CARDIAC OUTPUT CHANGES WITH ALTERED ACID-BASE STATUS DURING METHOXYFLURANE ANAESTHESIA

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THE PURPOSE OF this study was to determine the effects upon cardiac output of alterations in acid-base states during methoxyflurane anaesthesia in dogs.

Studies of varied acid-base states on cardiac functions have been described *in vitro*¹ and *in vivo*.^{2,3} A clear understanding of cause and effect relationships has been prevented by disparity of results, lack of correlation with surface area or weight, and the inability to correlate effects between dogs. Carson *et al.*⁴ were first to be able to quantitate the separate and opposed effects of change in pH and P_{CO_2} upon cardiac output in studies in dogs with pentobarbital. Cardiac output was shown to be linearly related to pH and exponentially related to P_{CO_2} . From this data, a nomogram was presented in which changes in cardiac output could be predicted from variations in pH and P_{CO_2} . Similar relationships have been described by Tomlin *et al.*⁵ in dog studies with halothane, and by Stoyka *et al.*⁶ in studies with fluroxene in dogs. The present study proposes to determine whether similar effects upon cardiac output are produced by varied acid-base states during methoxyflurane anaesthesia.

METHODS

Mongrel male dogs, with chronically implanted electromagnetic flow probes on the ascending aorta, were induced with thiopentone and the trachea was intubated. Anaesthesia was maintained with a constant expired concentration of 0.23 per cent methoxyflurane (MAC-1)⁷ using a copper kettle vaporizer. Ventilation was achieved with a volume controlled animal respirator during succinylcholine apnoea. Expired carbon dioxide was monitored with an infra-red analyzer to facilitate maintenance of ventilation appropriate to an arterial carbon dioxide tension of 40 ± 3 torr.

The femoral artery was cannulated and blood pressure was recorded using a resistance transducer. Arterial cannulation allowed blood sampling for determinations of arterial pH, P_{O_2} , P_{CO_2} and electrolytes. Arterial blood levels of methoxyflurane were determined by gas chromatography. A central venous pressure catheter was inserted for measurement and intravenous infusions. Oesophageal temperature was measured by a telethermometer and maintained at $37 \pm 1^\circ\text{C}$. Blood gas analyses were corrected to animal temperature using appropriate correction factors.^{8,9}

Figure 1 illustrates the laboratory set up which is utilized for this study.

The electromagnetic flow probe was connected to a recording dynograph and a flow wave was obtained. An integral of this wave form was triggered by the electrocardiogram QRS to obtain a trace of stroke volume for each heart beat, according to

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FIGURE 1
Illustration of the methodology and parameters to be measured in this study.

FIGURE 2
A tracing of the recorded flow wave form amplified and integrated to obtain stroke volume. Other data are included in this tracing.

the method of Scher.¹⁰ Comparison of this method for determination of cardiac output with that of dye dilution technique has shown a correlation coefficient of 0.9.¹¹

Figure 2 shows an actual tracing of flow wave forms and stroke volumes obtained along with other dynograph recorded parameters.

Four acid-base states were produced and studied; metabolic acidosis and alkalosis, respiratory acidosis and alkalosis. Metabolic acidosis data was obtained by two methods. A form of exogenous metabolic acidosis was produced by the intra-

FIGURE 3
Data from two metabolic acidosis experiments illustrates the linear relationship of pH to cardiac output with P_{aCO_2} constant.

venous infusion of 20 mls of 0.6 M hydrochloric acid. Metabolic acidosis data was also obtained by subjecting animals to deliberate hypoxia. Cardiac output measurements and arterial blood gas determinations were made approximately 25 and 40 minutes after acid infusion, or after 20 minutes recovery from hypoxia. Metabolic alkalosis was produced by the intravenous infusion of 30 mls of 5 per cent sodium bicarbonate. Once again cardiac output measurement and blood gas determinations were made approximately 25 and 40 minutes after alkali infusion.

Respiratory acidosis was studied during alterations of respired concentrations of carbon dioxide at steps of 0, 5, 10, 15, 20, 15, 10, 5, and 0 per cent. Cardiac output measurements and blood gas determinations were obtained 20 minutes after each change in percent carbon dioxide. Respiratory alkalosis data were obtained using constant volume hyperventilation and incremental removal of mechanical dead space. Cardiac output determinations and blood gas determinations were obtained 20 minutes after each decrease in mechanical dead space.

A laboratory animal was subjected to one acid-base state on one laboratory day. Occasionally, an animal was re-subjected to the same acid-base state to determine whether similar results would be obtained. Where possible, laboratory animals were subjected to other acid-base states after a suitable recovery period from earlier experiments. These animals were only used when baseline values for cardiac output and blood gas determination were shown to be similar to previous acid-base studies.

RESULTS

Metabolic acidosis data showed a series of cardiac output values at varied pH levels consequent upon hydrochloric acid infusion. Figure 3 represents sample

FIGURE 4

Data from all metabolic acidosis studies converted to a percentage to show the linear relationship of pH to percent cardiac output. A mathematical equation is shown for this linear relationship.

data from two animals which show that cardiac output declines in a linear fashion with decreasing pH, with PCO_2 held constant at 40 ± 3 torr. Solid lines indicate the mean regression lines. In order to compare results from individual animals, cardiac outputs were converted to a percentage using the assumption that normal 100 per cent cardiac output occurred at a pH of 7.40. In example M, 100 per cent cardiac output is 2.36 litres. The regression line shows 50 per cent cardiac output to be 1.18 litres at a pH of 7.02.

When cardiac output data from eleven experimental animals are converted from litres/minute to a percentage of the normal cardiac output at pH 7.40, it is possible to compare the change in percent cardiac output between all metabolic acidosis experiments. Figure 4 illustrates a comparison of 11 individual linear slopes for the percent cardiac output - pH relationship. The mean slope is 154 with a standard deviation of ± 10.4 . This linear relationship between percent cardiac output and pH can be expressed mathematically as:

$$C.O. = 1.54 (pH - 7.4) + 1$$

Metabolic acidosis studies require several points of clarification. Base-line values for cardiac output and blood gas measurements are obtained at the start of each procedure. After injection of hydrochloric acid or after a period of hypoxia, cardiac output was seen to increase above base-line values due to an increase in heart rate and a slight increase in stroke volume. In this study baseline values were taken, but not used to calculate cardiac output-pH relationships.

Normal blood gas values in the dog are not identical to humans. It is the experi-

ence of this laboratory that both the anaesthetized and the conscious dog manifest a slight metabolic acidosis with normal pH of 7.35–7.38 and P_{CO_2} of 34–38. In this study six animals were shown to have a pH of approximately 7.30 after one infusion of hydrochloric acid. It was therefore necessary to take a further five animals, previously infused with sodium bicarbonate, to obtain actual recorded pH values above 7.40 after one acid infusion. Since the slopes of the five pre-treated animals were also linear and similar to the untreated animals, the relationship of percent cardiac output to pH was concluded to be constant from 7.40 down to 7.00 in eleven experimental animals.

Metabolic alkalosis studies were obtained from six dogs by intravenous infusion of sodium bicarbonate. Cardiac output rose linearly as pH increased consequent upon alkaline infusion; with the P_{CO_2} stable at 40 ± 3 torr. Repetition of this procedure was continued to the point where cardiac output no longer increased or started to fall. The average pH for this point was 7.48. To compare individual experiments, cardiac output values were converted to a percentage and the individual slopes of percent cardiac output plotted against pH were compared. The mean slope was 146.7 with a standard deviation of ± 36.4 . The relatively slight difference in slopes between metabolic acidosis and alkalosis may be due to the volumes of buffer infused, or to the addition of bicarbonate ions. Metabolic studies therefore reveal the linear relationship of cardiac output to pH through a pH range of approximately 7.00 to 7.50.

It is interesting at this point to analyze cardiac output values above 7.48. Preliminary studies reveal that a parabolic relationship is suspected around this point. A rise in pH above 7.48 produces a fall in cardiac output; which becomes greater as the pH rises. It is also postulated that the optimum pH for cardiac output may be below 7.48 but that the addition of volumes of buffers may be the cause and effect of cardiac output increase.

Respiratory acidosis data were obtained from seven dogs subjected to incremental increases in carbon dioxide. Observed cardiac output was shown to increase with each increment in respired carbon dioxide and decreased as carbon dioxide was withdrawn. The results from one respiratory acidosis experiment are illustrated in Figure 5.

With acid and alkali infusions, the P_{CO_2} was held constant at 40 ± 3 torr to evaluate the effect of the changing pH. In order to evaluate the effect upon cardiac output of P_{CO_2} changes per se, it would be desirable to maintain pH constant at 7.4. However, during hypercapnoea there is an inherent change in pH accompanying the CO_2 accumulation. Therefore, changes in cardiac output from carbon dioxide are the result of the combined effects of pH and P_{CO_2} . To evaluate the stimulant effect of carbon dioxide elevation from the opposed depressant effect of pH requires a devious method.

A factor is applied from the percent cardiac output-pH relationship previously obtained in Figure 4 from metabolic acidosis studies. Each observed cardiac output was mathematically adjusted to the value which would have been obtained by that level of carbon dioxide had there been no depressant effect of pH changes coincident to hypercapnoea. The result is as though pH had been held constant at

FIGURE 5

The solid line illustrates the results of one respiratory acidosis study with combined pH and PaCO₂ effects on cardiac output. The dashed line illustrates the exponential relationship of PaCO₂ to cardiac output when pH effect is mathematically eliminated (pH adjusted).

FIGURE 6

Data from Figure 5 is converted to a straight line by plotting on semi-logarithmic paper to show the linear relationship of PaCO₂ to pH adjusted cardiac output.

FIGURE 7

Data from all respiratory acidosis studies converted to a percentage to show the linear relationship of P_{aCO_2} to pH adjusted percent cardiac output. A mathematical equation is shown for this linear relationship.

7.4. The exponential relationship of pH adjusted cardiac output to PCO_2 per se is evident in Figure 5.

This exponential relationship can be converted to a straight line when pH adjusted cardiac output is plotted on a logarithmic scale against PCO_2 on an arithmetic scale as shown in Figure 6. Data and the regression line from one hypercapnoea experiment are illustrated. Normal or 100 per cent pH adjusted cardiac output is assumed to occur at a PCO_2 of 40 torr, which is 1.38 litres. A pH adjusted cardiac output of 200 per cent is 2.76 litres at a PCO_2 of 76 torr on the mean regression line.

Conversion of pH adjusted cardiac output in litres/minute to a percentage change allows comparison between hypercapnoea experiments. A comparison of individual slopes for seven hypercapnoea experiments is illustrated in Figure 7. The mean slope is 0.00883 with a standard deviation of ± 0.00045 . The relationship between percent pH adjusted cardiac output and PCO_2 can be expressed mathematically as:

$$C.O. = 10^{0.00883 (P_{CO_2} - 40)}$$

Respiratory alkalosis data were obtained in 5 dogs using constant volume hyperventilation and incremental removal of mechanical dead space. Cardiac output was observed to decrease with hypocapnoea. When observed cardiac output was pH adjusted and converted to a percentage, the mean slope from hypocapnoea studies was 0.01823 with a standard deviation of ± 0.0022 . These findings are similar to our own observations with fluroxene⁶ and to the observation of Morgan *et al.*¹² with nitrous oxide and oxygen, that cardiac output decreased during respiratory alkalosis. Other factors may account for the hypocapnoea slope. They include possible changes of mean intrathoracic pressure with time, subsequent decrease in venous return, and reduced sympathetic nervous system activity during respiratory alkalosis observed by Moster *et al.*¹⁵

The separate and opposed effects upon cardiac output of pH and PCO_2 can be

FIGURE 8

A nomogram is illustrated to predict percent cardiac output for any pH and P_{aCO_2} values. This is based on observed cardiac outputs with varied acid-base states measured in this study.

combined mathematically. The computed cardiac output is a product of the pH effect upon cardiac output, the PCO_2 effect upon cardiac output, and the normalized or 100 per cent cardiac output at pH 7.4 and PCO_2 40.

$$C^1C^1 = [1.54.(pH - 7.40) + 1] [10^{0.00883 (P_{aCO_2} - 40)}] C\dot{N}$$

When cardiac output observed in hypercapnoea studies is compared with computed cardiac output, the correlation co-efficient is 0.91. The co-efficient of variance is 3.6 per cent. Hypocapnoea studies revealed a similar correlation co-efficient of 0.93. The co-efficient of variance is 4.1 per cent.

The excellent correlation shown between observed and computed cardiac output enables the derivation of a computed nomogram to predict the effect of any paired values of pH and PCO_2 upon cardiac output. The derived nomogram illustrated in Figure 8 is superimposed on the Siggaard-Andersen nomogram to show percentage cardiac output values of 50, 75, 100, 125, 150 and 175 per cent at various pH and PCO_2 values. The nomogram reflects computed change within the range of measurements in this study. It may be useful to give two examples from the nomogram. Metabolic acidosis with a pH of 7.15 and PCO_2 of 35 would be expected to produce a cardiac output of 50 per cent of normal. Respiratory acidosis with a pH of 7.12 and PCO_2 of 70 would be expected to produce a cardiac output of 100 per cent due to PCO_2 stimulation balancing co-incident opposed pH depression.

CONCLUSIONS

The effects upon cardiac output of induced metabolic and respiratory changes were studied in dogs during methoxyflurane anaesthesia. Cardiac output declined

in a linear fashion when pH was altered from 7.48 to 7.04 by acid and alkali infusion, while Pco_2 was held constant at 40 ± 3 torr. Cardiac output increased moderately with a rising Pco_2 from 16.5 to 132 torr, despite concomitant changes in pH. When observed cardiac output was mathematically adjusted to maintain pH at 7.4, the pH adjusted cardiac output was shown to increase in an exponential fashion with Pco_2 elevation.

The response of cardiac output to changes in pH and Pco_2 occurred in predictable fashion. Equations were utilized to express the separate relationships of pH and Pco_2 to cardiac output. The combined effect of pH and Pco_2 upon cardiac output was expressed mathematically to obtain computed cardiac output. A nomogram was presented to show expected percentage change in cardiac output at any combination of pH and Pco_2 values.

This study warrants several statements to be made for clinical anaesthesia. Alterations in acid-base states in patients undergoing anaesthesia should affect cardiac output. The degree and extent of cardiac output changes may vary widely from this study done in dogs, but it should be considered when severe derangements in acid-base status occur. This animal model has now been used to study halothane,⁵ fluoroene,⁶ and methoxyflurane. It is obvious that similar models utilized to study other agents, will permit scientific comparison to be made of the effects of all inhalation anaesthetic agents on cardiac output. The results of such studies may eventually dictate which specific agent will have the soundest physiological basis for use in a particular acid-base disturbance.

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RÉSUMÉ

Au cours de l'anesthésie au méthoxyflurane sur des chiens, nous avons étudié les effets sur le débit cardiaque de changements respiratoires et métaboliques provoqués. Le débit cardiaque a diminué de façon linéaire lorsque le pH a été modifié de 7.48 à 7.04 par l'infusion d'acide ou d'alcalin alors que la Pco_2 était maintenue constante à 40 ± 3 torr. Le débit cardiaque a augmenté légèrement avec l'augmentation de la Pco_2 de 16.5 à 132 torr, malgré les changements concomitants du pH. Lorsque le débit cardiaque observé était mathématiquement ajusté pour maintenir le pH à 7.4, le débit cardiaque ajusté au pH augmentait de façon exponentielle lorsqu'on élevait la Pco_2 .

La réponse du débit cardiaque aux changements de pH et de Pco_2 survient de façon prévisible. Nous avons utilisé des équations pour exprimer les rapports séparés du pH et de la Pco_2 avec le débit cardiaque. L'effet associé du pH et de la

PCO_2 sur le débit cardiaque a été exprimé de façon mathématique pour obtenir le débit cardiaque en ces circonstances. Nous avons présenté un nomogramme pour indiquer le pourcentage de changement prévu du débit cardiaque à n'importe quelle variation des valeurs du pH et de la PCO_2 .

Cette étude permet de faire plusieurs affirmations sur l'anesthésie clinique. Des modifications de l'équilibre acide-base chez des malades soumis à l'anesthésie devraient modifier le débit cardiaque. Le degré et les limites des changements du débit cardiaque peuvent varier beaucoup selon cette étude faite sur des chiens, mais il faut en tenir compte s'il survient de forts dérangements de l'équilibre acide-base. Actuellement, nous avons utilisé cet animal type pour étudier l'halothane,⁵ le fluroxène⁶ et le méthoxyflurane. Il est évident que de semblables modèles utilisés pour étudier d'autres agents vont permettre de faire une comparaison scientifique des effets de tous les agents anesthésiques par inhalation sur le débit cardiaque.

Les résultats de telles études pourraient éventuellement indiquer quel agent spécifique sera le choix le plus physiologique à employer dans un cas particulier de déséquilibre acide-base.

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