THE EFFECT OF CARDIAC SYMPATHETIC BLOCKADE ON THE
RELATIONSHIP BETWEEN CARDIAC OUTPUT AND CARBON DIOXIDE TENSION IN THE ANAESTHETIZED DOG

BY
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SUMMARY

In dogs anaesthetized with either halothane or chloralose cardiac output was measured at three levels of arterial carbon dioxide tension. As the carbon dioxide tension was raised there were significant increases in cardiac output. After the administration of a selective cardiac beta-receptor blocking agent (practolol) there were no significant changes in cardiac output as the carbon dioxide tension was increased. It was concluded that the increased cardiac output seen with a raised arterial carbon dioxide tension was brought about by an increased activity in the sympathetic nervous system.

Under anaesthesia, an increase in the arterial carbon dioxide tension is accompanied by an increase in cardiac output both in man (Prys-Roberts et al., 1967) and in the dog (Carson et al., 1965). When halothane has been used as the anaesthetic agent, increases in cardiac output are seen but to a lesser extent than when pentobarbitone or a nitrous oxide-analgesic technique is used (Tomlin et al., 1966; Prys-Roberts et al., 1968).

Increases in cardiac output may result from an increased filling of the heart and from the effects on the heart of the activity of the sympathetic nerves and of circulating catecholamines. It is known that with a respiratory acidaemia there is an increased level of catecholamines circulating in the blood (Sechzer et al., 1960; Morris and Millar, 1962). It seemed probable, therefore, that the increases in cardiac output seen with a respiratory acidaemia were due to an increase in the activity of the sympathetic nervous system. If this is so, then an abolition of the effects of catecholamines on the heart would prevent an increase in cardiac output as the carbon dioxide tension rises.

Experiments were performed to test this hypothesis using the specific cardiac beta-receptor blocking agent practolol (Eraldin, ICI.50,172; Imperial Chemical Industries Limited; Dunlop and Shanks, 1968). The results show that in the anaesthetized dog practolol abolishes the increase in cardiac output seen with a respiratory acidaemia. A preliminary account of these findings has been given (Norman and Atkinson, 1970).

METHODS

Dogs of weight between 11.4 and 20.9 kg were premedicated with a subcutaneous injection of diethylthiambutene hydrochloride (Themalon, Burroughs Wellcome Ltd; dose 25 mg); 30 minutes later anaesthesia was induced with an intravenous injection of thiopentone sodium (dose 25 mg/kg). In the first group of ten dogs (mean weight 16.8 kg) anaesthesia was subsequently maintained with an inspired concentration of 0.8 per cent halothane. In the second group of six dogs (mean weight 16.2 kg) anaesthesia was subsequently maintained with an inspired concentration of 0.8 per cent halothane. In the second group of six dogs (mean weight 16.2 kg) anaesthesia was subsequently maintained using an initial slow intravenous infusion of a warm solution of chloralose (BDH; strength 1 g/100 ml saline) in a dose of 80 mg/kg. Subsequent injections of 3 mg/kg were given at half-hourly intervals. Skeletal muscle relaxation was produced by injections of suxamethonium chloride (dose 1-5 mg every 30 minutes).

A tracheal cannula was inserted and artificial ventilation commenced as soon as possible after induction of anaesthesia using a mixture of oxygen (40 per cent) and nitrogen (60 per cent) delivered from an anaesthetic machine incorporating a Starling Ideal pump (Ledsome, Linden)

and Norman, 1967). The machine incorporated a calibrated Fluotec vaporizer (Cyprane Ltd) for the administration of halothane, and also allowed the administration of known constant concentrations of carbon dioxide.

A short stainless steel cannula (bore 1.5 mm) was inserted into the right femoral artery and a nylon cannula was inserted into the right femoral vein with the tip high in the inferior vena cava. Pressures from these sites and from a side-arm of the tracheal cannula were recorded by attaching to the cannulae strain-gauges (Model P23 Gb, Statham Laboratories Inc., Puerto Rico) the outputs of which were amplified (SE Laboratories carrier amplifier system) and displayed on a direct-writing ultraviolet light recorder (SE Laboratories Ltd, Feltham, Middlesex). The manometers were calibrated using a mercury manometer with zero pressure being recorded postmortem as the pressure at the cannula tip with the tip in air free of blood and other tissue. An electrocardiogram was recorded from the right foreleg and the left hindleg and the heart rate was counted over 20-second periods from this record. The rectal temperature of the animal was maintained at 38±2°C by adjusting heaters beneath the animal table.

Cardiac output was measured using the indicator dilution technique employing indocyanine green. A bolus of known volume (1 ml = 2.5 mg) was injected from a calibrated 1-ml glass-and-metal syringe at the end of expiration into a catheter inserted through the right external jugular vein with the tip in the pulmonary arterial tree. This bolus was flushed into the pulmonary artery immediately with 10 ml of saline. Simultaneously arterial blood was withdrawn by a constant rate withdrawal syringe (model 105-81, Gilford Instrument Laboratories Inc., Oberlin, Ohio, U.S.A.) from a nylon catheter inserted in the left femoral artery with the tip in the abdominal aorta. This blood was withdrawn through a cuvette densitometer (model 103(IR), Gilford Instrument Laboratories Inc.) and the resultant concentration curve was recorded on the ultraviolet light recorder. Values obtained from the curve were plotted on semilogarithmic paper to allow extrapolation of the initial down slope to obtain the concentration curve during the first circulation of the dye. This curve was replotted on the initial curve and the area under the curve was measured using a planimeter. Known concentrations of the dye sample used in each experiment were prepared in blood obtained from the dog and these solutions were used to prepare a calibration curve for the densitometer. The cardiac output was calculated from the formula:

\[ Q = \frac{60i}{A} \]

where \( Q \) = the cardiac output; 
\( i \) = the amount of dye injected (mg); 
\( A \) = the area under the curve expressed in concentration time units (mg sec/l.).

 Duplicate estimations of the output were always made and 95 per cent of these duplicates agreed within 10 per cent.

Arterial blood samples were withdrawn anaerobically from a nylon catheter in the left femoral artery into 5-ml plastic syringes whose dead-spaces were filled with a solution of heparin, (1000 units/ml). The samples were analyzed immediately for \( pH \), \( P_{CO_2} \) and \( P_{O_2} \) using a blood-gas analyzer (model 48C, Electronic Instruments Ltd, Richmond, Surrey). The 95 per cent tolerance limits for these determinations were: \( pH \pm 0.01 \) units, \( P_{CO_2} \pm 2.5 \) per cent of the measured value, and \( P_{O_2} \pm 0.7 \) per cent of the measured value. Each value was corrected for any difference in temperature between the electrode system and the animal, using the correction factors of Kelman and Nunn (1966). The \( P_{O_2} \) values were corrected for the blood-gas difference for this electrode as determined by tonometry using the tonometer described by Adams and Morgan-Hughes (1967). The haemoglobin concentration was measured using the cyanmethaemoglobin method. Base excess was derived from the \( pH \), \( P_{CO_2} \) and haemoglobin values using the nomogram of Siggaard-Andersen (1963).

After completion of the experimental preparation each animal was ventilated to give an initial arterial carbon dioxide tension of approximately 30 mm Hg. After 20 minutes at this ventilation the cardiac output was determined and an arterial blood sample taken. Keeping the ventilation volume constant, the arterial carbon dioxide tension was increased by adding carbon dioxide to the inspired gas mixture in such a concentration as to raise the \( P_{CO_2} \) to about 55 mm Hg; after 20 minutes the cardiac output was redetermined.
and a further blood sample taken. The inspired carbon dioxide concentration was then further increased so as to give an arterial tension of approximately 75 mm Hg for a further 20 minutes at the end of which the cardiac output was measured and a blood sample taken. The carbon dioxide administration was discontinued and after 20 minutes further samples were taken and the cardiac output measured. Practolol (dose 0.4 mg/kg) was injected intravenously over 30 seconds and the cardiac output and blood-gases were re-determined after 20-minute periods without carbon dioxide administration and with the same inspired concentrations as those used in the initial part of the experiment.

The effectiveness of practolol as a cardiac beta-receptor blocking agent was assessed by comparing the mg/min heart rate produced by an intravenous injection of isoprenaline sulphate (usual dose 0.5 μg/kg) at each carbon dioxide tension before and after the administration of practolol.

Values for means, standard deviations and standard errors were calculated using conventional formulae. Linear regression equations were fitted to some of the data using formulae given by Diem (1962). The statistical significance of the results was assessed using Student's t test.

RESULTS

Acid-base balance.

In every animal the administration of carbon dioxide led to the expected rise in the arterial carbon dioxide tension and decrease in pH. The results obtained in both series of dogs are summarized in tables I and II; the mean values for the carbon dioxide tension and pH are shown in figures 1 and 2. In both series there was an initial slight metabolic acidemia as shown by the base excess values being −3.9 m.equiv/l. for the dogs given halothane and −2.8 m.equiv/l. for the dogs given chloralose. As the carbon dioxide tension increased there was a fall in the base excess values but these returned towards the initial levels when the carbon dioxide inhalation was stopped. Indeed there were no statistically significant differences between the mean values for pH, carbon dioxide tension and base excess in the three sets of arterial blood samples taken when carbon dioxide was not being administered.

The apparent increase in the metabolic acidemia with the respiratory acidemia is of a similar degree to that found in other investigations (e.g., Shaw and Messer, 1932; Norman, 1969). A comparison of the results obtained at similar inspired carbon dioxide concentrations before and after the administration of practolol shows no statistically significant difference between the mean values for carbon dioxide tension, pH and base excess.
Changes in acid-base balance in arterial blood in ten dogs anaesthetized with halothane.
Ordinate, Pco₂; abscissa, pH; ○ the average initial value for pH and Pco₂; ● intermediate values; X final value; ---- the expected change for blood in vitro.

excess. Thus any change brought about by practolol could not be attributed to a change in acid-base balance.

The inspired oxygen concentration was kept constant in each dog throughout the experiment. Tables I and II give the values obtained for the arterial oxygen tension at each stage of the experiments. As the arterial carbon dioxide tension rose there were no falls in the oxygen tensions, suggesting that the alveolar-to-arterial oxygen tension gradient had decreased.

**Effects of practolol.**

The effectiveness of the dose of practolol administered (0.4 mg/kg) was assessed by comparing the responses seen after an intravenous injection of isoprenaline at each carbon dioxide level before and after the injection of practolol. The test dose of isoprenaline was constant in any one animal and was usually 0.5 μg/kg. In only one animal, and in this animal at the high carbon dioxide tension, did this test dose lead to an arrhythmia when the electrocardiogram showed a run of ventricular extrasystoles. Isoprenaline produced a tachycardia, an increase in pulse pressure and a decrease in mean arterial pressure when injected at the low carbon dioxide levels. At higher carbon dioxide tensions, often the lowering of mean blood pressure was not seen but the tachycardia and increase in pulse pressure were constant features. As far as the heart was concerned, the most consistent feature seen after the administration of isoprenaline was the tachycardia and was assessed as the maximum heart rate achieved when counted over a 10-second period.

After the administration of practolol the maximum heart rate seen with isoprenaline was much less. Table III gives the values for the maximum heart rates after the administration of 0.5 μg/kg of isoprenaline in six dogs anaesthetized with halothane and five with chloralose. At each carbon dioxide level the maximum heart rate achieved was much less after practolol and was statistically significantly less for the lowest and highest carbon dioxide levels (P<0.01). In the remaining dogs where smaller doses of isoprenaline were used similar results were seen.

The test dose of isoprenaline usually produced a tachycardia of the same order as that seen when the sympathetic nerves to the heart are stimulated maximally (e.g., Linden and Norman, 1969). Practolol is a competitive beta blocker (Dunlop and Shanks, 1968) and the reduction in the maximum heart rate achieved probably indicates
a significant block of the response of the heart to both circulating and locally released catecholamine. Certainly this dose of practolol abolishes most of the response of the heart to submaximal rates of stimulation of the sympathetic nerves (Norman and Atkinson, in preparation).

The immediate effects produced by the injection of practolol were studied by comparing the results obtained immediately before and after injection of the drug. The fourth columns of tables IV and V show the results obtained immediately before practolol was given, and the fifth columns show the results immediately after practolol. In the dogs anaesthetized with halothane.

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**TABLE III**

<table>
<thead>
<tr>
<th>Pco₂ (mm Hg)</th>
<th>Control: maximum heart rate (beats/min)</th>
<th>Pco₂ (mm Hg)</th>
<th>Practolol (0.4 mg/kg): maximum heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Probability</td>
</tr>
<tr>
<td>30.9</td>
<td>216 ± 31</td>
<td>159 ± 20</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>57.7</td>
<td>196 ± 41</td>
<td>174 ± 21</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>78.1</td>
<td>196 ± 19</td>
<td>156 ± 23</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td><strong>Chloralose (5 dogs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.7</td>
<td>237 ± 17</td>
<td>31.8</td>
<td>174 ± 38</td>
</tr>
<tr>
<td>54.0</td>
<td>248 ± 12</td>
<td>52.2</td>
<td>189 ± 20</td>
</tr>
<tr>
<td>77.0</td>
<td>239 ± 6</td>
<td>73.8</td>
<td>187 ± 25</td>
</tr>
</tbody>
</table>

Values for Pco₂ are mean values; for the maximum heart rates are means ± 1 SD. The probability refers to the significance of the difference between the mean values for the maximum heart rates.

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**TABLE IV**

**Effect of carbon dioxide on the cardiovascular state (halothane, 10 dogs).**

<table>
<thead>
<tr>
<th>Pa₆₆₃ (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Heart rate (beats/min)</th>
<th>Stroke vol. (ml)</th>
<th>Venous pressure (mm Hg)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Control</th>
<th>After practolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.9</td>
<td>1.84</td>
<td>126</td>
<td>15.4</td>
<td>5.0</td>
<td>103</td>
<td>1.84 ± 0.46</td>
<td>1.76 ± 0.15</td>
</tr>
<tr>
<td>57.7</td>
<td>2.22</td>
<td>129</td>
<td>17.7</td>
<td>4.9</td>
<td>102</td>
<td>2.22 ± 0.94</td>
<td>1.68 ± 0.14</td>
</tr>
<tr>
<td>78.1</td>
<td>2.57</td>
<td>126</td>
<td>18.2</td>
<td>4.5</td>
<td>103</td>
<td>2.57 ± 0.82</td>
<td>1.81 ± 0.19</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD.

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**TABLE V**

**Effect of carbon dioxide on cardiovascular state (chloralose, 6 dogs).**

<table>
<thead>
<tr>
<th>Pa₆₆₃ (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Heart rate (beats/min)</th>
<th>Stroke vol. (ml)</th>
<th>Venous pressure (mm Hg)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Control</th>
<th>After practolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.7</td>
<td>2.19</td>
<td>153</td>
<td>14.9</td>
<td>4.2</td>
<td>111</td>
<td>2.19 ± 0.68</td>
<td>2.15 ± 0.74</td>
</tr>
<tr>
<td>54.0</td>
<td>3.04</td>
<td>154</td>
<td>19.6</td>
<td>3.2</td>
<td>114</td>
<td>3.04 ± 0.75</td>
<td>2.30 ± 0.92</td>
</tr>
<tr>
<td>77.0</td>
<td>3.14</td>
<td>158</td>
<td>19.8</td>
<td>4.3</td>
<td>117</td>
<td>3.14 ± 0.86</td>
<td>1.86 ± 0.92</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD.
thene the only obvious effect was a small fall in heart rate but this did not achieve statistical significance. In the dogs anaesthetized with chloralose cardiac output, stroke volume, venous pressure and mean arterial pressure rose and the heart rate fell. But of these changes only the increase in stroke volume and the fall in heart rate approached statistical significance (stroke volume $0.2>P>0.1$; heart rate $0.3>P>0.2$). Thus practolol did not produce any major immediate changes in the cardiovascular system at the low carbon dioxide tension which could be interpreted as showing a direct myocardial depression.

**Effect of carbon dioxide on cardiac output.**

**Halothane anaesthesia.** The effects of the administration of carbon dioxide on the cardiac output in one dog anaesthetized with halothane are shown in figure 3. The increase in the carbon dioxide tension was accompanied by increases in the cardiac output, stroke volume, heart rate and arterial blood pressure before beta-blockade. After blockade the output fell as the carbon dioxide tension rose. Similar changes were seen in most of the remaining animals, with the output increasing with carbon dioxide before block and showing either a much smaller increase, no change or a small decrease in output after block. In one dog the pattern was somewhat different (fig. 4). Here, before blockade, the output did not increase as the carbon dioxide tension was increased; after blockade the output was reduced from 1.96 l./min to 0.74 l./min and remained at this low level. With the fall in output there was a marked fall in blood pressure; the heart rate and stroke volumes were both less than the initial volumes.
The average effects at each stage are summarized in table IV. Before practolol was given, as the carbon dioxide tension rose there was an increase in cardiac output with an increase in both heart rate and stroke volume. After practolol, as the carbon dioxide tension increased there was a small increase in heart rate and a fall in stroke volume; overall cardiac output did not change. In the control stage the first increase in the carbon dioxide tension from 30.9 to 57.7 mm Hg was associated with an average increase in cardiac output of 0.38 l./min. This increase just fails to achieve statistical significance (0.1>P>0.05). The increase in carbon dioxide tension to 78.1 mm Hg led to a further increase in output of 0.35 l./min; this increase was statistically significant (P<0.005). After practolol the changes in output seen as the carbon dioxide tension was increased were not statistically significant (P>0.25).

Figures 5 and 6 are scatter diagrams showing the results obtained for cardiac output and arterial carbon dioxide tension. Linear regression equations were calculated for these values. The lines given by these equations, together with the lines showing the 95 per cent confidence limits for the points given by the equations are also shown in figures 5 and 6. In the control stage the regression equation was:

\[ Q = 2.14 + 0.0145\text{ Pco}_2 - 50 \text{ l./min} \]
\[ (r = +0.38; P<0.01) \]

The rate of rise of cardiac output per mm Hg rise in carbon dioxide tension (14.5 ml/min/mm Hg) is statistically significantly different from zero (P<0.01). After practolol was given the corresponding equation was:

\[ Q = 1.72 + 0.0036\text{ Pco}_2 - 52 \text{ l./min} \]
\[ (r = +0.098; P>0.05) \]

The rate of rise of cardiac output per mm Hg rise in carbon dioxide tension (3.6 ml/min/mm Hg) is not statistically significantly different from zero (P=0.30).

Chloralose anaesthesia. Figure 7 shows the changes seen in one dog anaesthetized with chloralose as the carbon dioxide tension was increased. The pattern of an increase in output before block and no real change after block is similar to that seen with halothane. The other dogs showed a similar pattern apart from one where the cardiac output was not greatly changed with carbon dioxide before block but fell after block. The average results for the six dogs are given in table V. As with the halothane series the cardiac output rose before practolol was given; after practolol the increase was much less. In the control stage the increase in the carbon dioxide
tension from 31.7 mm Hg to 54.0 mm Hg was associated with a rise in output of 0.85 l./min; this rise was statistically significant (P<0.05). The further increase in carbon dioxide tension to 77.0 mm Hg was associated with a rise in output of 0.10 l./min; this rise was not statistically significant but the total rise in output (0.95 l./min) from the initial to the highest carbon dioxide tension was (P<0.025). After practolol the increases in output were +0.15 l./min (PcO₂ 31.8 to 52.2) and +0.14 l./min (PcO₂ 52.2 to 73.8).

Neither of these increases nor the overall increase (0.285 l./min, PcO₂ 31.8 to 73.8) achieved statistical significance.

The values obtained were used to calculate regression equations. The lines given by these together with the 95 per cent confidence limits are shown in figures 8 and 9. The equations were:

Before practolol

\[ Q = 2.56 + 0.0233 \times (PcO₂ - 49) \text{ l./min} \]
\[ r = +0.52, P<0.001 \]

After practolol

\[ Q = 2.30 - 0.0004 \times (PcO₂ - 53) \text{ l./min} \]
\[ r = -0.0099, P>0.05 \]

The increase in output per mm Hg change in carbon dioxide tension before practolol was given (23.3 ml/min/mm Hg) was statistically significantly different from zero (P<0.005) whilst the
change after practolol (−0.9 ml/min/mm Hg) was not (P>0.05).

Thus with both halothane and chloralose before the administration of practolol there were significant increases in cardiac output as the carbon dioxide tension was increased. After blockade of the cardiac beta receptors no significant changes in output occurred.

Heart rate and stroke volume.

In the ten dogs given halothane the increase in cardiac output with the increase in the carbon dioxide tension was accompanied by a statistically significant increase in stroke volume (P<0.05) whilst the change in heart rate was not significant. After blockade there were no significant changes in heart rate and stroke volume. In the dogs anaesthetized with chloralose in the initial stage the increase in carbon dioxide tension was accompanied by an increase in stroke volume and a small increase in heart rate but these did not achieve statistical significance (P>0.05). After the administration of practolol the heart rate rose significantly as the carbon dioxide tension rose (P<0.05) but the stroke volume fell although not statistically significantly.

Venous pressure.

The average values for the venous pressure as expressed by the mean pressures recorded high in the inferior cava are shown in tables IV and V. In the halothane series prior to blockade the increase in the carbon dioxide tension was accompanied by a small fall in the venous pressure whilst after blockade as the tension rose so did the venous pressure. Regression analysis showed that the change before blockade was not significant whilst the change after blockade was (P<0.05). In the animals anaesthetized with chloralose there were no significant changes in the venous pressure either before or after practolol.

DISCUSSION

Changes in acid-base balance have been known to affect the performance of the heart since Gaskell's demonstration in 1880 that lactic acid would diminish the beat of the frog's heart. Studies using the heart-lung preparation have shown that carbon dioxide leads to a slowing and dilatation of the heart and a reduced output for any given filling pressure (Jerusalem and Starling, 1910; Patterson, 1915; Price and Helrich, 1955).

But the performance of the heart may be considerably changed by the effects of activity in the efferent autonomic nerves. In particular, the sympathetic nerves when stimulated lead to increases in both the rate and the force of contraction of the heart (Gaskell, 1900). It has been thought that an acidemia, however produced, will lead to a diminished response to the catecholamines (e.g., Andrus, 1924; Burget and Visscher, 1927; Thrower, Darby and Aldinger, 1961). But more recently Downing, Talner and Gardner (1965) and Linden and Norman (1969) have found no evidence of a diminished inotropic response of the heart to catecholamines and only a slightly diminished chronotropic response at low rates of stimulation of the efferent sympathetic nerves. The changes found by others may represent a different responsiveness of the peripheral vasculature (Bygdeman and Von Euler, 1962).

Thus in the intact animal with a functioning sympathetic nervous system the direct depressant action of carbon dioxide on the heart may be countered if there is an increased sympathetic discharge during the acidemia. Increases in cardiac output as the carbon dioxide tension rises have been described by Carson and associates (1965) and Tomlin and associates (1966) in the dog and by Prys-Roberts and associates (1967, 1968) in man. The results presented here in both series of dogs show an increase in output as the carbon dioxide tension rises in the control stage of the experiments.

In the control stages of the experiments the changes in cardiac output as the carbon dioxide tension rose were greater in the dogs anaesthetized with chloralose than in those anaesthetized with halothane. This difference (23.3 ml/min/mm Hg for chloralose; 14.5 ml/min/mm Hg for halothane) may be due to the effect of chloralose in enhancing sympathetic reflexes (Brown and Hilton, 1956) and to a greater direct depressant action of halothane on the heart.

In the results reported by Prys-Roberts and associates (1968) the increases in output in man were accompanied by increases in the right atrial pressure and they speculated that this rise in the filling pressure might account for the increase in output. But in the dogs studied here there
were no significant increases in the venous pressure in the control stages of the experiments whilst the output did rise. Thus it appears that in the dog the increase in cardiac output is due to the effects of the sympathetic nervous system on the heart.

This suggestion that the increase in output is due to sympathetic activity is supported by other evidence. First, Brown and Miller (1952) found that, normally, carbon dioxide could be added to the inspired gases in dogs until the arterial blood pH was 6.4 before cardiac arrest occurred, whilst if the adrenal glands were removed death occurred at a much higher pH (and lower carbon dioxide concentration). Clowes, Hopkins and Simeone (1955) found similar results in that five of seven dogs subjected to a total sympathectomy arrested when the inspired carbon dioxide concentration was 55 per cent, whereas six dogs with an intact sympathetic nervous system survived the inhalation of this mixture. This suggests that not only must the heart be responding to catecholamines during the respiratory acidaemia but that they are essential to maintaining any output.

Secondly, there is evidence of increased activity in the sympathetic system during a respiratory acidaemia. Increased blood catecholamine concentrations have been described by Sechzer and colleagues (1960) and Morris and Millar (1962). Millar and Bisce (1966) found that there was an increased activity in the efferent sympathetic cardiac nerves in the rabbit as the PCO₂ was increased. Downing and Siegel (1963) also found evidence of an increased activity in the sympathetic nerves and were able to demonstrate that this activity was due to the action of carbon dioxide at sites other than the peripheral chemoreceptors, for denervation of the carotid and aortic bodies did not alter the increased discharge seen with carbon dioxide. Moster and associates (1969) have shown that overventilation with a fall in carbon dioxide tension is associated with a reduction in cardiac output and in postganglionic sympathetic activity.

The results described here show that beta-blockade was not accompanied by a marked reduction in cardiac output at the low carbon dioxide tensions but at the high tensions the output was lower after blockade than before. In anaesthesia, arrhythmias are more likely to be seen at high carbon dioxide tensions, and beta-blocking agents, if used to abolish the arrhythmia, could lead to a fall in output. It should also be noted that on occasion practolol did lead to a marked fall in output at a low carbon dioxide tension (fig. 4). The animals in which this was seen tended to have a high initial heart rate and showed some signs of hypovolaemia. It would seem advisable in these conditions where an adequate cardiac output is only maintained by the activity of the sympathetic nervous system that beta-blocking agents should be administered with caution.

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