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Research Article

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Regional Blood Flow Distribution in Dog during Induced Hypotension and Low Cardiac Output

SPONTANEOUS BREATHING VERSUS ARTIFICIAL VENTILATION

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ABSTRACT Respiratory muscle blood flow and organ blood flow was studied in two groups of dogs with radioactively labeled microspheres to assess the influence of the working respiratory muscles on the regional distribution of blood flow when arterial pressure and cardiac output were lowered by pericardial tamponade. In one group ($n = 6$), the dogs were paralyzed and mechanically ventilated (Mv), while in the other ($n = 6$), they were left to breathe spontaneously (Sb). Cardiac output fell to 30% of control values during tamponade in both groups and was maintained constant. None of the dogs was hypoxic. Ventilation in the Sb group peaked after 50 min of hypotension, but remained unchanged in the Mv group. Duplicate measurements of blood flow were made during a control period and after 50 min of tamponade (corresponding to the peak ventilation in Sb). Blood flow to the respiratory muscles increased significantly ($P < 0.001$) during tamponade in Sb (diaphragmatic flow increased to 361% of control values), while it decreased in Mv. Although the arterial blood pressure and cardiac output were comparable in the two groups, blood flow distribution during tamponade was different. In Sb, the respiratory muscles received 21% of the cardiac output, compared with only 3% in the Mv group. Thus, by muscle paralysis and Mv, a large fraction of the cardiac output used by the working respiratory muscles can be made available for perfusion of other organs during low cardiac output state: blood flows to the liver, brain, and quadriceps muscles were significantly higher during tamponade in the Mv group compared with the Sb group. Similarly, blood lactate at all times after the induction of low cardiac output and hypotension was significantly lower in the Mv animals ($P < 0.005$).

INTRODUCTION

The ability of skeletal muscle to sustain rhythmic contraction at high work rates depends upon muscle blood flow; while it is probable that this pertains equally to the respiratory muscles, few estimates of flow to these muscles have been made (1, 2). Although it has been shown that diaphragmatic perfusion is somewhat related to the level of cardiac output (3), Johnson and Reid (4) have shown in dogs that diaphragmatic blood flow is determined by the arterial pressure; this was found by paralyzing the diaphragmatic vasculature (by infusion of adenosine and nitroprusside) while the animals breathed against an inspiratory resistance and a low oxygen gas mixture. Predictably, respiratory muscle blood perfusion should be reduced during hypotension and/or low cardiac output. This prediction was tested in this study.

In the face of a decreased arterial blood pressure and cardiac output, respiratory muscle blood flow might become limited and thus be unable to maintain aerobic metabolism. Theoretically, this may lead to lactate production, respiratory muscle fatigue, and respiratory failure (5). Although the blood flow to the respiratory muscles under those conditions might be insufficient to support the energy demand of the work of breathing, it may still be inordinately large. One may therefore predict that during a low cardiac output state, if the respiratory muscles are at work, less blood will be available for the rest of the body than when

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these muscles are at rest. Thus, the aim of this investigation was to estimate the blood flow to the working respiratory muscles during a state of induced low cardiac output and hypotension, and to see to what extent the institution of artificial respiration would increase the perfusion of vital organs and reduce lactic acidosis.

METHODS

Animal preparation. 12 healthy adult mongrel dogs, weighing between 23 and 25 kg were studied in the supine position. They were anesthetized with an initial dose of 20 mg/kg sodium pentobarbital i.v. This was supplemented during the surgical procedure as required to maintain a constant level of anesthesia while keeping the corneal reflex intact. The animals were intubated with a No. 9.5 cuffed oroendotracheal tube and were mechanically ventilated with a Harvard respirator throughout the surgical procedure (Harvard Apparatus Co., Inc., The Ealing Corp., St. Natick, MA). Polyethylene catheters were placed into the right brachial and left femoral arteries for the monitoring of arterial blood pressure in duplicate. The signals were displayed on an oscilloscope and recorded on a Hewlett-Packard 8-channel strip chart recorder (Hewlett-Packard Co., Palo Alto, CA). The placement of two catheters allowed the frequent sampling of arterial blood gases, without interrupting the blood pressure tracing. The left brachial and right femoral arteries were also cannulated with polyethylene catheters for withdrawal of reference samples to determine blood flow. To avoid trapping microspheres between the arterial wall and the catheter, the ligature was tied as close as possible to the tip of the catheter. A silastic catheter was advanced into the pulmonary artery via the right jugular vein for withdrawal of mixed venous blood. An incision was made into the fifth left intercostal space for placement of a silastic catheter into the pericardial sac. A low cardiac output state and hypotension were produced by controlled cardiac tamponade as described by Pierce (6). A small polyvinyl catheter was also placed into the left atrium via the pulmonary vein of the left cardiac lobe of the lung for injection of the microspheres. The position of this catheter was always confirmed at the end of the experiment. After the catheters were positioned, the chest, in spontaneous breathing experiments, was closed and the residual pneumothorax expelled by vacuum suction through a catheter in the pleural space. The chest, in the artificial ventilation experiments was not surgically closed, although the ribs were brought close together. Throughout this procedure and throughout the period of tamponade the animals were on 5 cm H_2O positive end-expiratory pressure to prevent lung atelectasis and hypoxemia, both of which, from our previous experience, are very common in the absence of positive end-expiratory pressure.

Ventilation and blood gases. One group of dogs (n = 6) was left to breathe spontaneously throughout the experiment (Sb);[1] in this group, flow rate was measured with a Fleisch pneumotachograph and a MP 45 differential pressure transducer (Validyne Engineering Corp., Northridge, CA). The signal was integrated to measure changes in volume, and both were recorded on an 8-channel strip chart recorder. The other group of dogs (n = 6) was paralyzed with Pancuronium bromide (0.08 mg/kg) and was mechanically ventilated at a constant rate and volume throughout the experiment (Mv). Arterial and mixed venous blood was sampled every 10 min during the experiment and was analyzed for P_{O_2}, P_{CO_2}, and pH on a Corning 500 blood gas analyzer (Corning Glass Works, Science Products Div., Corning, NY). Blood lactate, serum creatinine, and urea were also measured, by standard techniques.

Cardiac output. Cardiac output was determined every 10 min by the oxygen Fick technique. Expired gas was collected into a Douglas bag for 3 min through the expiratory port of a two-way valve connected to the pneumotachograph. Arterial and mixed venous blood was sampled simultaneously during the second minute of the 3-min gas collection. O_2, CO_2, and N_2 concentrations were measured with a Perkin-Elmer mass spectrometer (Perkin-Elmer Corp., Instrument Div., Norwalk, CT). An IL 213 Co-Oximeter was used to analyze arterial and mixed venous oxygen contents. At each blood flow determination, cardiac output was also determined by the microsphere technique (described below), since measurement of cardiac output by an independent method may add a source of error when determining regional blood flow (7). However, our results, as obtained by the two techniques, were not different.

Blood flow determination. Respiratory muscle and organ blood flow was determined with a radioactive microsphere technique as described by Rudolph and Heymann (8). Carbonized radioactively labeled microspheres (25-μm diam) were obtained from the Nuclear Products Division of Minnesota Mining & Manufacturing Co., St. Paul, MN. While microspheres of 25 μm may not accurately describe regional differences within an organ, they accurately reflect total flow to an organ (9). Four different isotope labels were used (^{125}I, ^{85}Sr, ^{141}Ce, and ^{46}Sc) to make duplicate measurements of blood flow during control and after 50 min of tamponade. Injection of a particular isotope was random and was always varied. When injected into the circulation, the microspheres are distributed in proportion to flow and become entrapped in the microvascular beds of the organs. The relative radioactivity of an organ is then taken as an index of its relative blood flow. The principle has been validated for many organs (10–15), and the modification and reproducibility of the technique for measuring respiratory muscle blood flow have been described by Robertson et al. (9). Before injection, $\sim 10^6$ microspheres were collected into a cone-shaped injection chamber and mixed thoroughly with a vortex mixer. The chamber was then connected to the clamped left atrial catheter for injection.

When cardiac output, heart rate, and arterial blood pressure were stabilized, the microspheres, combined with 20 ml of saline at body temperature, were injected over 30 s into the left atrium. Although all the microspheres that leave the injection vial enter the left atrium after ~5 ml of injectate, it has been shown by Archie et al. (7) that an additional 10–15 ml of saline guarantees that there is no residual radioactivity in the catheters between the injection vial and the left atrium. Reference samples were collected at a constant rate (7.4 ml/min) with a Harvard infusion/withdrawal pump from the two reference arteries beginning 10 s before the injection of microspheres and continuing for 2 min thereafter. The use of two reference samples allows an index of randomness of mixing of the spheres. Where these counts differed by >10%, the runs were discarded. We calibrated the pump after each experiment with the animal's blood by timed volume collections.

The animals were killed at the end of the experiment with an overdose of anesthetic. All the respiratory muscles in the

[1] *Abbreviations used in this paper:* Mv, mechanical(ly) ventilation (ventilated); Sb, spontaneously breathing.

dog, as indentified by Miller et al. (16), were carefully dissected out. Other organs, such as the liver, were also excised, cleared of superficial fat, and weighed.

The tissues were cut into ~1-cm^3 pieces and placed into appropriately sized counting vials. The empty injection chambers, withdrawal syringes, catheters, stopcocks, reference bloods, tissues, and standards of ech isotope label used were counted in a Packard 5375 well-type scintillation counter (Packard Instrument Co., Downers Grove, IL) in four separate energy windows appropriate to the nuclides used. Corrections for spillover of counts between windows were made by solving a series of four simultaneous equations whose coefficients were determined for each experiment. The average count per sphere was used to show that each reference sample has at least 400 microspheres. This is the minimum number that allows enough precision of measurement of blood flow. Calculations by Buckberg et al. (14) show that this number allows 95% confidence that the values of blood flow reported were within 10% of true values. Muscle blood flow and cardiac output were then calculated with the following equations:

$$\text{Organ flow (ml/min)} = \frac{\text{arterial ref. flow (ml/min)} \times \text{organ nuclide activity}}{\text{arterial reference nuclide activity}};$$

$$\text{Cardiac output (ml/min)} = \frac{\text{organ flow (ml/min)}}{\text{organ nuclide activity/injected nuclide activity}}.$$

Experimental protocol. 1 h after the completion of the surgical procedure, control measurements were made in both groups of dogs. Arterial and mixed venous blood gases, serum lactate, and expired gas volume and concentrations were measured, and $\dot{V}O_2$ and cardiac output were calculated by the Fick principle. When blood pressure and heart rate were stable, duplicate injections of microspheres were performed for control blood flow determinations in both groups.

Tamponade was then induced by injecting warm saline (37°C) through the catheter fitted into the pericardium until the cardiac output decreased to 30% of control values. It was maintained at that level throughout the run in both groups by adjusting the volume of pericardial fluid. Simultaneously, the arterial blood pressure decreased, averaging ~55 mmHg, and was also maintained constant throughout the run. The mixed venous oxygen tension, which was measured every 5 min remained at ~25 mmHg.

Cardiac output, arterial and mixed blood gases, serum lactate, and $\dot{V}O_2$ were measured throughout the hypotensive period in both groups every 10 min. Microspheres were again injected (in duplicate) 50 min after the induction of tamponade in both groups. This corresponded to the time of peak ventilation in the Sb animal.

Statistical analyses were performed using either Student's *t* test or the analysis of variance accordingly.

RESULTS

Fig. 1 depicts the time course of ventilation during tamponade in the two groups of dogs. It can be seen that in the Sb group, ventilation increased progres-

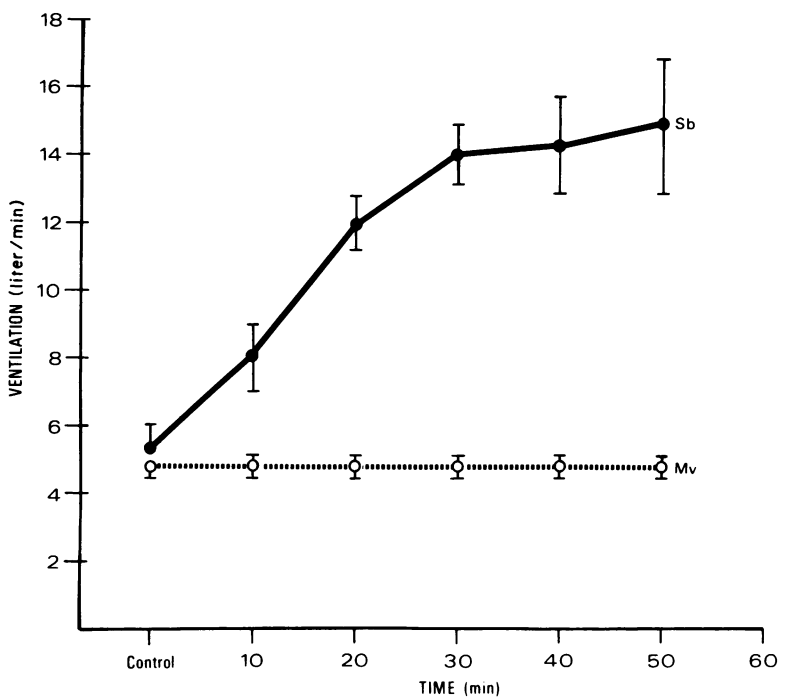

FIGURE 1 Mean changes in minute ventilation during tamponade. Solid line represents the Sb dogs, hatched line the Mv animals. Bars are standard error. Ventilation increased progressively throughout the hypotensive period in Sb, reaching a peak value 50 min (average) after the onset of tamponade. It remained unchanged in the Mv group.

sively from a control value of 5.21±0.84 (mean±SE) liters/min to reach a peak value of 14.85±2.6 (mean±SE) liters/min ($P < 0.001$) on the average 50 min after the onset of tamponade. In the Mv group, ventilation remained constant throughout the experiment at 4.75±0.31 (mean±SE) liters/min. Cardiac output (Fig. 2) was not significantly different between the two groups during control, being 2.02±0.08 and 1.96±0.09 liters/min (mean±SE) for the Sb and Mv groups, respectively ($P < 0.1$). It fell during tamponade by 70% in both groups and thereafter remained unchanged (0.6±0.07 liters/min in the Sb and 0.62±0.06 liters/min in the Mv animals).

Arterial systolic blood pressure fell during tamponade from control values of 185±5 and 180±6 mmHg to 55±2 and 54±1 mmHg (mean±SE) in the Sb and Mv groups, respectively. Heart rate, as measured from the blood pressure tracing, averaged 168±5 and 172±4 beats/min during the control period, and increased after the induction of tamponade to 288±6 and 271±8 beats/min (mean±SE) in the Sb and Mv dogs, respectively. It should be noted that after hypotension had stabilized (5–10 min), there was no further change in either of these parameters throughout the period studied (50 min).

None of the dogs was hypoxemic at any time (Fig. 3). It should be noted that the statistical appraisal between the two groups regarding the difference in P_{O_2}, P_{CO_2}, pH, and lactate was made with the analysis of variance. Arterial pH at any given time of the hypotensive period in Sb was significantly lower ($P < 0.01$) than in Mv animals, except during the control period, during which no statistical difference was found between the two groups. Similarly, lactate was no different during the control period between the two groups of dogs, but during the hypotensive period blood lactic acid was higher in the Sb than in Mv animals ($P < 0.01$). During the control periods in the Mv dogs, P_{CO_2} tended to be lower, whereas during the hypotensive period it tended to be higher compared with breathing group, but this was not significant ($P < 0.1$) at any time. Serum urea increased from 11.6±1.30 mg/dl in the ventilated group to 15.0±1.30 and 16±1.14 mg/dl (mean±SE), respectively, at 50 min of the run. Similarly, serum creatinine increased from 0.83±0.09 and 0.87±0.06 mg/dl to 1.09±0.12 and 1.05±0.03 mg/dl (mean±SE) in the two groups, respectively ($P < 0.005$).

Blood flow per 100 g of tissue per min to each of the respiratory muscles during control period and tamponade in the two groups are compared in Figs. 4 and 5. Fig. 6 shows the change in tissue blood flow expressed as a percentage of control. The quadriceps are included as nonrespiratory control muscles. Blood flow

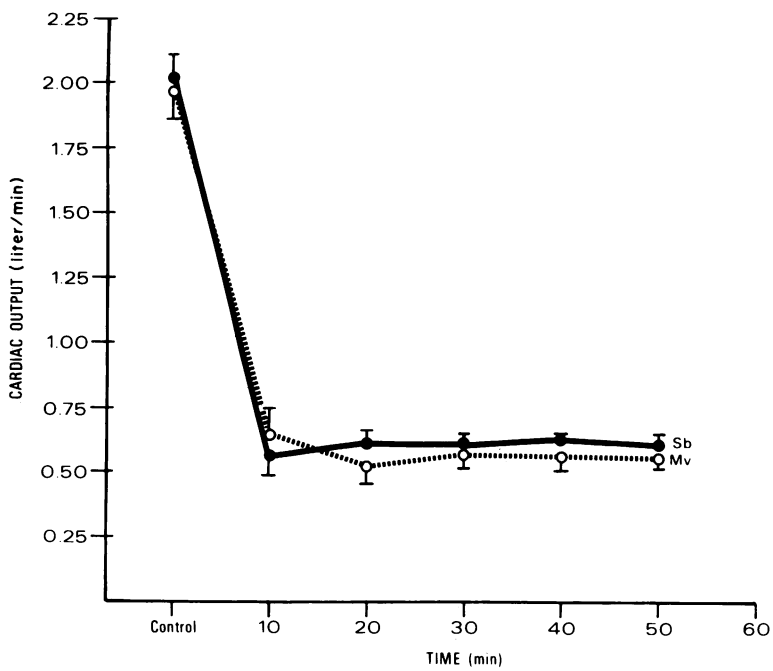

FIGURE 2 Time course of cardiac output during tamponade in the two groups of dogs. First point represents the control value. Cardiac output fell by 70% in both groups and thereafter remained constant. Symbols as in Fig. 1.

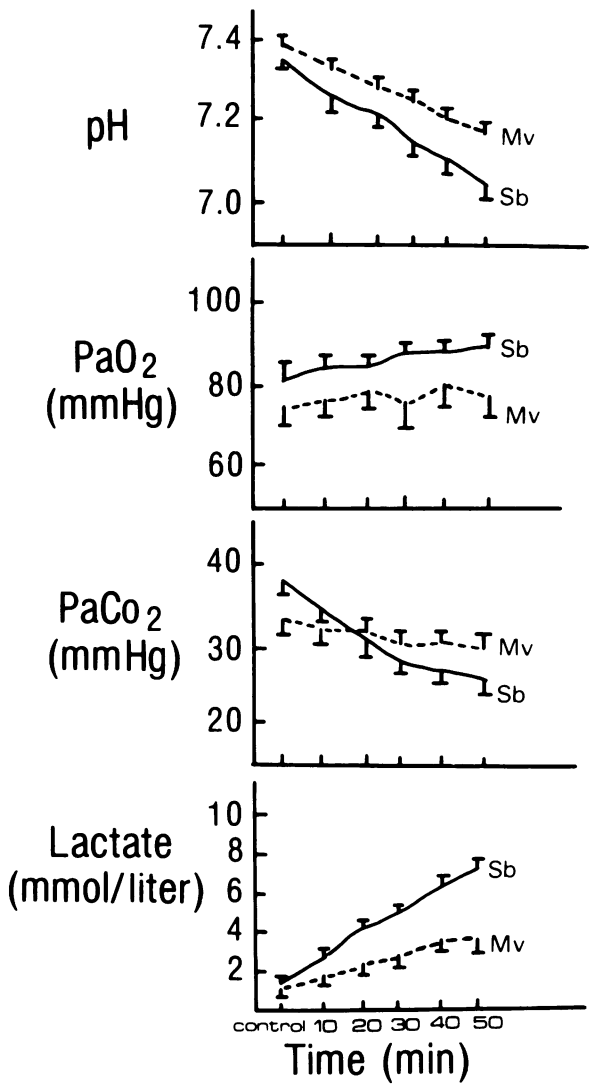

FIGURE 3 Evolution of arterial pH (panel *A*), blood gases (panels *B*, *C*), and lactate (panel *D*) during the course of low cardiac output state in the two groups of dogs. Symbols as in Fig. 1. Note that while arterial P_{O_2} and P_{CO_2} were not significantly different between the two groups, pH was significantly lower ($P < 0.001$) and lactate significantly higher in the Sb group at any time during the hypotensive period ($P < 0.005$).

to the diaphragm and external and internal intercostals was slightly, but significantly, greater during control period in Sb animals ($P < 0.01$), in which blood flow to the diaphragm, external and internal intercostal, internal oblique, and transverse abdominis muscles increased significantly during tamponade ($P < 0.001$) (Fig. 5). The diaphragm was the most perfused of the respiratory muscles both during control period and tamponade, and showed the greatest increase in perfusion during the low cardiac output state: 361±45% (mean±SE) of control values (Fig. 6). By contrast, in the Mv group, all the respiratory muscles showed significantly decreased flows during tamponade as compared with control period ($P < 0.001$), except the transverse abdominis, which showed no change.

To quantitate the total amount of blood flow received by the working respiratory muscles during tamponade, we calculated the absolute blood flow (in milliliters per minute) to each of the muscles by multiplying blood flow per gram by the muscle weight. The weights of the various respiratory muscles, except the intercostals, were measured. Our findings were no different from those of Robertson et al. (9). Thus, we assumed that the weight of the intercostals in our study was similar to that obtained by Robertson et al. (9). With this assumption, we used the values of intercostal muscle weight given in their study and calculated the blood flow that these muscles would predictably have received in our experiments. The sum of these flows was then taken as the total blood flow received by the respiratory muscles. Whereas the total respiratory muscle blood flow was not significantly different between the two groups during control period, respiratory muscle perfusion during tamponade was dramatically increased in the Sb group ($P < 0.001$), while being significantly decreased in the Mv group [127±13 vs. 21.39±9.8 ml/min (mean±SE), respectively ($P < 0.001$)] (Fig. 7). In the face of a decreased cardiac output, these differences become more pronounced and important, as shown in Fig. 8, which illustrates respiratory muscle blood flow expressed as a percentage of the total cardiac output. The increased flow received by the working respiratory muscles in the Sb animals during tamponade amounted to 21% of the total cardiac output during low cardiac output state, compared with only 3% in the Mv group.

There was no difference in blood flow to the quadriceps between the two groups during control period. During tamponade, this fell in both groups, although the decrease was significantly greater in the Sb group (23% of control values) than in the Mv animals (32% of control values) ($P < 0.001$).

The effect of Mv on regional blood flow distribution during tamponade is depicted in Fig. 9. During tamponade, while the respiratory muscles received significantly higher blood flows in the Sb group ($P < 0.001$), flows to the liver, brain, and quadriceps were significantly higher in the Mv group ($P < 0.005$).

DISCUSSION

The major finding of this study is that a marked increase in blood flow to working respiratory muscles arises during a low blood pressure state and low cardiac

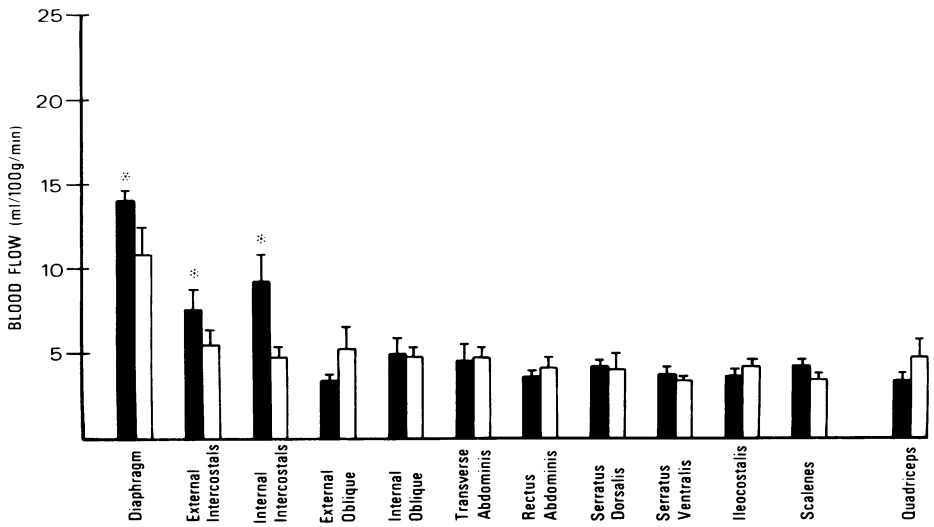

FIGURE 4 Respiratory muscle blood flow during the control period in the two groups of dogs. Solid columns (■) represent the Sb dogs, open columns (□) the Mv animals. Quadriceps are included as nonrespiratory control muscles. Bars are standard error.During the control period, flow to the diaphragm, external, and internal intercostals was significantly greater in Sb (*) ($P < 0.001$).

output state (tamponade). This increase caused a highly significant redistribution of the cardiac output (21%) to the respiratory muscles. However, when muscle paralysis was induced and Mv was instituted, the respiratory muscles received only 3% of the cardiac output. Since cardiac output was comparable, the rest of the body thereby benefited from a better blood flow.

Critique. The validation of the use of labeled microspheres for the study of regional circulation has been previously reported (10–15). However, under compromised circulatory conditions, such as cardiogenic shock, pericardial tamponade, or hemorrhagic shock, its application requires further consideration. The first of these is the hemodynamic effect of the microspheres in the presence of hypotension and/or a low cardiac output state. Microspheres have been shown to have no hemodynamic effect in normal, normotensive dogs (15), whereas a decreased cardiac output and coronary blood flow have been reported in sick dogs (17). Thus, the effect of the microspheres must be evaluated for a particular type of study, if serial injections are to be made. In the present study, there were no discernible hemodynamic consequences to the use of microspheres. The state of hypotension was not affected by the initial administration of the microspheres. The intracardiac injection produced no large changes in arterial blood pressure, heart rate, or cardiac output in any of the animals. Furthermore, in this animal model, we were able to correct any minor changes in blood pressure and cardiac output by adjusting the pericardial fluid.

A second consideration is the effect of arteriovenous shunting on the distribution of the microspheres. Previous reports indicate no significant shunting in normal dogs (13), although, because of the possibility of A-V shunting during the later stages of shock, ~20 ml of blood were withdrawn continuously from the inferior vena cava at the time of injection of the microspheres. The radioactivity of this blood was not significantly above background, and thus we can exclude the possibility of shunting in our model.

A third consideration in our study was whether the microspheres were evenly distributed to the various parts of the body as a result of adequate mixing and even flow distribution. The correlation found regarding the blood flow per unit weight of the left and right halves of the diaphragm (0.98), the left and right kidneys (0.97), and the two reference samples (0.99) indicate a good and an even distribution of the spheres. Furthermore, the validity of the technique for studying blood flow distribution in this model is confirmed by the reproducibility between duplicate measurements (0.98).

Another consideration was the possible influence of tissue water accumulation, Mv, and Pancuronium on our observations. Blood flow to the various tissues, as measured by the microsphere technique, can be affected by the amount of water present. Thus, blood flow to edematous tissues will be underestimated when expressed as milliliters per gram. In our model, water retention in the organs due to elevated venous pressures is probable. The magnitude of these effects can-

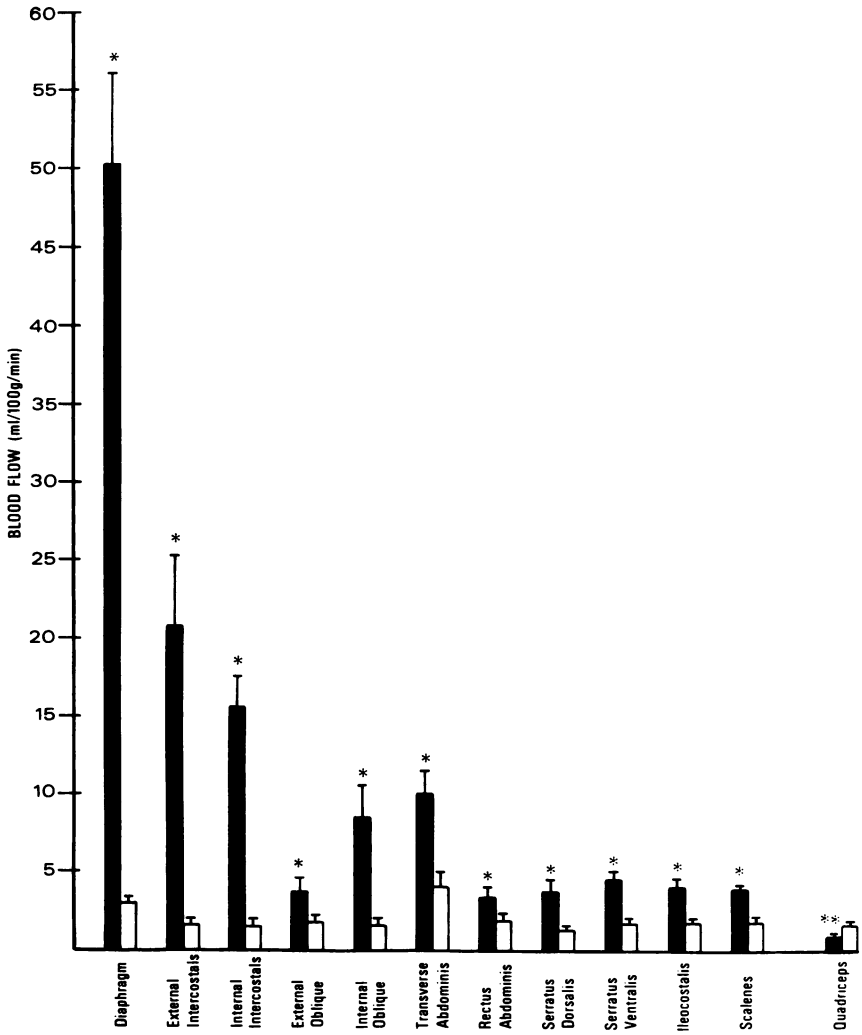

FIGURE 5 Comparison of respiratory muscle blood flow after 50 min tamponade in the two groups of dogs. Symbols as in Fig. 4. While flows to each respiratory muscle were significantly greater (*) in Sb ($P < 0.001$), flow to the quadriceps was significantly less (**) than in Mv ($P < 0.001$). Sb (■), Mv (□).

not be predicted. Furthermore the excess water may have been accumulated in some tissues predominantly in one group of dogs as compared with the other. A plausible mechanism that may account for such a difference in fluid distribution between the two groups is the intrathoracic and abdominal pressures applied to the two groups. In the Sb group, ventilation was associated with negative pleural pressure and usually with positive abdominal pressure, whereas in the Mv animals, breathing was achieved with positive alveolar pressure and perhaps minimal, if any, positive pleural pressures. These differences in the applied pressures may theoretically have altered hydrostatic forces and redistributed water, thereby affecting our results. Clearly, we had no direct evidence to disprove this proposition. However the wet/dry tissue weight ratios in all organs were determined and these were not different in the two groups of dogs, a finding that, admittedly not very sensitive, gives credence to the assumption that no large difference in the water distribution occurred between the two groups of animals, and therefore the comparison between the two groups, at least at the state of low cardiac output, is valid.

To facilitate the interpretation of our results obtained from the ventilated group, we chose to administer Pancuronium to ensure that breathing efforts did not occur. To our knowledge, there are no reports on the effects of Pancuronium on blood flow distribution.

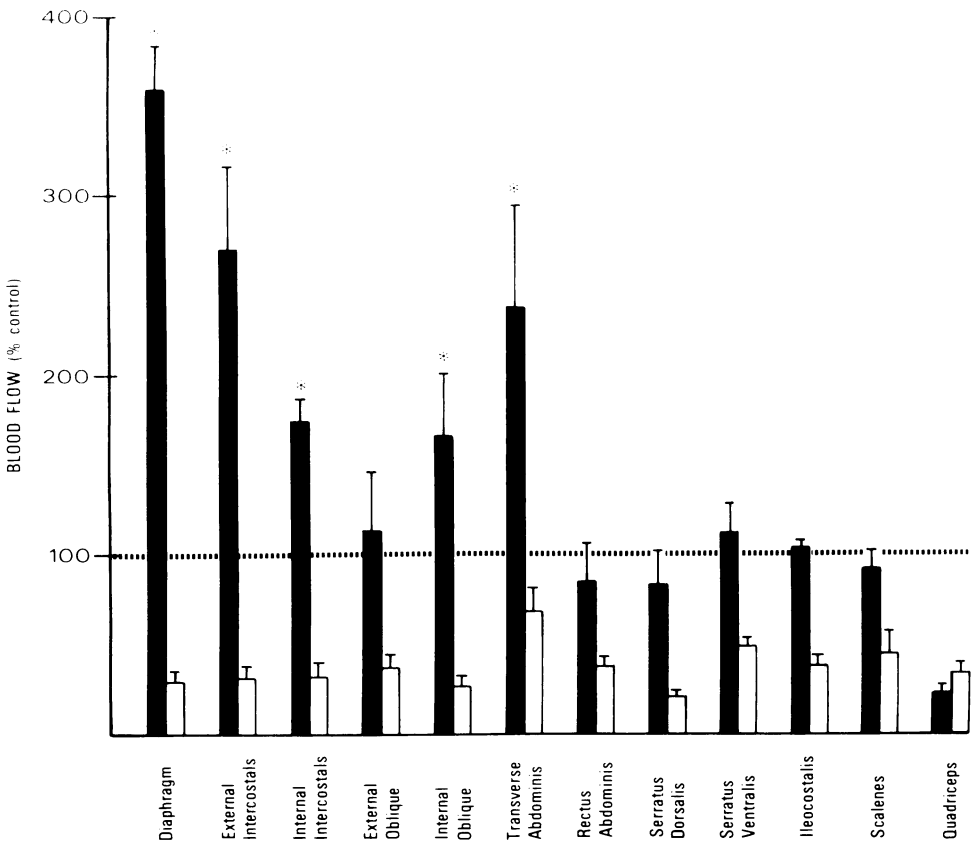

FIGURE 6 Mean changes in blood flow to the respiratory muscles after 50 min of tamponade expressed as a percentage of the control value. The line at 100% represents control. Columns above indicate increased flows with tamponade; columns below, decreased flows. Symbols as in Fig. 4. Note that while all the respiratory muscles in the Mv group (□) manifested significantly decreased flows with low cardiac output, significant increases in flow were seen for most of these muscles (*) in the Sb animals (■) ($P < 0.001$).

However, it is unlikely that it had an influence on our results. Previous reports on respiratory muscle blood flow during mechanical ventilation (without Pancuronium) with normal circulation are in excellent agreement with our results (18). Furthermore, after we completed this study, we measured the blood flow distribution in three dogs at equal levels of low blood pressure and cardiac output either with or without previous administration of Pancuronium. We found no measurable difference in the two measurements. It is not surprising that during control measurements we found a difference between the two groups (Fig. 4), in blood flow distribution. Robertson et al. (18) had previously reported similar changes in the magnitude of blood flow distribution when animals resumed their spontaneous breathing after having been ventilated without muscular paralysis. Thus, it seems reasonable to assume that Pancuronium had no measurable effects on blood flow distribution and could not have accounted for the large differences observed between the two groups.

An important factor that may influence blood flow distribution is the acid-base changes and arterial P_{CO_2}. We attempted to minimize these differences between the two groups. Arterial P_{CO_2} was not statistically different between the two groups. Thus, we believe that the differences in blood flow distribution found during tamponade were not seriously affected by the levels of P_{CO_2}. Even during the control period, when the P_{CO_2} in the spontaneously breathing dogs tended to be greater than in the Mv group, the total blood flow to the respiratory muscles was not different between the two groups (Fig. 7). The greater blood flow received by some muscles (diaphragm and intercostals) during control, related to the fact that they were contracting rather than to other factors, as for example

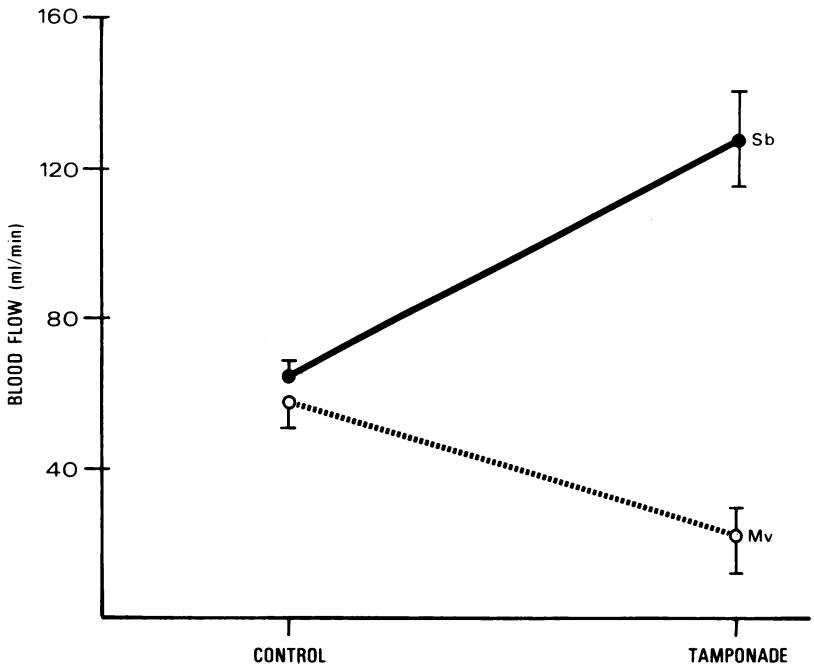

FIGURE 7 Comparison of the total respiratory muscle blood flow during control and tamponade in the two groups of dogs, expressed in milliliters per minute, and obtained by summing individual muscle flows. Symbols as in Fig. 1. Despite a decreased cardiac output, absolute respiratory muscle blood flow increased significantly in the Sb group ($P < 0.001$).

the levels of P_{CO_2}. It has been previously reported that blood flow to the diaphragm increases with spontaneous breathing as compared to mechanical ventilation (18). However, even if the P_{CO_2} had been responsible for the greater blood flow to some muscles during control period, the large increase in flow in the Sb dogs and the decrease in the Mv animals during tamponade, when P_{CO_2} tended to be lower in the breathing dogs, is underestimated. Therefore, the qualitative and quantitative significance of our results remains valid and important. The argument that pH may be responsible for the large differences observed between the two groups of dogs is not tenable either. The quadriceps muscles received more blood flow in the Mv compared with the Sb group, despite the fact that the pH was lower in the latter. Clearly, although P_{CO_2} and pH might have had some effect on our results, we believe that this effect was negligible.

Influence of blood pressure and/or cardiac output on respiratory muscle blood flow. The highest blood flow per gram of tissue received by the diaphragm (~400 ml/100 g per min) (19) approaches that for the heart (~500 ml/100 g per min) (20) and is clearly greater than that observed for other skeletal muscles (21). Furthermore, a limit in the ability of the respiratory muscles and particularly of the diaphragm to increase their perfusion under high resistive loads (22) has not yet been shown. By contrast, in limb skeletal muscle at very high work rates, blood flow fails to increase in proportion to energy demands (23).

The respiratory muscles, notably the diaphragm, increase their blood flow as the work of breathing is increased by a variety of stimuli. Perfusion per unit mass of the diaphragm (and of other respiratory muscles) increases substantially during hyperventilation induced by hypercapnia, hypoxia, or exercise (2, 24–26). Perfusion to these muscles will also increase when the work of breathing is increased by an inspiratory or expiratory resistance to airflow (3, 9, 27, 28). At low and moderate levels of ventilation, the relationship between the work of breathing and blood flow is linear for all respiratory muscles. As the work of breathing becomes greater than 4 cal/min, blood flow to the diaphragm has been shown to increase exponentially (9). Robertson et al. (9) found that during inspiratory resistive breathing, increments in the work of breathing, up to 15 times the initial value, resulted in an exponential increase in diaphragmatic blood flow of 26-fold. High diaphragmatic blood flow has also been observed during exercise (24), heat stress (25), and intermittent electrophrenic stimulation.

Cardiac output has been shown to be related to dia-

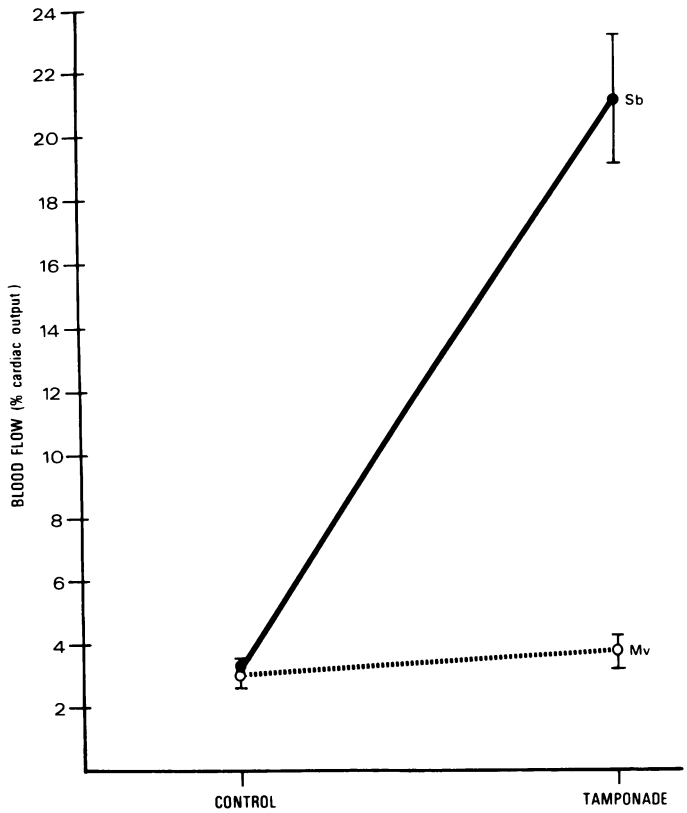

FIGURE 8 Total respiratory muscle blood flow during control and tamponade in the two groups of dogs expressed as a percentage of the cardiac output. Symbols as in Fig. 1. Note that the fractional distribution of cardiac output to the respiratory muscles increased more than fivefold during tamponade in the Sb group.

phragmatic blood flow at rest, during exercise, low O_2 breathing, as well as during unobstructed hyperventilation (2, 12, 24, 29). Thus, it is possible that in the face of a decreased cardiac output, diaphragmatic blood flow may reach a limit or fail to increase in proportion to energy expenditure. It is almost certain that during shock the energy demands of the respiratory muscles are increased because of hyperventilation elicited by acidemia, hypoxia, and alterations in pulmonary mechanics secondary to pulmonary vascular congestion. However, when energy supplies are decreased, as occurs with decreased cardiac output, respiratory muscle blood flow may become limited to levels less than those required to sustain the increased work of breathing. In fact, we have previously shown (5) that dogs in a low cardiac output state induced, as in this study, by tamponade, die of respiratory failure due to respiratory muscle fatigue. Thus, the present study was undertaken partly to determine whether in fact the precipitating factor leading to respiratory failure during a low cardiac output state might be a reduced blood flow to the respiratory muscles. Yet we found that despite a 70% decrease in cardiac output, respiratory muscle blood flow increased significantly, whether expressed in terms of a percentage of cardiac output ($P < 0.001$) (Fig. 7) or in abolute values (Fig. 8) ($P < 0.001$). In fact, during tamponade, 21% of the total cardiac output went to the respiratory muscles, compared with only 3% during control.

It thus appears that during a low cardiac output state, blood flow is redistributed in a manner that greatly increases blood flow to the respiratory muscles, notably the diaphragm, which receives 12% of the cardiac output. However, it should be stressed that these measurements of blood flow were made during peak ventilation. Therefore, ventilation decreased with eventual respiratory failure. This suggests that perhaps a maximum blood flow had been reached, and that any further demands for energy supplies by the respiratory muscles could not be met. The subject can be approached from a theoretical point of view. Johnson and Reid (4) have attempted to calculate the maximum

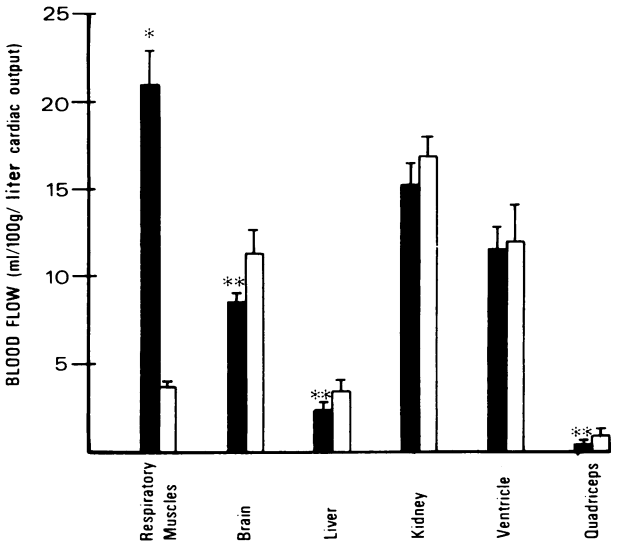

FIGURE 9 Comparison of the fractional distribution of cardiac output during tamponade in the two groups of dogs. Symbols as in Fig. 4. Bars represent standard error. Note that while the respiratory muscles received a significantly (*) greater portion of the cardiac output in the Sb group ($P < 0.001$), the brain, liver, and quadriceps muscles received significantly less (**) ($P < 0.001$). Sb (■), Mv (□).

blood flow to the diaphragm in the dog, by reproducing a flaccid diaphragmatic vasculature that could not autoregulate. This was achieved by infusing large doses of adenosine and nitroprusside, and by breathing 6% O_2 against added resistance. The vascular conductance (C_{di}), which was linearly related to the rate of diaphragmatic work of breathing before the vasodilation, then became a linear function of aortic blood pressure (P) and independent of work load. The maximal blood flow to the diaphragm could then be estimated by the following equation: $Q_{di}(max) = 0.078\ P + 0.0145\ P^2$, where $Q_{di}(max)$ is expressed in milliliters per minute per 100 g.

This equation predicts that with a mean blood pressure of ~55 mmHg (as observed in our study), the $Q_{di}(max)$ will be ~50 ml/min per 100 g. This estimation then indicates that in our study, in which we observed a diaphragmatic blood flow of 50 ml/min per 100 g, the maximum blood flow that could be achieved was indeed reached.

Our finding that the working respiratory muscles were receiving 21% of the total cardiac output during tamponade is surprising, since the idea that the energy demands of the respiratory muscles may represent such a large fraction of the cardiac output is not familiar (30), especially in view of the fact that ventilation increased only modestly (threefold) (Fig. 1). It is thus interesting to note that for equal increases in minute ventilation, as was observed in our study, Robertson et al. (18) found that during unobstructed hyperventilation with intact circulation, diaphragmatic blood flow increased to only 20 ml/min per 100 g, as compared with 50 ml/min per 100 g as we found during tamponade. In his study, cardiac output doubled and thus the increased flow was found to represent only 1% of the total cardiac output, in sharp contrast to the 12% observed in our study. Total respiratory muscle blood flow during hyperventilation was found to represent only 2% of the cardiac output (18).

The inordinately large blood flow requirements of the respiratory muscles during a low cardiac output state compared with that of a normal cardiac output (for equal degrees of hyperventilation) indicates that either the efficiency of these muscles is greatly reduced, that the work of breathing is increased during hypotension, or both. We can provide no direct evidence for or against either proposition. We may speculate, however, on certain aspects of this statement. Increases in lung and/or chest wall resistance or decreases in their compliance will result in an increased work of breathing, which will increase the energy requirements of the respiratory muscles. We have already shown (5) that the mechanics of the lung are not altered during pericardial tamponade; therefore, such a mechanism cannot account for an increase in the work of breathing. However, the chest wall may have decreased its compliance and increased its resistance, which could account for greater energy and blood flow requirements. Pericardial tamponade may produce venous pooling of blood in the chest wall and abdominal contents. Thus, the respiratory muscles may need to overcome high opposing forces to expand the thorax and therefore their work and energy requirements increase. However, such a proposition is not supported by some indirect evidence available. Our previous finding in a similar model showed that the functional residual capacity remained unaltered with tamponade (5). Should a large amount of water have accumulated in the chest wall, its compliance would have decreased and functional residual capacity dropped. Alternatively, the reduced pH or other toxic factors produced with hypotension may have impaired the ability of the muscles to extract substrates or oxygen from the blood, possibly resulting in greater needs in blood flow to meet the increased energy demands.

Muscle paralysis and Mv. Regardless of the cause, during tamponade, the respiratory muscles require an inordinately large blood flow to maintain even modest levels of ventilation. Thus, we wondered whether the regional distribution of blood flow during shock in animals would change if we put the respiratory muscles at rest by Mv. We thought that as the working respiratory muscles were receiving 21% of the cardiac out-

put, perhaps by putting them at rest (i.e., Mv), a substantial portion of the cardiac output would become liberated for use by the rest of the body. Indeed, we found that Mv resulted in a significant decrease in respiratory muscle blood flow (Fig. 6). Only 3% of the cardiac output was received by these muscles when Mv was instituted, compared with 21% in the Sb animals. This may explain the increased arterial lactate observed in the Sb group (Fig. 3).

Skeletal muscle has been shown to be a major site of lactate production during shock (31, 32). This has been attributed to a relative oxygen deficit, which is believed to be flow related. A reduction in hepatic lactate extraction has been shown to occur as a result of diminished blood flow to the liver (33, 34). Under severely low cardiac output and hypotension, the liver itself may produce lactic acid (35, 36). In this study and in a previous one from our laboratory (37), we have shown that Mv reduces the level of blood lactate during low cardiac output state. Although this is partly due to a reduced lactate production by the respiratory muscles (37), clearly a preservation in liver blood flow, as shown in this study, may well contribute to a lower blood lactate in the ventilated animal. Thus, our finding that Mv preserves blood flow to vital organs and minimizes lactic acidosis may have important clinical implications regarding the outcome of shock due to lactic acidosis, as survival rate after shock has been inversely related to the severity of this acid-base derangement (5, 38, 39).

In conclusion, our results clearly demonstrate that during pericardial tamponade, the respiratory muscles receive very large blood flows. Mv and muscle paralysis were found to preserve that portion of cardiac output used by the respiratory muscles during tamponade and thus may serve to liberate oxygen and energy supplies needed for use by the rest of the body.

REFERENCES

1. Wright, D. L., and R. R. Sonnenschein. 1969. Muscle force and electromyogram with alteration in flow and composition of blood. *Am. J. Physiol.* 261:1075–1080.
2. Rochester, D. F. 1974. Measurement of diaphragmatic blood flow and oxygen consumption in the dog by the Kety-Schmidt technique. *J. Clin. Invest.* 53:1216–1225.
3. Rochester, D. F., and G. Bettini. 1976. Diaphragmatic blood flow and energy expenditure in the dog. Effects of inspiratory airflow resistance and hypercapnia. *J. Clin. Invest.* 57:661–672.
4. Johnson, R. L., Jr., and M. Reid. 1979. Limits of oxygen transport to the diaphragm. *Am. Rev. Respir. Dis.*
5. Aubier, M., T. Trippenbach, and Ch. Roussos. 1981. Respiratory failure during cardiogenic shock. *J. Appl. Physiol.* 51:499–508.
6. Pierce, C. 1974. An inquiry into the nature of circulatory shock: development and use of an experimental model utilizing controlled cardiac tamponade. Ph.D. Thesis, University of Saskatchewan, Canada.
7. Archie, J. P., D. E. Fixler, D. J. Ullyot, J. I. E. Hoffman, J. Utley, and E. L. Carlson. 1973. Measurement of cardiac output with end-organ trapping of radioactive microspheres. *J. Appl. Physiol.* 35:148–154.
8. Rudolph, A. M., and M. A. Heymann. 1967. The circulation of the foetus in utero. *Circ. Res.* 21:163–184.
9. Robertson, C. H., Jr., G. H. Foster, and R. L. Johnson, Jr. 1977. The relationship of respiratory failure to the oxygen consumption of lactate production by and distribution of blood flow among respiratory muscles during increasing inspiratory resistance. *J. Clin. Invest.* 59:31–42.
10. Neutze, J. M., F. Wyler, and R. M. Rudolph. 1968. Use of radioactive microspheres to assess distribution of cardiac output in rabbits. *Am. J. Physiol.* 215:486–495.
11. Kaihara, S., P. D., VanHeerden, T. Migita, and H. N. Wagner. 1968. Measurement of distribution of cardiac output. *J. Appl. Physiol.* 25:696–700.
12. Adachi, H., H. W. Strauss, H. Ochi, and H. N. Wagner. 1976. The effect of hypoxia on the regional distribution of cardiac output in the dog. *Circ. Res.* 39:314–319.
13. Hoffbrand, B. I., and R. P. Forsyth. 1969. Validity studies of the radioactive microsphere method for the study of the distribution of cardiac output, organ blood flow and resistance in the conscious rhesus monkey. *Cardiovasc. Res.* 3:426–432.
14. Buckberg, G. D., J. C. Luck, D. B. Payne, J. I. E. Hoffman, J. P. Archie, and D. E. Fixler. 1971. Some sources of error in measuring regional blood flow with radioactive microspheres. *J. Appl. Physiol.* 31:598–604.
15. Domenech, R. J., J. I. E. Hoffman, M. I. M. Noble, K. B. Saunders, J. R. Henson, and S. Subijanto. 1969. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. *Circ. Res.* 25:581–595.
16. Miller, M. E., C. Christensen, and H. E. Evans. 1964. Myology. *In* Anatomy of the Dog. W. B. Saunders Co., Philadelphia, PA. 131–266.
17. Kaihara, S., R. B. Rutherford, E. P. Schwentker, and H. N. Wagner. 1969. Distribution of cardiac output in experimental hemorrhagic shock in dogs. *J. Appl. Physiol.* 27:218–222.
18. Robertson, C. H., Jr., M. A. Pagel, and R. L. Johnson, Jr. 1977. The distribution of blood flow, oxygen consumption, and work output among the respiratory muscles during unobstructed hyperventilation. *J. Clin. Invest.* 59:43–50.
19. Buchler, B., S. A. Magder, Ch. Katsardis, Y. Jammes, and Ch. Roussos. 1982. Factors affecting diaphragmatic blood flow. *Clin. Invest. Med.* 213:47B.
20. Manohae, M., J. Thueman, W. J. Tranquilli, M. Devais, M. Theodorakis, R. Shawley, D. Feller, and J. Benson. 1981. Regional myocardial blood flow and coronary vascular reserve in unanesthetized young calves with severe concentric right ventricular hypertrophy. *Circ. Res.* 48:785–796.
21. Horstman, D. H., M. Gleser, and J. Delhunt. 1976. Effects of altering O_2 delivery on oxygen consumption of isolated working muscle. *Am. J. Physiol.* 230:327–334.
22. Rochester, D. F., and A. M. Briscoe. 1979. Metabolism of the working diaphragm. *Am. Rev. Respir. Dis.* 119:101–106.
23. Hirvonen, L., and R. R. Sonnenschein. 1962. Relation between blood flow and contraction force in skeletal muscle. *Circ. Res.* 10:94–104.

24. Fixler, D. E., J. M. Atkins, J. H. Mitchell, and L. D. Horowitz. 1976. Blood flow to respiratory cardiac and limb muscles in dogs during graded exercise. *Am. J. Physiol.* 231:1515–1519.
25. Hales, J. R. S. 1973. Effects of heart stress on blood flow in respiratory and non-respiratory muscles in the sheep. *Pfluegers Arch. Eur. J. Physiol.* 345:123–130.
26. Mogoni, P., F. Saibene, G. Sant'Ambrogio, and E. Camparesi. 1974. Perfusion of inspiratory muscles at different levels of ventilation in rabbits. *Respir. Physiol.* 20:171–179.
27. Busse, J. 1977. Blood flow and metabolism of the diaphragm of intact dogs. Thesis, University of Cologne.
28. Robertson, C. H., Jr., W. L. Eschenbacher, and R. L. Johnson, Jr. 1977. Respiratory muscle blood flow distribution during expiratory resistance. *J. Clin. Invest.* 60:473–480.
29. Rochester, D. F., and M. Pradel-Guena. Measurement of diaphragmatic blood flow in dogs from xenon 133 clearance. *J. Appl. Physiol.* 34:68–74.
30. Macklem, P. T. 1980. Respiratory muscles. The vital pump. *Chest.* 78:735–758.
31. Daniel, A. M., H. M. Shizgal, and L. D. MacLean. 1978. The anatomic and metabolic source of lactate in shock. *Surg. Gynecol. Obstet.* 147:697–700.
32. Karlsson, J., J. T. Willerson, J. J. Leshin, C. B. Mullins, and J. M. Mitchell. 1975. Skeletal muscle metabolites in patients with cardiogenic shock or severe congestive heart failure. *Scand. J. Clin. Lab. Invest.* 35:73–79.
33. Sriussadaporn, S., and J. M. Cohn. 1968. Regional lactate metabolism in clinical and experimental shock. *Circulation.* 37(Suppl. 6):187*a*. (Abstr.)
34. Berry, M. N., and J. Scherner. 1967. Splanchnic lactic acid metabolism in hyperventilation, metabolic alkalosis, and shock. *Clin. Exp. Metab.* 16:537–546.
35. Schroeder, R., J. R. W. Gumpert, J. R. Fluth, W. K. Eltringham, M. E. Jenny, and R. M. Zollinger. 1969. The role of the liver in the development of lactic acidosis in low flow states. *Postgrad. Med. J.* 45:566–570.
36. Loyd, M. H., R. A. Iles, B. R. Simpson, J. M. Layton, and R. D. Cohen. 1973. The effect of stimulated metabolic acidosis on intracellular pH and lactate metabolism in the isolated, perfused liver. *Clin. Sci. Mol. Med.* 45:543–549.
37. Aubier, M., N. Viires, S. Sillye, and Ch. Roussos. 1980. Effect of mechanical ventilation on lactic acidosis in shock. *Am. Rev. Respir. Dis.* 121:311.
38. Daniel, A. M., H. M. Shizgal, and L. D. MacLean. 1976. Endogenous fuel in experimental shock. *Surg. Forum.* 27:32–53.
39. Broder, G., and M. H. Weil. 1964. Excess lactate: an index of reversibility of shock in human patients. *Science (Wash. DC).* 143:1457–1459.