EARLY CHANGES IN LUNG WATER AFTER HAEMORRHAGIC SHOCK IN PIGS AND DOGS

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MANY INVESTIGATORS have described a syndrome occurring after shock which is characterized by hypoxia and radiographic evidence of pulmonary oedema. Pathologically congestion, oedema and haemorrhage in the lungs are seen. This results in a fall in pulmonary compliance, increased respiratory work, a widened alveolar to arterial oxygen gradient with shunting and a low arterial oxygen tension.

This lung failure has had many labels including adult respiratory distress syndrome, De Nang lung, Viet Nam lung, wet lung or shock lung. Confusion is rampant in the subject primarily because we do not understand its aetiology. The syndrome has been ascribed to loss of surfactant,[1] to pulmonary capillary hypoxia and increased permeability,[2] micro-emboli of the lung,[3] fat embolism,[4] myocardial failure (either directly or due to fluid overload); to proteolytic substances, pulmonary vasomotor effects and hormonal influences on lung tissue. Underlying all of these factors has been an increased pulmonary extra-vascular water volume.

Usually the syndrome is not detected for days or weeks after the shock period. This could be because methods available to measure lung water are insensitive to small changes which occur immediately. We have developed a new technique to measure lung water, ETV_L.[5,6] The ETV_L technique was used in both pigs and dogs to follow lung water changes both during shock created by removing blood and after that blood was reinfused. This experiment documents an immediate rise in lung water after the shock period and reinfusion of blood.

METHODS

Dogs were chosen for these studies because of their availability and ease of handling. The dog has been criticized as a shock model[7] and has extensive collateral ventilation in the lung. Therefore the pig was chosen as a second shock model, since the lung lobulation prevents collateral ventilation. These anatomical differences surround those in the human so that if both animals responded similarly we could be more confident that the human lung would give similar results.

In 26 dogs and 7 pigs anaesthesia was induced with intravenous pentobarbitone (20–30 mg/kg initially with supplements as necessary). The animals breathed air spontaneously while lying supine. Femoral arterial and venous catheters were inserted for pressure monitoring and for the withdrawal or infusion of blood. A flexible injection catheter was floated into the pulmonary artery. A CVP line was inserted. In five of the dogs a left atrial catheter was inserted from the internal carotid artery. Blood gases were followed. Finally, a special aortic sensing catheter for temperature and blood electrical conductivity was passed up a femoral artery

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to the arch of the aorta to measure ETV_L. Lines were kept patent by flushing with normal saline (no heparin was used).

The thermodilution method ETV_L was used to measure lung water, cardiac output and central blood volume.[5] Systemic vascular resistance and pulmonary vascular resistance (P.V.R.) were calculated.

P.V.R. = Pulmonary artery pressure – left atrial pressure/cardiac output

The animals breathed through a low resistance Lloyd non-rebreathing valve and mixed expired gas was collected for O_2 and CO_2 analysis. At the same time mixed venous blood from the pulmonary artery line and arterial blood were taken for blood gas analysis. These values allowed shunt fraction and VD/VT or dead space values to be calculated.

The experiment was conducted as follows. Control values were determined four times. Blood was then removed to ACD blood packs to keep the mean arterial pressure between 40 and 50 mm Hg for at least two hours. Towards the end of two hours of shock it was often necessary to reinfuse some blood to maintain the 40 to 50 mm Hg mean pressure. Measurements were continued in the shock period. At the end of the shock period all of the blood was reinfused, using an ordinary blood filter and the measurements were repeated. $NaHCO_3$ was then infused to return the base excess to control values. The temperature of the animals was monitored and maintained between 37° and 38° C.

At the end of the experiment the animal was sacrificed by injection of KCl and the lungs were removed, weighed and dried to obtain an independent measure of lung water.

Results

The shock period was associated with a 50 per cent mortality rate in both pigs and dogs. There was no significant difference in measurements made in the control period between the group that died and those that survived; that is, we would not predict in the control period by any of our measurements which animal would survive shock. Once in shock, however, animals that died had slightly lower mean arterial pressure, cardiac output pH and base excess. This suggests that 50 mm Hg arterial pressure was severe shock and momentary pressure falls to below this level could not be tolerated. As shock progressed metabolic acidosis developed which, if allowed to progress below pH 7.0, usually leads to death. In a few animals death occurred as blood was reinfused quickly after the shock period. Since the pH of the blood infused was about 6.3 we ascribed death to the effects of a new acid load on an already acidotic myocardium. This supports the importance of giving a bicarbonate infusion to anyone in shock before blood is infused. In the control period several measurements were different between pigs and dogs. For example, base excess was +1.6 in pigs while −6.9 in dogs. This resulted in a lower pH of 7.27 in dogs as opposed to 7.48 in pigs. Mean arterial pressure in dogs (150 mm Hg) was higher than that found in pigs (107 mm Hg). Although these differences existed between pigs and dogs the trends in and out of shock in both groups were the same.

Figure 1 gives the results in dogs only and illustrates the changes in the mean arterial pressure and cardiac output in the phases of the experiment. In the con-

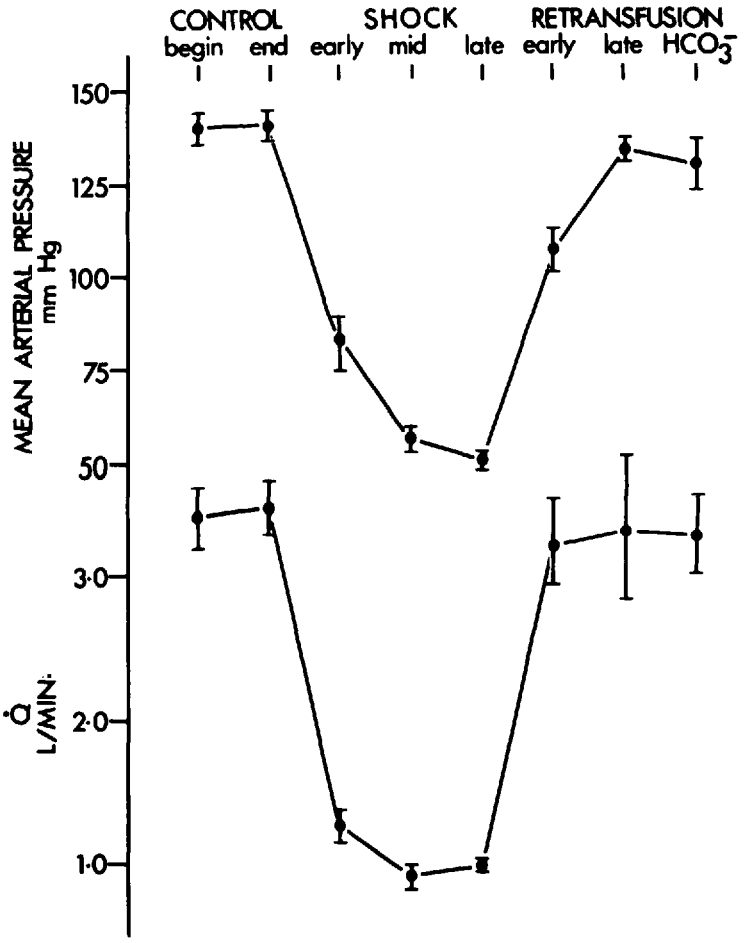

FIGURE 1. Changes in mean arterial pressure and cardiac output at the beginning and end of the control period, through the early, middle and late shock period, after blood was retransfused (early and late), and then after $NaHCO_3$ was infused to return base excess to control values in dogs.

trol period the mean values at the beginning and at the end are plotted with their standard deviations. Both pressure and cardiac output fell as blood was removed, as the shock period progressed from early to middle to late periods. Then the blood was reinfused but neither pressure nor cardiac output returned to control values even after $NaHCO_3$ had been infused to return the base excess to control values.

ETV_L is our value for lung water (Figure 2). As systemic pressure was reduced lung water fell but on reinfusion of the blood ETV_L values rose above control values by 34 per cent. This represents a large increase in lung water. In other studies we have found lung water must be increased by 100 to 200 per cent before we can detect it clinically by listening with a stethoscope or looking at routine chest X-rays. Why did this 34 per cent increase in lung water occur? An elevated hydrostatic pressure could account for part of it. The pulmonary artery pressure

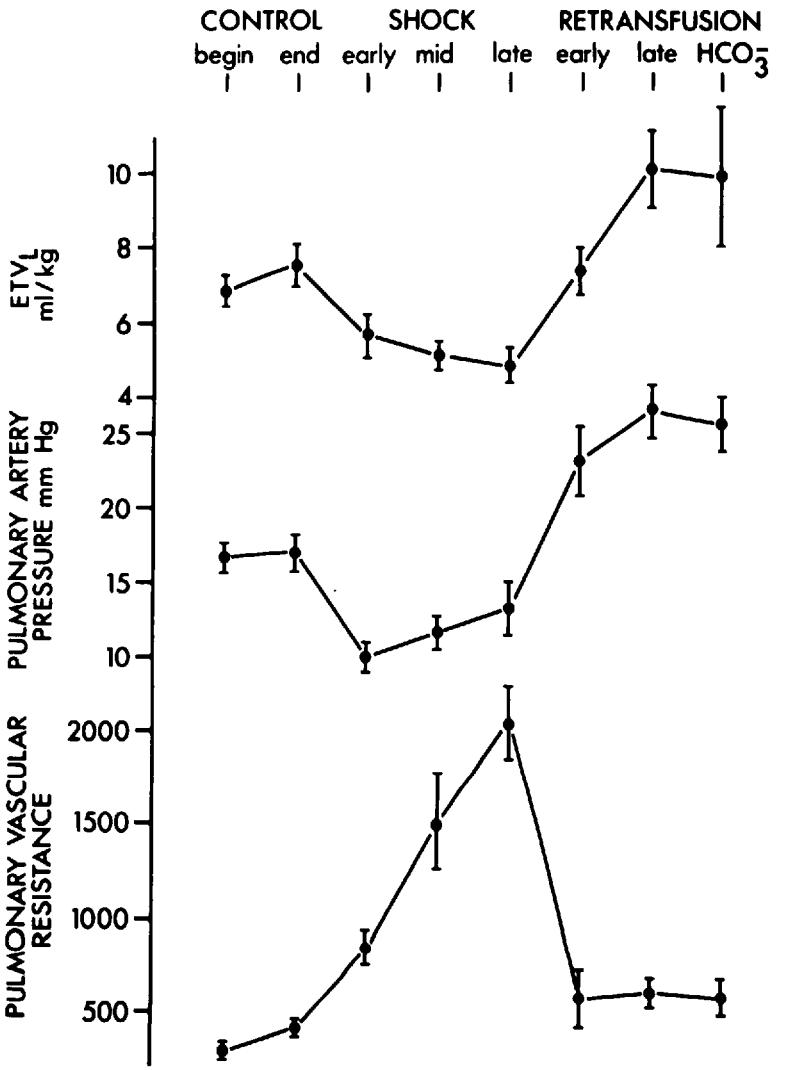

FIGURE 2. Changes in ETV_L (lung water), pulmonary artery pressure, and pulmonary vascular resistance (dynes-sec-cm^{-5}) during the phases of the experiment in dogs.

initially fell with blood removal but then rose as the shock period continued (Figure 2). This was different from the systemic pressure, which fell slightly at the same time (Figure 1). As blood was reinfused a dramatic rise in pulmonary artery pressure occurred which was associated with the higher lung water value, at a time when systemic pressures were well below normal. The high pulmonary artery pressure would tend toward pulmonary œdema. Pulmonary vascular resistance (Figure 2) rose progressively through the shock period, but after reinfusion never returned to control values even after $NaHCO_3$ was infused to correct acidosis. The increased pulmonary vascular resistance after shock might be due to platelet emboli, to venous hypoxia, to too rapid an infusion rate or to release of toxic substances from damaged tissues.

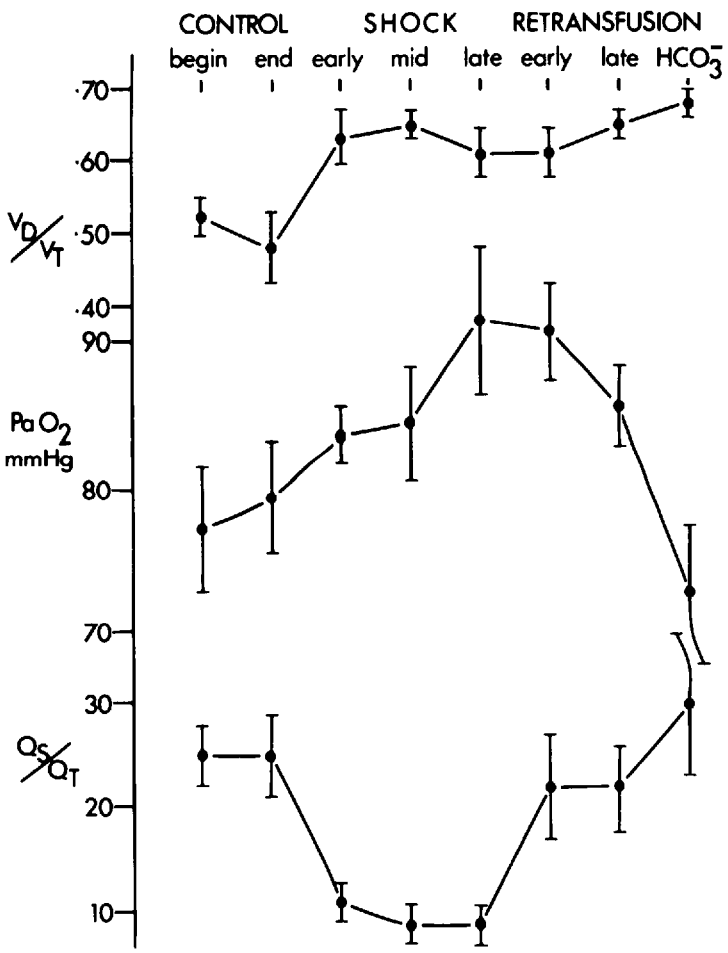

FIGURE 3. Changes in VD/VT (dead space ratio), PaO_2 and QS/QT (shunt fraction) during phases of the experiment in dogs.

We related rises in pulmonary artery pressure, left atrial pressure and central venous pressure to the amount of lung water after blood was reinfused. Although all three pressures increased as lung water rose the data were scattered and no significant relationship emerged. Of the three, a rising pulmonary artery pressure gave the best relationship to the increasing lung water, although this was not statistically significant (per cent control $ETV_L = 59 + 0.36$ per cent control pulmonary artery pressure, $r = 0.38$). This suggests that other factors than rises in pressure were at least partly responsible for the elevated lung water.

In support of the concept that part of the pulmonary vascular bed has been closed or obstructed in shock is the rising VD/VT ratio even after blood was reinfused (Figure 3). The initial rise in VD/VT as blood was removed was due to lack of lung perfusion as hypotension occurred and an increase in respiratory frequency. After the blood was return and after acidosis was corrected, however, the VD/VT should have returned to control values. That it did not do so suggests

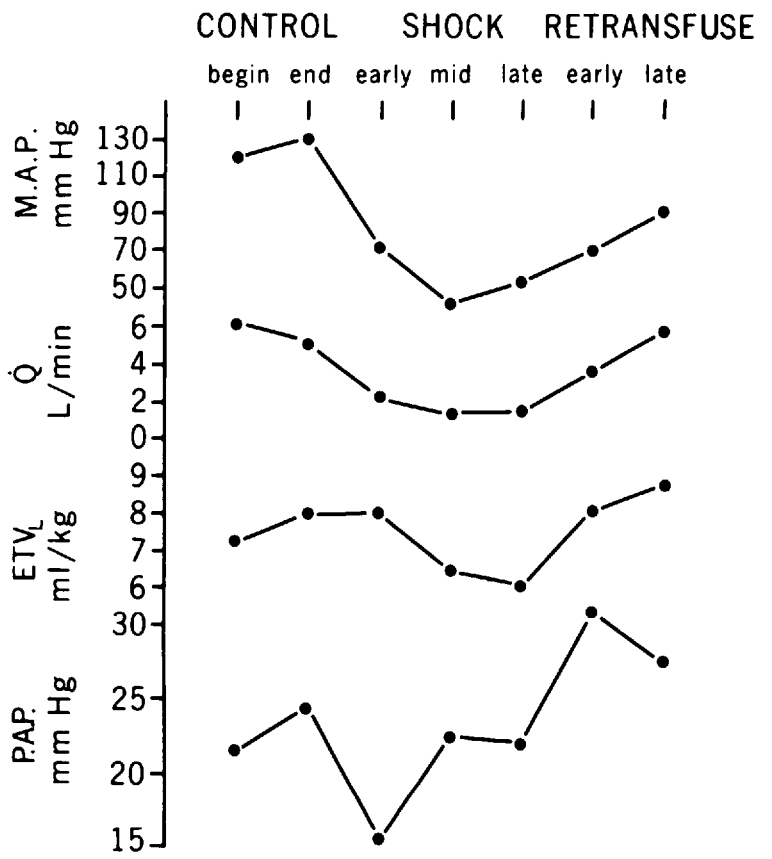

FIGURE 4. Mean values for mean arterial pressure (M.A.P.), cardiac output ($\dot{Q}$), ETV_L and pulmonary artery pressure (P.A.P.) in pigs during phases of the experiment.

obstructed pulmonary vessels, obstructed perhaps by platelet emboli. Arterial oxygenation rose in shock due to hyperventilation and a reduced O_2 consumption and then returned to control values after reinfusion. The lung changes which occurred were not severe enough to create shunts through the lungs or to widen the alveolar to arterial oxygen gradient. Figure 4 is a plot of mean values from pigs to indicate that directionally the same changes occurred.

Figure 5 is a plot of left atrial pressure against stroke volume. X represents control data and indicates that dogs with higher left atrial pressure have a higher stroke volume. If we assume a constant after-load the slope of the regression line represents myocardial performance. As the slope falls performance falls within the limitation of an unchanged afterload. As the shock period was entered left atrial pressure fell. This represented a fall in preload and should be associated with a low stroke volume. However the slope also fell and in the face of a reduced afterload means reduced myocardial performance. As shock progressed from early to middle to late periods performance continued to fall.

Figure 6 is the same plot with control values repeated. After blood reinfusion the slope has not improved from the late shock period, indicating a marked reduc-

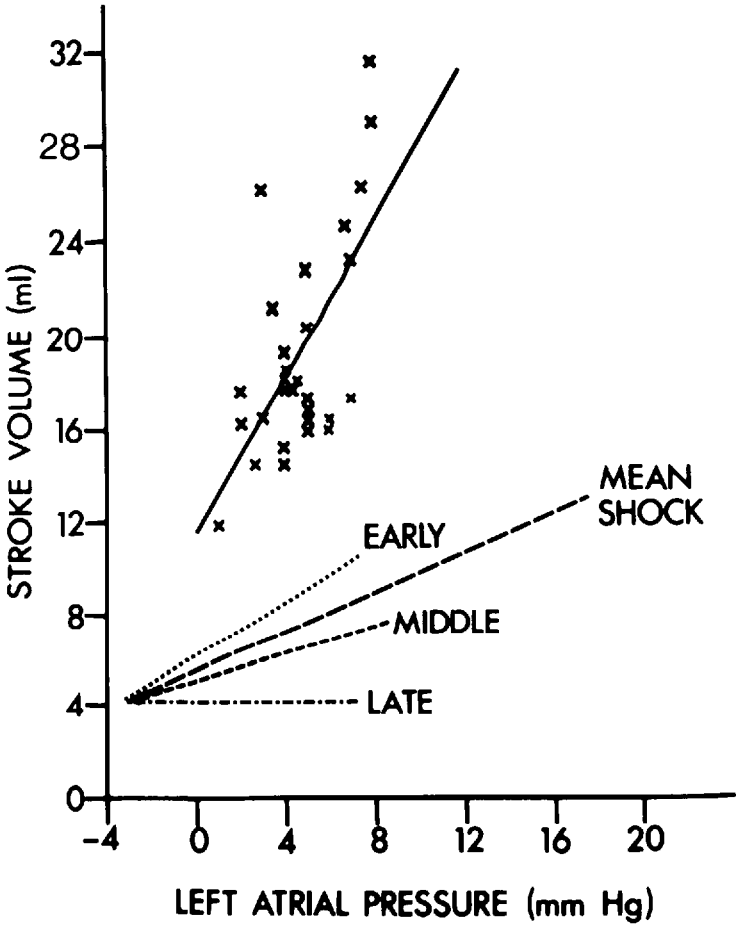

FIGURE 5. Left Atrial pressure is plotted against stroke volume in dogs. The lines are regression lines through the Xs in the control period and then in the early middle and late shock periods. The mean shock line is the regression line for all shock values.

tion in myocardial performance from the control period in spite of a reduced afterload, since arterial pressure is lower than in the control period. $NaHCO_3$ infused to correct the metabolic acidosis improved myocardial performance but it was still far from normal.

Reduced myocardial performance could be the result of myocardial damage or of any number of circulating enzymes and toxins present as a result of the shock period. Whatever the cause, decreased myocardial function, high pulmonary artery pressure and high pulmonary vascular resistance over a period of days could lead to a gross collection of lung water.

DISCUSSION

A real concern in this experiment was the question of fluid overload. We infused a total of 60 ml/kg of fluids in order to keep lines patent and to maintain adequate

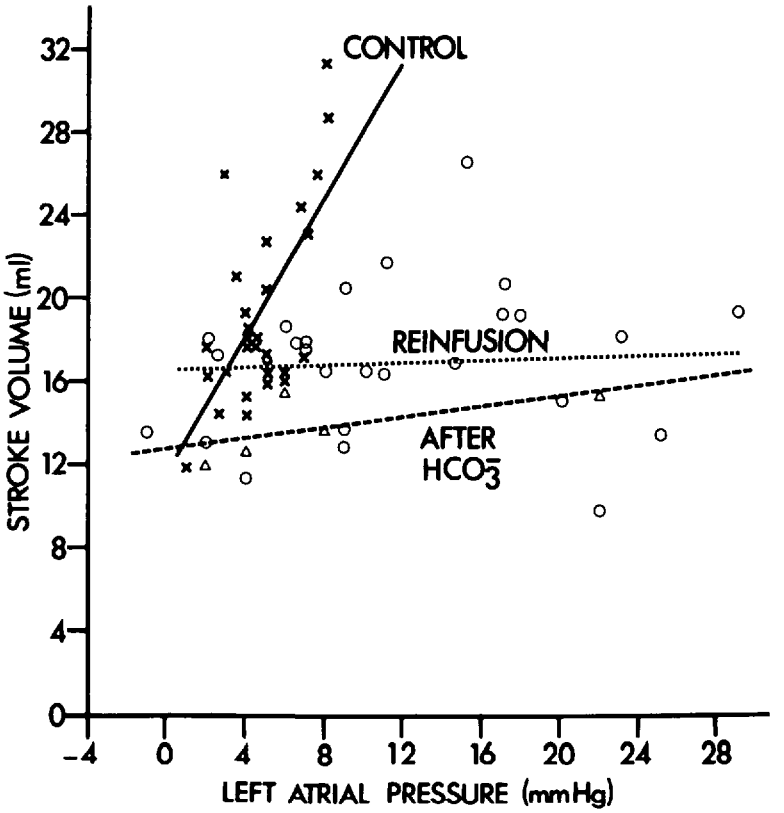

FIGURE 6. Left Atrial pressure, stroke volume relationship indicating regression lines for the control period (X), late reinfusion (open circles) and after $NaHCO_3$ was infused (open triangles) in dogs.

hydration. Since the dogs did not have fluids for 16 hours preoperatively and the experiment went on for eight hours we felt that this only assured adequate hydration. The blood was removed into ACD packs but since we only removed two to three bottles of blood to maintain hypotension the 180 ml of ACD solution in three bottles did not represent a problem. Transvascular filling from extravascular tissues represented a greater problem. While the shock period progressed Hbg levels fell from control of 12.9 ± 0.31 Gm % to 8.31 ± 0.49 Gm %. This represented dilution of blood and if blood removed were reinfused it could lead to over-load. On retransfusion the Hbg climbed to 11.65 ± 0.80 Gm % suggesting that most of the extra fluid was returned to the extravascular compartment. As further support of the proposition that these animals were not over-loaded, the central venous pressures did not rise when control values (3.29 ± 0.67 cm H_2O) are compared to those after infusion of bicarbonate (3.8 ± 1.43). Central blood volume started at 11.2 ± 0.67 ml/kg in the control period, fell to 3.85 ± 0.40 ml/kg in late shock and rose to only 8.67 ± 2.29 ml/kg after retransfusion of blood and bicarbonate.

Pulmonary vascular resistance (P.V.R.) rose during the shock period. Since pulmonary artery and left atrial pressures both fell, the greater fall in cardiac output meant that fewer pulmonary vessels were perfused and, therefore, resistance was

elevated. On retransfusion, however, P.V.R. did not return to control values but was significantly higher. This suggests that pulmonary vessels were either constricted or obstructed. The venous and arterial pH were returned to control values. Venous and arterial P_{CO_2} were back to control levels after bicarbonate. These factors should not have created constriction. However, the multitude of pulmonary vasomotor substances released in shock could have led to pulmonary vasoconstriction. Obstruction of pulmonary vessels by platelet emboli might also have played a part.[9] If constriction is the predominant factor the elevated intravascular pressure could produce pulmonary oedema. If obstruction predominates the fluid must be leaking before the obstruction or through vessels that have remained patent. If obstruction from platelet emboli were a factor, systemic vascular resistance (S.V.R.) might also be expected to be high. After bicarbonate S.V.R. was elevated (4300 dynes sec cm^{-5}) above control values (3400 ± 250 dynes sec cm^{-5}) but again other vasoconstricting influences might still be active.

Lung water (ETV_L) appears to fall during the shock period (Figure 2). This might represent a true fall in the lung water or might be a result of reduced perfusion of the lung. We do not have post-mortem values to compare with the ETV_L in shock values. However, when blood was removed quickly at the beginning of the shock period perfusion dependence of ETV_L should have resulted in an immediate fall in ETV_L. ETV_L values are not all plotted in Figure 2 and on closer inspection ETV_L falls gradually while blood is removed quickly, thus supporting an actual fall in lung water rather than an artefact produced by perfusion dependence of ETV_L. To further substantiate the accuracy of ETV_L (as a measure of lung water) the lungs were removed, weighed, homogenized and dried to give us an independent value for lung water at the end of the experiment. The ratio of ETV_L/post mortem values in previous experiments was 1.20 ± 0.29.[6] This was not significantly different from the value of 1.35 ± 0.30 obtained at the end of this experiment.

Table I indicates the alveolar to arterial oxygen gradients during the experiment. In shock the $A\text{–}aO_2$ gradient did not change significantly. QS/QT fell and PaO_2 rose in the same period (Figure 3) indicating that hyperventilation had increased the alveolar oxygen tension. Once blood and bicarbonate were infused ventilation was reduced and $A\text{–}a\Delta O_2$, QS/QT and PaO_2 returned to control values. While the end mean $A\text{–}a\Delta O_2$ value of 29.1 mm Hg was higher than the end control mean value of 23.7 mm Hg the difference was not significant. This agrees with the QS/QT and PaO_2 values. With a 34 per cent increase in lung water and the pulmonary vascular changes which occurred, a reduction in arterial oxygenation might have been ex-

TABLE I

ALVEOLAR TO ARTERIAL O_2 GRADIENTS
in the phases of the experiment (mmHg)

	Control		Shock			Retransfusion		
	Begin	End	Early	Mid	Late	Early	Late	HCO_3^-
$A\text{-}aO_2$	18.4	23.7	21.7	28.7	26.0	19.4	23.4	29.1
1 S.D.	2.5	3.7	3.2	3.7	4.9	2.1	2.4	4.1

pected. However, in hypervolaemic pulmonary oedema we found that arterial oxygenation did not fall until lung water had increased more than 60 per cent.[10] The pulmonary vascular constriction or obstruction seen here did change VD/VT but, unless there was also reduced ventilation to perfused areas of the lung, vascular changes would not be expected to lower PaO_2. Our data agree with the clinical findings that shocked patients are often seen with a normal PaO_2 and that it is not for days or weeks after the shock period that significant hypoxia develops.

Summary

This study has demonstrated a 34 per cent rise in lung water after shock and retransfusion of blood. This extra lung water was associated with increased pulmonary artery pressure, increased pulmonary vascular resistance and reduced myocardial performance. These findings occurred despite the failure of arterial pressure to return to normal after retransfusion of blood. Although this increased lung water is less than anything which can be detected clinically it may represent the beginnings of the shock lung syndrome as oedema progresses over period of weeks. A reasonable approach to the problem should include attempts to reduce the elevated pulmonary vascular resistance. $NaHCO_3$ should be infused before or during administration of the first bottle of blood in an attempt to improve myocardial function and reduce pulmonary vascular resistance. Fluids should not be infused simply to return arterial pressure to a level considered normal but with consideration to pressures in the pulmonary vascular bed. Pulmonary artery and wedge pressure monitoring with Swan Ganz catheters may improve the management of shock patients.

Résumé

Cette étude effectuée chez l'animal a démontré une augmentation de 34 pour cent du volume liquidien pulmonaire après production de choc hémorragique et retransfusion du sang enlevé. On a observé parallèlement une augmentation de la pression de l'artère pulmonaire, de la résistance vasculaire pulmonaire et une diminution du débit cardiaque. Ces changements sont survenus bien que les chiffres de P.A. n'aient pas remonté aux niveaux précédant la saignée. Bien que l'augmentation du volume liquidien pulmonaire observée soit trop petite pour être diagnostiquée cliniquement, elle peut être le début d'un syndrôme de "poumon de choc" alors que l'oedème continue à progresser durant les semaines suivantes.

Considérant ces faits, un traitement préventif devrait viser à diminuer la pression vasculaire pulmonaire.

L'on devrait administrer du bicarbonate avant ou durant l'administration du sang (acide) afin d'améliorer la fonction myocardique et diminuer la résistance vasculaire pulmonaire. L'on devrait garder à l'esprit les problèmes pulmonaires possibles lorsque l'on refait le volume sanguin et ne pas uniquement viser à retrouver la pression artérielle initiale. A cet égard, la mesure des pressions pulmonaires à l'aide d'un catéther Swan-Ganz peut rendre de grands services dans le traitement du choc hémorragique.

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