Pulmonary blood volume in hemorrhagic shock in the dog and primate

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Pulmonary blood volume, vascular resistance, and diffusing capacity for carbon monoxide were compared in the baboon and the dog during experimental hemorrhagic shock. Control pulmonary blood volume represented a larger proportion (6.8%) of total blood volume in the monkey than in the dog (5.4%) associated with greater pulmonary vascular resistance. Proportional decreases in volume occurred in both species during hemorrhagic and postinfusion shock, accompanied by increased resistance. Pulmonary diffusing capacity for carbon monoxide decreased during the bleeding and postinfusion periods, paralleling the decrease in pulmonary arterial and left atrial pressures. No evidence was found for significant pooling of blood in the pulmonary vascular system. The baboon showed a significant decrease in \(^{131}I\) measured blood volume during the later portions of the postinfusion phase. Total systemic resistance failed to increase in the dog experiments.

METHODS

The experiments were carried out in six mongrel dogs weighing from 10.0 to 14.5 kg and in five young baboons weighing from 8.8 to 10.5 kg. Two weeks prior to the hemorrhagic shock procedure each animal was subjected to a left thoracotomy under barbiturate anesthesia. A light-weight, air-core, electromagnetic flow probe was placed about the main pulmonary artery. Silastic catheters were positioned in the left atrium and pulmonary artery, the latter via a purse-string closed incision in the pulmonary outflow tract. The catheters were filled with concentrated heparin solution; the flowmeter and catheter...
ters were brought out of the chest cavity and buried under the skin in the left dorsal scapular region. At the time of the hemorrhagic shock procedure the dogs were premedicated with morphine sulfate (3 mg/kg im) 1 hr prior to receiving sodium pentobarbital (15 mg/kg iv). The primates received the same anesthesia except for the use of 1 mg/kg morphine and additional small doses of im methohexital sodium (Brevital, Lilly) for transient anesthesia and handling of the animal. In all other respects the two groups of animals were similarly treated. All experiments were performed using sterile technique and rigorously cleaned tubing and blood containers. Following anesthetization and the insertion of an endotracheal tube, the implanted probe leads and catheters were identified, and connected to the flowmeter (1) and pressure gauges (Statham P23 series). Polyethylene catheters for bleeding and reinfusion were inserted into the femoral artery and vein; the arterial catheter was connected to a pressure transducer and also to the bleeding bottle. A platinum bipolar electrode catheter was introduced through either a femoral or carotid artery and positioned, under fluoroscopic guidance, at the root of the aorta.

The animals were subjected to a standardized hemorrhagic shock procedure. Following a 30-min control period, they were given heparin (3 mg/kg) and bled from the femoral artery cannula into the bleeding bottle. The height of the bottle was adjusted as necessary to maintain the mean arterial pressure of the animal at 40 mm Hg. Bottle volumes were read at 10-min intervals, and note made of the maximum bottle volume. When the animal had spontaneously taken back 30% of the maximum bleeding volume, the remaining blood was reinfused into the femoral vein and the animal followed until death.

Rectal temperature was monitored and kept at approximately 37 C by means of a heat lamp. Pressures were recorded from the femoral artery catheter and the implanted pulmonary artery and left atrial catheters. Zero level of the pressure gauges was roughly at the right atrial level (midthoracic position). Stroke volumes were obtained by using an analogue computer; the ascending limb of the pulmonary artery flow waveform actuated a relay comparator to produce integration of the flow signal during the period of systole with a reset occurring at the end of each systolic period. Zero flow was considered to be the diastolic flow signal. Central blood volume was estimated by slug injection of ascorbic acid into the implanted pulmonary artery catheter in 40-ml doses. The circulating ascorbic acid was sensed by the positively polarized platinum electrode at the root of the aorta and a resultant indicator-dilution curve obtained from an operational amplifier used as a current indicating device (16). Noise was largely eliminated from the signal by means of a 1-sec time constant averaging circuit. Mean transit time (MTT) was obtained from the resultant indicator-dilution curves by planimetry of the computer-integrated curve, by direct calculation using the formula (26):

$$\text{MTT} = \frac{\int_0^\infty C(t) \cdot t \, dt}{\int_0^\infty C(t) \, dt}$$

or through the use of an analogue computer estimation procedure (manuscript in preparation). Appropriate computer or arithmetic corrections were made for recirculation by extrapolating the exponential decays obtained to the original baseline. All indicator curves used for mean transit time studies were performed in duplicate. "Central blood volume" was calculated as (cardiac output/60) X mean transit time where mean transit time is in seconds and cardiac output is in milliliters per minute. "Left heart blood volume" was calculated from the mean transit times of the curves obtained by similar rapid injections of the indicator into the implanted left atrial catheter. "Pulmonary blood volume" represents central blood volume minus left heart blood volume. Total blood volume was determined by measuring the dilution of the injected 131-I-labeled serum albumin with a "Volemetron" (25) following a mixing period of 10 min.

All parameters except total blood volume were usually measured every 10 min in the control period, every 10 min after hemorrhage for 30 min, every 10 min after reinfusion for 30 min, and every 30 min throughout the remainder of the bleeding and postinfusion phases until death. Total blood volume was determined in duplicate during the control period; single determinations were made approximately every 30 min during the postinfusion period. In some of the very long experiments ascorbic acid and 131I injections were made at 1-hr intervals to avoid adding large amounts of fluid to the animal.

At the end of each experiment the electromagnetic flow transducer was calibrated by perfusion in situ with the appropriate dog or monkey blood, collecting the perfused blood in a graduated cylinder for timed intervals. In some cases the flow probe was removed and calibrated in vitro using an excised portion of pulmonary artery or aorta; the calibration curve for a particular probe is not altered by using either arteries or veins (4).

Breathholding diffusion capacity for carbon monoxide (DLCO) was determined in another set of experiments in an additional five dogs and four baboons subjected to the same hemorrhagic shock procedure. In each instance the anesthetized animal was placed on its back in an airtight box with an endotracheal tube connected through the wall of the box to the ventilating apparatus. By means of a Hans-Rudolph five-way valve attached to the box, the interior could be vented to the atmosphere during periods between DLCO measurements or, alternately, connected to a source of negative or positive pressure when the diffusing gas mixture was to be inspired or the expired sample was to be collected. This method as modified for use with anesthetized animals has previously...
FIG. 1. Comparison of response of dog and monkey to hemorrhage and reinfusion. See text for details of procedure. Values shown are means ± se. Time in percent of duration of each period, C for control period.

RESULTS

The results are presented in Figs. 1–3 and Table 1. The left half of each figure represents the data obtained in the dog experiments, the right that from the monkey experiments. Time is given in percent of the total time that elapsed in a given animal during the period of hemorrhage or of postinfusion. For the dog experiments the mean time for the hypovolemic phase was 193 ± 26 min (mean ± se) with a range from 130 to 285 min. Postinfusion survival time was 179 ± 25 min with a range from 120 to 282 min. Corresponding times in the monkey experiments were 184 ± 11 min (range 110–300 min) for the hypovolemic phase and 413 ± 46 min (range 66–900 min) for the postinfusion period. The control period was 30 min in all animals.

Figure 1 indicates the alterations in systemic arterial pressure, pulmonary artery pressure, left atrial pressure, cardiac output, and heart rate during the course of these experiments. With a few exceptions the patterns in the monkey are the same as in the dog. Systemic arterial pressure was maintained at approximately 40 mm Hg during the period of hemorrhage. Following reinfusion, the dog's pressure returned to 75 mm Hg, or 76% of the control; the monkey's recovered to 73 mm Hg, 77% of control. At 50% of the postinfusion period the systemic pressures were 64 and 60 mm Hg in the dog and monkey, respectively. Both groups declined fairly steadily until death.

Pulmonary artery pressure decreased initially in both groups during hemorrhage, then tended to recover slightly. Following reinfusion pulmonary artery pressure was 121% of control in the dog and 107% in the baboon. Both groups declined slightly to about the control level, then remained constant until just before death. Left atrial pressure also declined during hemorrhage, returned to about the control level after reinfusion, but increased markedly at death, somewhat more so in the baboon than in the dog.

During hemorrhage, cardiac output fell to 38% of the control value in the dog and 43% in the monkey and remained at about this level throughout the period. On reinfusion the dog's cardiac output returned to 88% of control value and the monkey's to 105%. A gradual decline followed with a value of 59% in the dog and 80% in the monkey at 50% postinfusion time.

Heart rates were moderately higher (165 vs. 131) in the monkey than in the dog, increased moderately with
PULMONARY BLOOD VOLUME IN HEMORRHAGIC SHOCK

Dog Monkey

Hemorrhage Post-infusion

PULMONARY VASCULAR RESISTANCE (% of Control)

TOTAL PERIPHERAL RESISTANCE (% of Control)

TIME IN PERCENT

FIG. 2. Response of pulmonary vascular resistance and total peripheral resistance in dog and monkey to hemorrhage and rein-fusion. Units are percent of calculated value for control period (C). Otherwise as in Fig. 1.

hemorrhage, and decreased again during reinfusion. Subsequently, they increased in the dog until just before death, but remained relatively constant in the monkey.

Figure 2 was obtained by calculating the corresponding alterations in pulmonary and peripheral resistance. (Right atrial pressure was taken as zero for the systemic resistance calculations.) In the dog pulmonary resistance increased by about 225% during hemorrhage, decreased only partially on reinfusion, remained at this level until 40% time, then increased until death. (Since cardiac output at death is zero, resistance cannot be calculated at this time). Pulmonary resistance increased more in the monkey, to 378% of control, than in the dog, but with considerably more variation from animal to animal (4 of the 5 monkeys showed a marked increase).

Systemic peripheral resistance in the dog, however, showed almost no change throughout both periods, even decreasing below control values at certain times (approximately one-half showed a decrease). In the baboon there were increases up to 156% during the bleeding phase, but no change in the postinfusion period.

The relative changes in total blood volume, bleeding volume, and the volumes of the left heart, pulmonary bed, and central compartment are shown in Fig. 3. Total measured blood volume was 105 ± 6 ml/kg (mean ± SE) in the dog and 64 ± 2 ml/kg in the monkey.

After reinfusion, blood volume in the dog decreased to 86.5 ml/kg (this decrease is not statistically significant). It further decreased slightly until the 60% reading.

At the lowest point the mean volume was 67.4 ml/kg or 78% of the control volume. The monkey returned to about 99% of control after reinfusion, then fell gradually to 64% at 80% time (significant if the indicator is adequately mixed). Maximum bleeding volume was 52 ml/kg (49.5% of total blood volume) in the dog and 26 ml/kg (41% of total volume) in the monkey.

Central blood volume was comparable in the two groups, 11.2 and 10.2 ml/kg in the dog and monkey, respectively, during the control period. This was roughly divided into 55% and 45% in the left heart and pulmonary compartments, respectively. All three decreased during hemorrhage. Pulmonary blood volume decreased to 63% of the control value in the dog and to 45% in the monkey; left heart volume decreased to 46% in the dog and to 33% in the monkey. All returned to about 90% of control values on reinfusion, and declined only slightly until death. The curves were roughly parallel in the two species, although declining somewhat more rapidly in the postinfusion phase in the monkey. Similarly, there was no evidence of a disproportionate shift in volume between the left heart and pulmonary beds.

Table 1 lists the values obtained for diffusing capacity for carbon monoxide (DLco). The changes in the two species were of similar direction and magnitude, decreasing during bleeding, returning to control levels on reinfusion, and decreasing again in the later postinfusion period. In general they parallel the changes in the pulmonary artery and left atrial pressures shown in Fig. 1.
Sections of the lung were stained and examined microscopically. The larger vessels were moderately congested; this was slightly more prominent in the dog than in the monkey. Round cell infiltration was prominent in all sections, although no gross pneumonic process was evident. A few sections contained pink staining fluid in some of the alveoli.

**DISCUSSION**

The responses to hemorrhagic shock in this study were very similar in the two species. The hemodynamic changes shown in Figs. 1 and 3 fail to indicate marked differences. The increase in left atrial pressure terminally does not, by itself, constitute evidence for a failure in cardiac contractility as an important part of the shock picture. The decline in cardiac output during the postinfusion phase was paralleled by a drop in left atrial pressure and circulating blood volume in both species, suggesting that a decrease in venous return is the primary cause of the decrease in cardiac output, rather than the primary defect in cardiac function postulated by Crowell and Guyton (7).

Surprisingly, the dog showed only slight changes in systemic resistance, i.e., arterial pressure and cardiac output fell about equally during the entire procedure. The monkey appeared to vasoconstrict during bleeding but lost this ability during the postinfusion period. His survival times were considerably longer, however.

The lack of systemic vasoconstriction is in direct contradiction to previous studies by other workers in the dog (12, 18, 19), although Wiggers and Middleton (24) noted extremely variable changes in total peripheral resistance in response to similar bleeding techniques. Some of their animals showed a marked increase in resistance, others a marked decrease. The latter was particularly prominent during the period of bleeding. Wegrz et al. (22) also noted a decrease following transfusion in animals subjected to extensive surgery. To our knowledge this is the first such study in which systemic flow was directly measured by a flowmeter, rather than by the use of a circulating indicator-dilution technique. In view of the difficulties in the use of indicator techniques, particularly during the bleeding phase, the previous measurements may have been in error. It may be, however, that the degree of stress plays an important role in determining the amount of constriction produced. Our animals were subjected only to minor surgical procedures, but were bled to the 40-mm Hg level and kept there until 30% uptake had occurred. Unfortunately, the number of animals is too small to make any conclusive statements in this regard. However, further studies are now required to substantiate the concept that the hemodynamic disturbance in hemorrhagic shock is really postarteriolar in location (12).

Total blood volumes were considerably smaller in the monkey than in the dog, as were bleeding volumes. The latter agree well with previous observations in the two groups (3, 9, 21). Since the blood volume is allowed to equilibrate with 131-labeled albumin for only 10 min,
PULMONARY BLOOD VOLUME IN HEMORRHAGIC SHOCK

**TABLE 1. Breathholding diffusing capacity for carbon monoxide (DL$_{co}$) in hemorrhagic shock**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th>Bleeding Phase, At Max Volume</th>
<th>Postinfusion Phase</th>
</tr>
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<tr>
<td></td>
<td>10 min</td>
<td>30 min</td>
<td>60 min</td>
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<tr>
<th>Dog No.</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Mean</th>
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<tbody>
<tr>
<td></td>
<td>7.7</td>
<td>8.1</td>
<td>7.4</td>
<td>4.5</td>
<td>9.6</td>
<td>7.5</td>
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<td></td>
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<td>±1.1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Baboon No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
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<td>3.0</td>
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<td>2.9</td>
<td>5.4</td>
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<tr>
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<td>±1.3</td>
<td>±1.3</td>
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The units are ml/min × mm Hg.

it is of course possible that the apparent decrease in measured volume during the postinfusion phase is not due to actual extravascular loss of volume, e.g., by an increase in vascular permeability, but rather due to sequestration in some particular area. In the dog this area may be the splanchnic bed; however, in the primate there is considerable evidence against such pooling (3, 9, 21). The control volumes (105 ± 6 ml/kg) were somewhat high (14, 17), but probably within normal limits considering the small number of animals involved.

Calculated central, left heart, and (by difference) pulmonary blood volume decreased proportionately in both groups during hemorrhage, returned to near control values on reinfusion, and declined slowly until death. The three curves are nearly parallel and do not differ significantly between the two species. “Left heart” blood volume has rather undefined boundaries. It should include the volume between the left atrial injection site and the sampling site just above the aortic valve, at least insular as adequate atria1 mixing occurs. The resultant control pulmonary blood volume measurements for the dog and the monkey are very similar and agree well with previous estimates (10, 20). Relative pulmonary blood volume was greater in the monkey than in the dog, being 6.8% of total blood volume for the monkey and 5.4% for the dog.

All injections were made during expiration in the dog experiments, with all but one of the dogs on an artificial respirator (16/min). No difference was seen in the exception. Since the transit time averaged about 8 sec from the pulmonary artery to the aorta, more than one respiratory cycle was involved. In preliminary experiments, we were unable to detect significant changes in transit time if the indicators were injected during inspiration or expiration. All of the monkeys were studied without the use of a respirator (which they seemed to tolerate much better than did the dogs) and the injections were given without regard to respiratory phasing.

Measured pulmonary vascular resistance increased in both groups during the hemorrhage and later postinfusion phases, although the magnitude of the increases was, again, not as marked as previously reported in the dog for the hemorrhage and early postinfusion phases (19). The increase in calculated resistance may reflect either active vasoconstriction or merely a passive change in calculated resistance. The latter would be expected when left atrial pressure becomes less than alveolar pressure and resistance becomes dependent on the pulmonary artery-alveolar gradient rather than on the pulmonary artery-left atrial gradient. Absolute values for pulmonary vascular resistance were much higher (about double) in the monkey than in the dog, due to somewhat higher pulmonary arterial pressures together with lower cardiac outputs. Control peripheral resistance was about 35% greater in the monkey than in the dog.

The hypothesis leading to these studies was that pooling might occur in the pulmonary bed during hemorrhagic shock. Our studies do not support that hypothesis as there was an increase in pulmonary vascular resistance accompanied by a decrease in pulmonary blood volume in both species.

The changes in pulmonary diffusing capacity observed in this series of experiments were similar in the dog and in the primate and correlated well with the pulmonary artery and left atrial pressures. These results are also similar to those previously reported for the dog alone by Jonassett-Strieder et al. (13). Other studies in man and in the isolated cat lung preparation have correlated changes in DL$_{co}$ with parallel changes in central vascular pressures (8, 15).

Finally, despite other serial studies in the dog (11) that do not show evidence of a decrease in circulating
blood volume, we did obtain a significant decrease in the monkey. Assuming that sequestration is not occurring in a particular bed, this would appear to be evidence for increased capillary permeability either in general or in some particular area not thus far studied. The congestion seen microscopically in the pulmonary vessels is probably terminal in nature and correlated with the late elevation in left atrial pressure.

In summary, these studies have failed to reveal a significant decrease in pulmonary vascular resistance during hemorrhagic shock in either the dog or the primate. Pulmonary diffusing capacity for carbon monoxide increased capillary permeability either in general or in some particular area not thus far studied. The congestion and probably no alteration in the alveolar membrane.

Significant areas of pooling may exist, however, in other sites in the primate, or there may be a generalized increase in vascular permeability. In general, the baboon demonstrated a more consistent response in his increased systemic and pulmonary resistance than did the dog. The primates withstood the shock procedure better, constricted more, bled less, and survived longer than did the dogs. Survival time may, however, be due to the young animals used, as this has not been consistently true of the monkey (3, 21), although Einheber and Cerilli (9) did find long survival times in their animals.

REFERENCES