THE EFFECTS OF VARIATIONS IN END-EXPIRATORY INFLATION PRESSURE ON CARDIORESPIRATORY FUNCTION IN NORMO-, HYPO- AND HYPERVOLAEMIC DOGS

BY

SUMMARY
The effects of altering end-expiratory inflation pressure were studied in mechanically ventilated dogs in the normo-, hypo- and hypervolaemic state. The mean fall in cardiac output resulting from an increase in end-expiratory pressure was smaller in the hypervolaemic group than in the other two groups. A positive end-expiratory pressure increased the mean deadspace/tidal volume ratio in all groups. A negative end-expiratory pressure increased venous admixture, particularly in the over-transfused animals, but the increase was not significant in the hypovolaemic group. A negative end-expiratory pressure did not affect deadspace/tidal volume ratio.

The effects of variations in end-expiratory inflation pressure on cardiorespiratory function during controlled ventilation have been studied by Frumin and associates (1959), Finley and associates (1960), Watson (1962), Nunn, Bergman and Coleman (1965), Grenvik (1966), Bergman (1967), Cheney, Hornbein and Crawford (1967) and McIntyre, Laws and Ramachandran (1969).

The object of the present studies was to discover whether the changes in cardio-respiratory function resulting from the use of various end-expiratory pressures would be affected by alterations in cardiac function resulting from hypovolaemia or cardiac failure. Since it proved difficult to induce a stable state of cardiac failure during acute experiments, the observations were restricted to the normo-, hypo- and hypervolaemic state.

METHODS
The studies were performed on nine greyhounds before and after haemorrhage and a further nine greyhounds before and after overtransfusion. The average weight of these two groups of dogs was 27.4 and 24.5 kg respectively. The general plan of the experiments, the analytical methods and the effects of haemorrhage and overtransfusion have been reported in a previous paper (Sykes et al., 1970).

Two ventilators were used during these studies. The first was a modified Cape Ventilator (Waine and Fox, 1962). The valve box of this machine was removed and replaced by two solenoid-operated valves situated close to the endotracheal tube. The solenoids were timed by micro-switches controlled by two special cams fixed to the camshaft of the ventilator. The cams were shaped so that the inspiratory:expiratory ratio was 1:2 but there was a 10° interval between each phase of respiration when both valves were closed. Inspiratory and expiratory gas streams were thus separated at all times. A positive end-expiratory pressure of 10 cm H2O was produced either by a weight-operated valve or by a screw clip on the expiratory tube, whilst the negative end-expiratory pressure was generated by the standard negative pressure bellows.

The second ventilator was a waveform generator of our own design. The positive pressure bellows was driven by a cam so that the inspiratory flow pattern was sinusoidal. The end-expiratory pressure was produced by a weight-
operated valve or a screw clip on the expiratory tube. The negative pressure phase was generated by the tension of a spring acting on a bellows, the latter being emptied during inspiration by a cam. The inspiratory-expiratory ratio was 1:2 and the direction of gas flow was controlled by poppet valves on the ventilator. The compressible volume of the ventilator tubing leading to the animal was 6.5 ml/10 cm H₂O.

The frequency was set at 20 b.p.m. and the tidal volume was adjusted to produce an end-tidal carbon dioxide concentration of 4-5 per cent.

All experiments commenced with an end-expiratory pressure of zero. After completing the first set of readings the end-expiratory pressure was adjusted to +10 or -10 cm H₂O and, after a period of at least 30 minutes, a second set of readings was taken. The end-expiratory pressure was then altered to the remaining pattern and the third set of readings was taken. The end-expiratory pressure was reset to zero and the animal either bled or overtransfused to the required level. After correction of any acid-base imbalance, the three sets of readings were repeated. Alternate dogs were bled and over-transfused and the order of the positive or negative end-expiratory pressures was varied randomly between dogs, although the same order was retained for both states of blood volume in each dog.

RESULTS

The effects of bleeding and overtransfusion have been detailed elsewhere (Sykes et al., 1970). The same symbols are used in this paper.

Normovolaemia.

The mean airway and blood pressures varied as would be expected (table I). Total thoracic compliance fell with the + - waveform, the fall increasing progressively with time. There was no fall in compliance with time with any of the other waveforms.

VT decreased significantly on adding an end-expiratory pressure (+ +) and increased slightly

![Table I](https://academic.oup.com/bja/article-abstract/42/8/669/436172/670)

Changes with end-expiratory inflation pressure in normovolaemic state. Means calculated from 18 dogs. Abbreviations as in text. All gas and blood-gas tensions expressed as at body temperature.
when a subatmospheric pressure was applied (+ -). Despite this VpPhys increased on ++ ventilation but was unchanged with + - ventilation. PaCO2 increased slightly with ++ and decreased slightly with + - ventilation. VCO2 decreased significantly with ++ ventilation but there were no changes in VO2. The A-a PO2 was least with the ++ waveform and greatest with the + - waveform. The reduction in Qs/Qt with the ++ waveform was not significant but there was a highly significant increase with + - ventilation. There was a significant fall in CO with ++ ventilation, the reduction in stroke output with this pattern of ventilation being partially compensated by an increase in pulse rate. There was no change in cardiac output on the + - waveform.

**Hypovolaemia.**

The mean of the mean arterial pressures was 67 mm Hg on the + o waveform (table II). In a series of preliminary experiments it proved difficult to reach much lower pressures than this since cardiac arrest frequently occurred, particularly when the ++ waveform was applied. Arterial pressure immediately increased when the + - waveform was used. Mean total thoracic compliance was significantly reduced on the + o waveform. There was a significant increase in VD/VT ratio on the ++ waveform and a small reduction on the + - waveform. There was a significant increase in VCO2 on the + - waveform but the change in VO2 was not significant. Changes in venous admixture were minimal even on + - ventilation, but there was a significant increase in cardiac output with this waveform.

**Hypervolaemia.**

Total compliance was significantly reduced on the + - waveform (table III). Changes in dead-space and PaCO2 were similar to the changes recorded in the normovolaemic and hypovolaemic
TABLE III

Changes with inflation pressure in hypervolaemic state. Means calculated from 9 dogs. Abbreviations as in text. All gas and blood-gas tensions expressed as at body temperature.

<table>
<thead>
<tr>
<th>Waveform</th>
<th>+ o</th>
<th>+ +</th>
<th>+</th>
<th>+ o/+ +</th>
<th>+ o/+ -</th>
<th>+ +/+ -</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>(S.D.)</td>
<td>Mean</td>
<td>(S.D.)</td>
<td>Mean</td>
<td>(S.D.)</td>
</tr>
<tr>
<td>Cr</td>
<td>36.9</td>
<td>(15.9)</td>
<td>36.9</td>
<td>(16.6)</td>
<td>24.5</td>
<td>(11.4)</td>
</tr>
<tr>
<td>Mean airway pressure (cm H₂O)</td>
<td>3.6</td>
<td>(1.0)</td>
<td>14.9</td>
<td>(2.8)</td>
<td>2.2</td>
<td>(2.3)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>133</td>
<td>(23)</td>
<td>142</td>
<td>(14)</td>
<td>149</td>
<td>(21)</td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>25.8</td>
<td>(5.7)</td>
<td>28.8</td>
<td>(4.7)</td>
<td>25.6</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Mean CVP (mm Hg)</td>
<td>15.2</td>
<td>(3.8)</td>
<td>15.0</td>
<td>(3.3)</td>
<td>13.9</td>
<td>(2.8)</td>
</tr>
<tr>
<td>VT (ml BTPS)</td>
<td>427</td>
<td>(110)</td>
<td>403</td>
<td>(103)</td>
<td>442</td>
<td>(103)</td>
</tr>
<tr>
<td>VD Phys (ml BTPS)</td>
<td>221</td>
<td>(61)</td>
<td>237</td>
<td>(61)</td>
<td>228</td>
<td>(59)</td>
</tr>
<tr>
<td>VD/VT (%)</td>
<td>51.6</td>
<td>(5.5)</td>
<td>58.7</td>
<td>(6.1)</td>
<td>51.2</td>
<td>(4.6)</td>
</tr>
<tr>
<td>a-V O₂ (mm Hg)</td>
<td>1.4</td>
<td>(3.2)</td>
<td>1.2</td>
<td>(2.9)</td>
<td>1.8</td>
<td>(4.1)</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>34.6</td>
<td>(4.6)</td>
<td>39.8</td>
<td>(8.0)</td>
<td>34.7</td>
<td>(4.2)</td>
</tr>
<tr>
<td>Vco, (ml/kg/min STPD)</td>
<td>6.28</td>
<td>(1.28)</td>
<td>5.55</td>
<td>(0.57)</td>
<td>6.29</td>
<td>(1.42)</td>
</tr>
<tr>
<td>Vo, (ml/kg/min STPD)</td>
<td>7.19</td>
<td>(1.04)</td>
<td>7.07</td>
<td>(1.05)</td>
<td>7.21</td>
<td>(0.89)</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>113</td>
<td>(9)</td>
<td>104</td>
<td>(9)</td>
<td>115</td>
<td>(5)</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>90</td>
<td>(13)</td>
<td>81</td>
<td>(16)</td>
<td>63</td>
<td>(11)</td>
</tr>
<tr>
<td>a-a Po, (mm Hg)</td>
<td>20</td>
<td>(10)</td>
<td>17</td>
<td>(10)</td>
<td>49</td>
<td>(10)</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>6.8</td>
<td>(5.3)</td>
<td>9.4</td>
<td>(12.8)</td>
<td>26.0</td>
<td>(12.6)</td>
</tr>
<tr>
<td>a-v O₂ (vols %)</td>
<td>4.19</td>
<td>(1.57)</td>
<td>4.27</td>
<td>(1.54)</td>
<td>4.10</td>
<td>(1.81)</td>
</tr>
<tr>
<td>CO (l./min)</td>
<td>4.34</td>
<td>(1.31)</td>
<td>4.37</td>
<td>(1.36)</td>
<td>5.15</td>
<td>(1.96)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>29.3</td>
<td>(8.8)</td>
<td>30.1</td>
<td>(7.1)</td>
<td>34.1</td>
<td>(13.0)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>159</td>
<td>(24)</td>
<td>148</td>
<td>(25)</td>
<td>163</td>
<td>(18)</td>
</tr>
</tbody>
</table>

states. There were no significant differences in Vo, and Vco but there was a fall in PaO₂ and increase in Qs/Qt on both the + + and + - waveforms. These changes were, however, only significant on the + - waveform. There were no significant changes in cardiac output.

DISCUSSION

Compliance.

The use of the end-inspiratory airway pressure to measure total thoracic compliance may cause an error if airflow is occurring when the measurement is made. No measurements of airflow were made during these studies but the presence of a reasonable plateau of pressure at the end of inspiration suggested that airflow at this time was negligible. It was therefore felt that the measurements provided a reasonable indication of changes in total thoracic compliance.

The addition of a subatmospheric phase invariably produced a fall in compliance, whatever the state of blood volume. The rate of fall after switching to the negative phase did not appear to vary with the state of blood volume and in all the animals the fall in compliance could be completely reversed by the Valsalva manoeuvre. Although the fall in compliance with the + - waveform was associated with an increase in venous admixture in the normovolaemic and hypervolaemic states, this was not observed in the hypovolaemic animals. This confirms the finding of Velasquez and Farhi (1964) that a fall in compliance is not necessarily associated with an increase in intrapulmonary shunting.

It was noteworthy that no increase in compliance resulted from the addition of positive expiratory pressure. Indeed, in the hypovolaemic state the compliance on the + + waveform was less than on the + o waveform. It has been suggested that, normally, the distension of the pulmonary vascular bed provides structural airway support which facilitates entry of gas into terminal respiratory units at diminished pressure, and that a reduction in pressure in the pulmonary circula-
EFFECTS OF VARIATIONS IN END-EXPIRATORY INFLATION PRESSURE

...tion might account for the fall in compliance sometimes reported after haemorrhage (Giannelli, Ayres and Buehler, 1967). However, compliance on the +o waveform was higher after haemorrhage than in the normovolaemic state and it would therefore seem more reasonable to postulate some other mechanism which might be induced by prolonged hypotension. For example, it is known that histamine is released in haemorrhagic shock and that this causes terminal airway collapse (Attinger, 1960; Marshall, 1969). Whatever the cause of the changes associated with changes in blood volume it would appear that there is little or no recruitment of previously closed alveoli when a positive end-expiratory pressure is applied.

**Tidal volume.**

Tidal volume fell when the end-expiratory pressure was raised and increased when a negative end-expiratory pressure was applied. The difference in volume could not be accounted for by the difference in volume compressed in the ventilator tubes and conducting airways since the difference in pressure between the end of inspiration and end of expiration remained approximately the same despite changes in end-expiratory pressure. The reduction in volume on the + + waveform was finally traced to three sources—slight leak-back at the inlet valve to the bellows, compression of the gas remaining in the bellows at the end of the compression stroke, and distension of the bellows. The increased tidal volume on the + - waveform was mainly due to the lowered end-expiratory position of the lungs: when the inspiratory poppet valve opened the subatmospheric pressure in the airways caused air to be sucked in through the gravity-operated inlet valve to the positive pressure bellows: the lungs were therefore able to return to the normal resting expiratory position before the compression stroke of the bellows once again closed the flap on the inlet valve. This fault was remedied in the later experiments by limiting the fresh gas inflow to the bellows.

**Deadspace/tidal volume ratio.**

In all the states of blood volume there was a marked increase in deadspace/tidal volume ratio when a positive end-expiratory pressure was applied. This could be due to an increase in anatomical deadspace or an increase in alveolar deadspace.

Martin and Proctor (1958) and Kilburn (1960) have demonstrated that the dog's trachea stretches when the transmural pressure is increased and it is now generally agreed that anatomical deadspace increases with end-inspiratory lung volume (Fowler, 1948; Shepard et al., 1957; Severinghaus and Stupfel, 1957). There is, however, some dispute about the changes in alveolar deadspace. Fawkow and Pappenheimer (1955) found an increase in series (anatomical) deadspace in cats when transpulmonary pressure was increased during mechanical ventilation and they also noted an increase in parallel (alveolar) deadspace at transpulmonary pressures of 13–20 cm H₂O in a number of animals. Similar changes were noted in two human subjects breathing against mean mask pressures of 20 cm H₂O. Bitter and Rahn (1956) confirmed this observation in dogs in which transpulmonary pressure was increased by the application of a subatmospheric pressure to the outside of the chest. On the other hand, both Severinghaus and Stupfel (1957) and Schorer and Piiper (1963) have demonstrated a reduction in alveolar deadspace with increasing lung volume in dogs whilst Workman and associates (1965) claim that there is no change in the proportion of alveoli without effective perfusion. The latter authors, however, had eliminated changes in pulmonary blood flow by utilizing a right heart bypass preparation.

In the present studies there was a small reduction in the arterial-to-alveolar Pco₂ difference when a positive end-expiratory pressure was applied, thus suggesting that there was a reduction in alveolar deadspace. Such a change in alveolar deadspace is of importance with that expected from the haemodynamic considerations put forward by West, Dollery and Naimark (1964). It would be expected that a rise in intra-alveolar pressure would diminish the capillary blood flow in the alveoli in the uppermost parts of the lung (where pulmonary arterial pressure was lowest) and that a rise in intra-alveolar pressure would therefore increase alveolar deadspace, the converse occurring with a fall in intra-alveolar pressure. This pattern would be expected to be accentuated by...
haemorrhage (when pulmonary arterial pressure is low). Although the changes in alveolar deadspace with haemorrhage and overtransfusion follow the expected pattern, the change with inflation pressure does not. The explanation may be that the change in airway pressure has a greater effect on the overperfused parts of the lung and so diverts blood away from this area, thereby improving the perfusion of the previously underperfused parts of the lung. This suggestion is supported by the increase in pulmonary artery pressure which occurs synchronously with each inflation phase. An alternative explanation is that the increase in lung volume resulting from an increase in end-expiratory pressure may improve the distribution of air so that more is delivered to the overperfused alveoli. As a result, less would be forced into the underperfused alveoli. Whatever the reason, it is apparent that in these experiments the increase in anatomical deadspace on the + + waveform was greater than the reduction in alveolar deadspace: \( \frac{V_d}{V_T} \) ratio was therefore increased. On the + - waveform the changes were in opposite directions and \( \frac{V_d}{V_T} \) ratio was unchanged. It is notable that the marked increase in \( \frac{V_d}{V_T} \) ratio on the + - waveform noted by Watson (1962) could not be confirmed.

Total venous admixture.

Since all these measurements were made when the animal was respiring 21 per cent oxygen the venous admixture effect could have been due to ventilation/perfusion inequality or right-to-left shunts in the lung or elsewhere. An increase in end-expiratory pressure could reduce the contribution of either of the intrapulmonary sources of venous admixture but without measurements on 100 per cent oxygen it is impossible to decide which of these two mechanisms predominated. However, the effects of the + + and + - waveforms in the hypovolaemic and hypervolaemic states were strikingly different. In the hypovolaemic state a negative phase caused no increase in venous admixture whilst in the hypervolaemic state the total venous admixture rose to 26 per cent of the cardiac output. The most likely explanation of these differences is that the application of a negative phase will increase intrapulmonary blood volume. When this is already increased by generalized hypervolaemia the further increase resulting from the negative phase will severely limit ventilation to the most congested regions of the lung and venous admixture will be increased.

Another possibility is that the negative phase may have induced pulmonary oedema by its action on the pressure gradients across the alveolar-pulmonary capillary wall. Indeed, in these experiments there is some evidence that pulmonary oedema must have been accumulating during the hypervolaemic period, for it may be seen that in this group of animals venous admixture was greater on the + + waveform than it was on the + o pattern of inflation. This difference is probably accounted for by the fact that the + o pattern was always studied first whilst the other two waveforms were investigated later.

A third possible explanation for the increased venous admixture with the + - waveform is that the negative phase produced alveolar collapse with a consequent increase in shunt. It was notable in a number of animals that when the negative phase was removed compliance remained low. If, however, the lungs were hyperinflated there was an immediate return of compliance and oxygen tension to normal levels. This strongly suggests that some alveolar collapse must have occurred.

Whatever the cause of the increased venous admixture with the negative phase it is evident that it is most likely to occur when blood volume is increased but least likely to occur during a period of haemorrhagic hypotension—the time when such a pattern of ventilation is most likely to be used in clinical practice.

**Table IV**

<table>
<thead>
<tr>
<th>Normovolaemia</th>
<th>Hypovolaemia</th>
<th>Hypervolaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ +</td>
<td>+ -</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>103</td>
<td>97</td>
</tr>
<tr>
<td>79</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiac output.**

Table IV shows the changes in cardiac output expressed as a percentage of the value obtained on the + o waveform. The application of the + -
waveform greatly increased cardiac output in the hypovolaemic state but in the hypervolaemic state cardiac output was little affected by changes in end-expiratory pressure.

The effects of overtransfusion are shown more dramatically in figure 1 and table V, where it can be seen that the normal hypotensive response to the Valsalva manoeuvre was completely abolished in the hypervolaemic state.

There are two possible explanations for this. First, the reduction in lung compliance accompanying hypervolaemia might have caused a decrease in the proportion of the airway pressure transmitted to the intrapleural space. This could not have affected intrapleural pressure in these experiments since tidal volume remained constant. Second, the increase in intrapleural pressure during the Valsalva manoeuvre represents a much smaller proportion of the increased transmural venous pressure gradient resulting from over-

transfusion (Watson, Smith and Spalding, 1962). It is of interest that both these mechanisms have also been shown to be operative during cyclopropane anaesthesia (Price et al., 1951)

In one animal, it proved possible to continue transfusion to a venous pressure of 20 cm H$_2$O. This resulted in arterial hypotension and a low cardiac output. It can be seen in table VI that the application of the ++ waveform produced no change in cardiac output even when the animal was in gross congestive cardiac failure.

The apparent difference between the degree of hypotension produced by the Valsalva manoeuvre and the relatively small changes in cardiac output produced by variations in end-expiratory pressure in the hypovolaemic state are probably due to the fact that the changes were recorded about 30 minutes after changing the applied waveform. Indeed in one hypovolaemic dog included in this study and in a number of others not included, cardiac arrest occurred before the reading on ++ ventilation could be completed. Furthermore, survival probably biased the results in favour of those with a minimal change. From an inspection of the blood pressure traces it would seem that the delay allowed maximal compensation for the change in airway pressure to occur.

**CONCLUSIONS**

Bergman (1967) has pointed out that the reduction in alveolar-arterial Po$_2$ difference resulting from an increase in mean airway pressure in the dog is not paralleled in the human. For similar reasons it would be unwise to conclude that all the observations made in these studies could be applied to anaesthetized or conscious humans.
Nevertheless, the observations do suggest that patients with a high venous pressure (provided this is not due to cardiac tamponade) should withstand the effects of a high intrathoracic pressure well. It is in such patients that high mean airway pressures may prove of value clinically (e.g., in the treatment of pulmonary oedema). Conversely a subatmospheric expiratory phase improves cardiac output most dramatically in those who are hypovolaemic. It must be used with circumspection, however, for such a pattern of ventilation tends to cause a progressive decrease in compliance with time.

ACKNOWLEDGEMENTS

The authors would like to thank the Misses B. Bird, E. Packham, S. Greenburgh, and Mr M. Kangalee and Mr M. K. Chakrabarti for skilled technical assistance. A. P. Adams was supported by the Wellcome Trust and the project was supported by the Wellcome Trust and Medical Research Council.

REFERENCES


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**SOMMAIRE**

Les effets du changement de la pression d’inflation à la fin de l’expiration ont été étudiés chez des chiens mécaniquement ventilés en condition normo-, hypo- et hypervolémique. La réduction moyenne du débit cardiaque, qui résulte d’une augmentation de la pression d’inflation expiratoire terminale fut moins grande dans le groupe hypervolémique que dans les deux autres groupes. Une pression positive en fin d’expiration augmenta le rapport moyen espace mort/volume courant dans les trois groupes. Une pression expiratoire terminale négative augmenta le mélange veineux, particulièrement chez les animaux surtransfusés, mais l’augmentation ne fut pas significative dans le groupe hypovolémique. La pression négative à la fin de l’expiration n’influença pas le rapport espace mort/volume courant.

VERÄNDERUNGEN DES END-EXPIRA- TÓRISCHEN DRUCKS UND SEINE WIRKUNG AUF DIE HERZ-ATEMFUNKTION IN NORMO-, HYPO- UND HYPERVOLAEMISCHEN HUNDEN

**ZUSAMMENFASSUNG**


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**MIDLAND SOCIETY OF ANAESTHETISTS**

**Programme for 1970/71**

**TUESDAY, OCTOBER 20, 1970, at the Postgraduate Centre, East Birmingham Hospital**

6.30 p.m. Buffet
7.45 p.m. “Ten years experience of nerve blocks” by Dr W. Brooks
“Critical appraisal of nerve blocks” by Dr E. Thomas

**TUESDAY, JANUARY 19, 1971, at the Postgraduate Centre, Selly Oak Hospital**

6.30 p.m. Buffet
7.45 p.m. Registrars’ papers

**TUESDAY, MARCH 30, 1971, at the Postgraduate Centre, Worcester Royal Infirmary**

6.30 p.m. Buffet
7.45 p.m. “The postoperative period” by Dr J. McN. Inglis and Dr M. E. H. Barrow

**SATURDAY, JUNE 12, 1971, at Coventry; all-day meeting, details to be announced later**