. Each symbol represents the mean of data for 16 calves.



when cardiac output was altered by changing heart rate. In the latter situation low cardiac output (<5 l/min) was also associated with increased  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ , and  $\bar{LAP}$ . However, high cardiac output (>8 l/min) from heart rate manipulations did not alter  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ , or  $\bar{LAP}$ . Thus, while a cardiac output of 13.2 l/min at a heart rate of 110 beats/min and a left ventricular air driving pressure of 5 psi was associated with  $\bar{LAP}$  6 torr, a  $\dot{Q}_s/\dot{Q}_t$  of approximately 10 per cent and a  $V_D/V_T$  of 0.35§§ (table 3 and figures 1 and 2),

the same cardiac output at a heart rate of 90 beats/min and left ventricular air driving pressure of 6.5 psi was associated with  $\bar{LAP}$  -2 torr, a  $\dot{Q}_s/\dot{Q}_t$  of 16 per cent, and a  $V_D/V_T$  of 0.59 (table 2 and figures 1 and 2). The closer association of  $\dot{Q}_s/\dot{Q}_t$  and  $V_D/V_T$  with  $\bar{LAP}$  than with cardiac output or any other variable measured in this study suggests that  $\bar{LAP}$  plays a more important role in influencing pulmonary shunt and dead space than any other cardiovascular modality.

Decreases in arterial blood pressure and cardiac out-

put comparable to those seen in this study are known to increase respiratory dead space and  $V_D/V_T$ .<sup>5,6,10,15</sup> The mechanism has been demonstrated to be secondary to a decrease in pulmonary arterial pressure and perfusion of areas of high  $\dot{V}/Q$  in the lung, with a subsequent increase in zone 1.<sup>6</sup> Significant increases in  $V_D/V_T$  with corresponding increases in  $\overline{LAP}$  to above 16 torr in this study are more difficult to explain because high  $\overline{LAP}$  values were associated with equally high PAP. The latter should have increased perfusion of pulmonary tissue with low  $\dot{V}/Q$  and decreased zone 1. However, increases in  $\overline{LAP}$  in this unanesthetized preparation also resulted in dramatic increases in respiratory rate and minute ventilation and a decrease in tidal volume. These changes were undoubtedly stimulated by pulmonary stretch receptors, which are not affected by implantation or function of an artificial heart. Increases in respiratory rate increase ventilation of lung tissue with high  $\dot{V}/Q$  ratios,<sup>15</sup> resulting in increased alveolar dead space and  $V_D/V_T$ .<sup>5,17</sup> Thus, the increase in  $V_D/V_T$  observed in this study at high  $\overline{LAP}$  may have been secondary to induced respiratory changes rather than a primary cardiovascular effect on the lung.

Although increases in  $\dot{Q}_s/\dot{Q}_t$  with  $\overline{LAP}$  values above 16 torr can be easily explained as due to a combination of rapid shallow respiration,<sup>5</sup> congestive atelectasis,<sup>7</sup> and impaired hypoxic vasoconstriction secondary to high  $\overline{LAP}$ ,<sup>18</sup> the mechanism producing increased  $\dot{Q}_s/\dot{Q}_t$  values at low  $\overline{LAP}$  is not so clear. One possible explanation could be that increased mixed venous blood oxygen tension associated with low  $\overline{LAP}$  and high cardiac output values reverses hypoxic vasoconstriction in poorly ventilated areas of the lung, thus allowing perfusion of low- $\dot{V}/Q$  regions of the lung and increasing  $\dot{Q}_s/\dot{Q}_t$ . Suter and co-workers<sup>19</sup> have presented evidence that this may be at least a partial explanation of the increased  $\dot{Q}_s/\dot{Q}_t$  that occurs during breathing of oxygen. The simultaneous and significant increases in mixed venous blood  $P_{O_2}$  and  $\dot{Q}_s/\dot{Q}_t$  with the high cardiac output and low  $\overline{LAP}$  associated with left ventricular air driving pressures of 6–6.5 psi (table 1) are consistent with impaired hypoxic vasoconstriction. Unfortunately, whether the increase in  $\dot{Q}_s/\dot{Q}_t$  could have been blocked by decreasing mixed venous blood  $P_{O_2}$  (by altering inspired oxygen concentration) while maintaining  $\overline{LAP}$  constant was not investigated in this study.

An alternative explanation for the increase in  $\dot{Q}_s/\dot{Q}_t$  observed with low  $\overline{LAP}$  values could be the significant increases in respiratory rate and minute volume and decrease in tidal volume that occurred concurrently. Simultaneous increases in  $\dot{Q}_s/\dot{Q}_t$ , respiratory rate, and minute ventilations and decreases in pulmonary ar-

terial wedge pressure and tidal volume in spontaneously breathing dogs subjected to hemorrhage have been observed by Malik and Newell.<sup>5</sup> In contrast, Wahrenbrock and co-workers<sup>7</sup> found that  $\dot{Q}_s/\dot{Q}_t$  remained unchanged or decreased with hemorrhage in a similar preparation in which respiration was controlled. It has been suggested that rapid shallow breathing may prevent full inflation of the lung and lead to atelectasis and increases in  $\dot{Q}_s/\dot{Q}_t$ .<sup>5</sup> On the other hand, increases in respiratory rate and minute ventilation may also produce wider-than-normal swings of intrapleural pressure. Wide swings in intrapleural pressure are known to redistribute pulmonary blood flow away from areas of normal  $\dot{V}/Q$  to areas of low or no ventilation.<sup>12</sup> Unfortunately, it was not possible to explore which, if either, of these mechanisms was responsible for the high  $\dot{Q}_s/\dot{Q}_t$  measured during conditions of low  $\overline{LAP}$  in this study.

The results of this investigation document that  $\overline{LAP}$ , or the change in respiration that accompanies a change in  $\overline{LAP}$  out of the normal range, plays an important role in influencing ventilation—perfusion relationships in the lung. Our data suggest that, at least in the unanesthetized, spontaneously breathing calf,  $\overline{LAP}$  may be more important than pulmonary arterial pressure or cardiac output in affecting distribution of blood flow. However, the calf lung has a two- to threefold greater vertical diameter than that of man and, probably because of this increased gravitational contribution to pulmonary venous pressure, the normal right-to-left shunt fraction (10 per cent) is significantly higher than that of normal man. These differences make it difficult to know whether changes in  $\overline{LAP}$  are as important in influencing pulmonary  $\dot{V}/Q$  relations in man as they are in the calf. The similarity of changes in respiratory dynamics,  $\dot{Q}_s/\dot{Q}_t$ ,  $V_D/V_T$ , and most other measures of ventilation—perfusion in response to pharmacologic or physiologic alterations in man and the calf<sup>1,20,21</sup> suggests, however, that  $\overline{LAP}$  probably plays as important a role in influencing  $\dot{V}/Q$  relations in man as it does in the calf.

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## Literature Briefs

Peter J. Cohen, M.D., Editor

Literature briefs were supplied by Drs. R. B. Clark and P. J. Cohen. Briefs appearing elsewhere in this issue are part of this column.

### Fetal Physiology

**DOPAMINE** The effects of dopamine on blood pressure and heart rate have been studied in continuously cannulated fetal lambs and adult sheep. Drugs were administered by direct intravenous injection into either the fetus or the adult sheep, and blood pressure was measured from an arterial cannula and heart rate was computed from the electrocardiogram (ECG). The magnitude of the fetal pressor response to dopamine increased slightly as the dose of dopamine increased (1, 10, 50, 100, and 200  $\mu\text{g}/\text{kg}$ ), but the magnitude of the response did not increase with advancing gestation (112 to 145 days). However, in the adult sheep, the dose-response relationship was much steeper. In both cases the pressor response was accompanied by a reflex bradycardia that was blocked by atropine (1 mg/kg). In the atropinized fetus, doses of 50-200  $\mu\text{g}/\text{kg}$  dopamine produced tachycardia (30 to 120 beats/min) and a greater pressor response than that in the unatropinized fetus. Thus, the fetal cardiovascular system is capable of responding to relatively large amounts of dopamine injected as a bolus, suggesting that relatively large amounts of endogenous

dopamine would have to be secreted by the mast cells to alter fetal cardiovascular function significantly. (Harris WH, and others, *The effects of dopamine on blood pressure and heart rate of the unanesthetized fetal lamb*, *Am J Obstet Gynecol* 130:211-215, 1978.)

### Obstetric Anesthesia

**BLOOD VOLUME** A great deal has been reported recently about the importance of hypovolemia in pre-eclampsia and eclampsia from the point of view of pathogenesis and management. Some authors even believe that the so-called hypovolemia represents an etiologic factor and should be "corrected." In this paper, the hemodynamic factors that maintain the circulation in the normal nonpregnant and pregnant states are discussed. These factors are then used as a background for explaining the pathophysiologic abnormalities of the acute hypertensive disease of pregnancy. It is concluded that the slight decrease in blood volume observed in pre-eclampsia has no hemodynamic relevance; the blood volume is merely "fitting" a contracted vascular bed. The major abnormality resides in the constricted arteriolar system and not in the blood volume. (Assali NS, and others, *Blood volume in pre-eclampsia: Fantasy and reality*, *Am J Obstet Gynecol* 129:355-359, 1977.)