CARDIORESPIRATORY RESPONSES TO AN I.V. INFUSION OF DOBUTAMINE IN THE INTACT ANAESTHETIZED DOG

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SUMMARY

The cardiorespiratory responses to an i.v. infusion of dobutamine hydrochloride were assessed in eight anaesthetized, mechanically ventilated dogs. As the rate of infusion of dobutamine was increased from 2 to 30 μg kg\(^{-1}\) min\(^{-1}\), there was a progressive decrease in arterial pressure, pulmonary wedge pressure and arterial pH. There was a significant decrease in arterial oxygen tension at the greater doses of dobutamine (15 and 30 μg kg\(^{-1}\) min\(^{-1}\)) from initial control values. Carbon dioxide output, arterial carbon dioxide tension, venous admixture and oxygen consumption increased during the infusion of dobutamine. However, oxygen supply increased further so that the oxygen consumption: supply ratio decreased. It is concluded that dobutamine may decrease arterial oxygen tension, but that the increased cardiac output and decreased arterial pH produced by dobutamine may increase oxygen supply to the tissues in spite of this.

Dobutamine hydrochloride (Dobutrex) is a new β\(_1\) adrenergic agonist, developed by systematic modification of isoprenaline (Tuttle and Mills, 1975). The most common clinical inotropic agents, isoprenaline and dopamine, have actions apart from those on the heart and have both been shown to cause arterial hypoxaemia (Fordham and Resnekov, 1968; Lemaire et al., 1976). It was of interest, therefore, to look at the cardiorespiratory effects of the new, relatively cardiospecific synthetic catecholamine, dobutamine hydrochloride, given in a series of doses within the range used clinically (2–30 μg kg\(^{-1}\) min\(^{-1}\)) to anaesthetized, mechanically ventilated dogs.

METHODS

Eight dogs of various breeds, weights 20–36 kg (mean ± SEM = 22.7 ± 2.54 kg) were anaesthetized with thiopentone 20–30 mg kg\(^{-1}\) and pentobarbitone 60–240 mg. The dogs were placed supine in a V-shaped trough, intubated, and ventilated at 15 bpm via a non-rebreathing valve (Sykes, 1969) from which expired gas could be collected. Tidal volume was adjusted to give an end-tidal carbon dioxide concentration close to 4.5%. The right femoral artery and vein were cannulated for measurement of cardiac output by dye dilution. The left femoral artery was cannulated for mean aortic pressure (P\(_{\text{AO}}\)) measurement and the withdrawal of arterial blood samples. The left femoral vein was cannulated for the administration of dobutamine and saline. A cannula was passed through the right external jugular vein into the pulmonary artery for the measurement of mean pulmonary artery pressure (P\(_{\text{PA}}\)) and the withdrawal of mixed venous blood samples. Mean pulmonary wedge pressure (P\(_{\text{w}}\)) was measured via a pulmonary artery catheter passed from the left external jugular vein. All pressures were measured using Consolidated Electrodynamics strain gauges and a heated stylus recorder. Anaesthesia was maintained with increments of thiopentone and pentobarbitone administered via a cannula placed in the left cephalic vein. Dog temperature, measured using a thermistor placed in the lower half of the oesophagus, was maintained at a mean temperature of 36.8 °C ± 0.2 (± SEM) by means of a heater under the trough.

The experimental programme consisted of an initial control period during which saline was infused into the left femoral vein at 0.1 ml min\(^{-1}\) by a calibrated infusion pump. The infusion was then changed to dobutamine infused at the same rate to give a dose of 2 μg kg\(^{-1}\) min\(^{-1}\). The infusion rate was subsequently increased to give doses of 7.5, 15 and 30 μg kg\(^{-1}\) min\(^{-1}\) of dobutamine followed by a final control period in which saline was infused at the same rate as the final dose of dobutamine.
Each period of drug infusion lasted approximately 20 min. The time between the cessation of the dobutamine infusion and the final control measurements was at least 45 min. The total volume of fluid infused was never greater than 150 ml, and the time taken to complete the programme never exceeded 3.5 h.

When a steady state had been reached, determined by vascular pressures and end-tidal carbon dioxide, a full set of measurements was taken in each control period and during each rate of dobutamine infusion. This consisted of drawing arterial and mixed venous blood samples which were analysed in duplicate for $P_{O_2}$, $P_{CO_2}$, pH and haemoglobin concentration, duplicate measurements of cardiac output, measurement of $P_AO_2$, $PPA$, $PW$, end-tidal carbon dioxide, mixed expired carbon dioxide and oxygen concentrations, expired gas temperature and volume and airway pressure (measured between the endotracheal tube and the collect valve).

Alveolar–arterial $P_O_2$ difference ($P_{AO_2} - P_{AO_2}$), venous admixture ($Q_{va}/Q_t$), oxygen uptake ($V_{O_2}$), carbon dioxide production ($V_{CO_2}$) and physiological deadspace ($VD/V^{T_t^o}$) were calculated from the measured variables using the computer program of Adams (1970) which uses standard formulae. Pulmonary vascular resistance (PVR), oxygen supply ($O_x CaO_2$) and oxygen consumption: supply were also calculated.

Statistical analysis of normally distributed variables was by a two-way analysis of variance followed by Duncan's multiple range test between treatments where indicated as necessary by the analysis of variance. Non-parametric variables ($Q_{va}/Q_t$ and $VD/V^{T_t^o}$) were analysed using a two-way non-parametric analysis of variance followed by a paired Wilcoxon's test.

RESULTS

The responses to the different doses of dobutamine are shown below:

- $2 \mu g \, kg^{-1} \, min^{-1}$. At this infusion rate there were no significant changes in any of the measurements.
- $7.5 \mu g \, kg^{-1} \, min^{-1}$. There was a significant ($P < 0.05$) decrease in pulmonary wedge pressure compared with the initial control value. No other measurements showed a significant change.
- $15 \mu g \, kg^{-1} \, min^{-1}$. This dose rate produced a further decrease in wedge pressure and also a significant decrease in arterial oxygen tension from control values ($P < 0.05$). There was an increase in oxygen consumption ($P < 0.01$) and in arterial and end-tidal carbon dioxide tensions from control values ($P < 0.05$ and $P < 0.01$ respectively).

$30 \mu g \, kg^{-1} \, min^{-1}$. In addition to the changes which occurred with an infusion rate of $15 \mu g \, kg^{-1} \, min^{-1}$, there was also a significant decrease from control values of arterial pH ($P < 0.01$), arterial pressure ($P < 0.01$) and an increase in carbon dioxide output ($P < 0.01$) and venous admixture ($P < 0.01$) from control values.

Although oxygen consumption increased significantly during infusion of dobutamine, oxygen supply increased further, so that the oxygen consumption: supply ratio decreased during the dobutamine infusion. However, this was greater than the initial control values during the final control period.

No significant changes in airway pressure, $PPA$, PVR, ($P_{AO_2} - P_{AO_2}$) and $Qt$ occurred.

The cardiovascular measurements are summarized in table I and respiratory measurements in table II. Changes in blood-gases, vascular pressures and cardiac output and oxygen consumption and supply are shown in figures 1, 2, and 3.
CARDIORESPIRATORY EFFECTS OF DOBUTAMINE

Table I. The effect of dobutamine on the cardiovascular system (mean ± SEM). Arabic numerals below means ± SEM denote significance: *P < 0.05; **P < 0.01

<table>
<thead>
<tr>
<th>Dobutamine infusion</th>
<th>Saline</th>
<th>2 (2 µg kg⁻¹ min⁻¹)</th>
<th>3 (7.5 µg kg⁻¹ min⁻¹)</th>
<th>4 (15 µg kg⁻¹ min⁻¹)</th>
<th>5 (30 µg kg⁻¹ min⁻¹)</th>
<th>Saline</th>
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<tr>
<td>PAO (mm Hg)</td>
<td>139.2</td>
<td>128.8</td>
<td>130.3</td>
<td>123.3</td>
<td>105.8</td>
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<td></td>
<td>±11.8</td>
<td>±11.2</td>
<td>±7.8</td>
<td>±8.1</td>
<td>±12.9</td>
<td>±8.6</td>
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<td></td>
<td>5**, 6*</td>
<td>5*</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PPA (mm Hg)</td>
<td>13.3</td>
<td>12.5</td>
<td>12.7</td>
<td>12.2</td>
<td>12.3</td>
<td>11.8</td>
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<td></td>
<td>±1.3</td>
<td>±1.6</td>
<td>±1.8</td>
<td>±1.8</td>
<td>±2.0</td>
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<tr>
<td>PW (mm Hg)</td>
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<td>2.3</td>
<td>1.7</td>
<td>1.2</td>
<td>1.2</td>
<td>2.7</td>
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<tr>
<td></td>
<td>±0.8</td>
<td>±0.8</td>
<td>±0.9</td>
<td>±0.7</td>
<td>±0.8</td>
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<tr>
<td></td>
<td>3*, 4**</td>
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<td></td>
<td></td>
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<td>5**</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q (litre min⁻¹)</td>
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<td>1.93</td>
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<td>2.43</td>
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<td>PVR (mm Hg litre⁻¹ min⁻¹)</td>
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<td>4.22</td>
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<td></td>
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<td>±2.70</td>
<td>±3.60</td>
<td>±2.40</td>
<td>±3.38</td>
</tr>
</tbody>
</table>

Discussion

In this study, some measurements during the final control period were significantly different from those made during the initial control period. All measurements were, however, returning towards the initial control values. This suggests either a time effect, or that dobutamine, despite a plasma half-life of only 2 min in the dog (Fasola, Lemberger and Murphy, 1976; Murphy, Williams and Kau, 1976) has an action, or products of its action, which persist for longer than 45 min (the time between S₃ and S₄). However, the recorded values were stable before the final control measurements were taken, which suggests a time effect caused by a change in condition of the preparation. The short half-life of dobutamine and the stability of measurements when a sample was taken at a particular infusion rate suggest that, despite a cumulative infusion, the effect seen at each dose rate represented those produced by that infusion rate. This view is partly supported by the findings of Anggard and colleagues (1978) who showed that, 30 min after discontinuing a dobutamine infusion, the plasma concentration of the drug had returned to the control value.

Although the plasma dobutamine concentration was not measured in the present study, Anggard and others showed a linear correlation between the infusion rate of dobutamine and plasma concentrations, with an infusion rate of 5 µg kg⁻¹ min⁻¹ giving a mean plasma concentration of 65 ng ml⁻¹ and an infusion rate of 15 µg kg⁻¹ min⁻¹ giving a mean plasma concentration of 190 ng ml⁻¹. There were, however, large variations between individuals.

**Oxygen consumption and carbon dioxide production**

The cumulative infusion of dobutamine in the present study was associated with an increase in oxygen consumption and carbon dioxide production. The stimulatory effects of β-agonists on metabolism have long been recognized (Himms-Haagen, 1967) and are observed during the administration of isoprenaline i.v. to dogs (Finlay, Wightman and Sykes, 1970), of dopamine i.v. to dogs (Hall, Young and Scott, 1979) and of salbutamol, a β₂-agonist, to asthmatic patients either orally or i.v. (Neville et al., 1977). However, in the present study oxygen supply also increased and the oxygen consumption: supply ratio decreased.

**Arterial oxygen tension**

The significant decrease in arterial oxygen tension observed in this study during the infusion of dobutamine at 15 and 30 µg kg⁻¹ min⁻¹ has also been shown during the infusion of dopamine to patients (Lemaire et al., 1976) and during the infusion of isoprenaline to dogs (Finlay, Wightman and Sykes, 1970) and to patients (Knudson and Constantine,


| Table II. The effect of dobutamine on the respiratory system (mean ± SEM or mean and range). Arabic numerals below means ± SEM denote significance: *P < 0.05; **P < 0.01 |
|-----------|--------------------------------------------------|---|---|---|---|---|
|           | 1                                                                 | 2 (2 μg kg⁻¹ min⁻¹) | 3 (7.5 μg kg⁻¹ min⁻¹) | 4 (15 μg kg⁻¹ min⁻¹) | 5 (30 μg kg⁻¹ min⁻¹) | 6 Saline |
|           |  | Pao₂ (kPa)                                               |  |  |  |  |  |
| Saline    |  | 11.22 ± 0.67                                            | 10.70 ± 0.68             | 11.08 ± 0.61           | 9.98 ± 0.45            | 9.75 ± 0.46           | 10.42 ± 0.59 |
| Dobutamine infusions |  | 4*, 5**                                                  | 4*, 5**                   | 5**, 6**                | 5**, 6**                | 5**, 6**                | 5**, 6**                |
| Paco₂ (kPa) |  | 4.85 ± 0.19                                             | 5.05 ± 0.23              | 5.20 ± 0.16            | 5.39 ± 0.28            | 5.76 ± 0.28            | 5.77 ± 0.34 |
| Arterial pH (unit) |  | 7.319 ± 0.013                                           | 7.306 ± 0.012            | 7.300 ± 0.011          | 7.277 ± 0.019          | 7.226 ± 0.022          | 7.238 ± 0.03 |
| (PaO₂ - PaCO₂) (kPa) |  | 5.62 ± 0.40                                             | 5.83 ± 0.43              | 6.03 ± 0.39            | 5.96 ± 0.40            | 5.97 ± 0.31            | 5.99 ± 0.34 |
| Qva/Qt (%) |  | 11.4 ± 0.67                                             | 14.4 ± 0.65              | 15.1 ± 0.65            | 18.9 ± 0.44            | 24.0 ± 0.58            | 17.0 ± 0.65 |
| VD/VT (%) |  | 40.4 ± 2.5                                             | 42.1 ± 3.1               | 42.2 ± 3.1             | 41.4 ± 3.1             | 42.2 ± 3.1             | 43.0 ± 3.1 |
| O₂ consumption (mmol min⁻¹) |  | 4.80 ± 0.52                                             | 4.84 ± 0.60              | 5.02 ± 0.60            | 5.60 ± 0.66            | 5.47 ± 0.49            | 5.15 ± 0.73 |
| CO₂ output (mmol min⁻¹) |  | 4.14 ± 0.46                                             | 4.03 ± 0.44              | 4.17 ± 0.40            | 4.30 ± 0.40            | 4.61 ± 0.43            | 4.39 ± 0.50 |
| O₂ supply (mmol min⁻¹) |  | 15.64 ± 0.46                                            | 16.01 ± 0.44             | 21.02 ± 0.44           | 21.04 ± 0.44           | 21.67 ± 0.44           | 12.7 ± 0.44 |
| O₂ consumption/O₂ supply |  | 0.31 ± 0.31                                             | 0.29 ± 0.31              | 0.24 ± 0.31            | 0.27 ± 0.31            | 0.25 ± 0.31            | 0.40 ± 0.31 |

1967; Fordham and Resnekov, 1968; Palmer and Diament, 1968; Palmer et al., 1970). However, unlike that of dopamine, the action of dobutamine does not appear to depend on the release of endogenous catecholamines (Bodem, Skelton and Sonnenblick, 1974) nor, as in the case of dopamine, is it likely to be further converted to another active form.

The decrease in arterial oxygen tension in this study was accompanied by a decrease in pH, principally caused by an increase in carbon dioxide tension, although at 30 μg kg⁻¹ min⁻¹ there was also a metabolic component to the acidosis. This may, in part, have been caused by the low pH of the infused dobutamine (pH = 6.1). This decreased pH would cause the oxygen dissociation curve to shift to the right so that, without changing diffusion gradients into the tissue, oxygen supply to the tissue would increase. The decrease in the oxygen consumption: supply ratio would tend to increase PVO₂ and, in the presence of a constant right to left shunt fraction, would tend to increase Pao₂. However, changes in PVO₂ were not significant in this study.
Possible causes of the decrease of $P_{A\text{O}_2}$

The decrease in arterial oxygen tension was caused by a decrease in alveolar $P_{O_2}$ secondary to the increase in alveolar $P_{CO_2}$ and to a small (but non-significant) increase in $(P_{A\text{O}_2} - P_{F\text{O}_2})$. The apparent discrepancy between the significant increase in venous admixture and the non-significant change in $(P_{A\text{O}_2} - P_{F\text{O}_2})$ may be caused by the increase in mixed venous $P_{O_2}$ resulting from the reduction in oxygen consumption: supply ratio, the hypoxaemia resulting from the increase in venous admixture being offset by the greater $P_{O_2}$ of the blood coming from the areas of lung with a low ventilation: perfusion ratio.

The cause of the increased venous admixture is uncertain although it has been noted previously (Gauthier-Lafaye, 1978). There were no significant changes in $P_{F\text{A}}$ nor in $V_D/V_T$ ratios and therefore no major changes in the distribution of blood flow between the upper and lower parts of the lung. PVR decreased, but not significantly, and this effect may have been caused by increase in cardiac output. Two possible causes of the decreased $P_{A\text{O}_2}$ therefore remain: first, that shunt channels may have been opened by the increase in cardiac output, although the changes in cardiac output did not attain significance. Second, the $P_{V\text{O}_2}$ of the blood from post-pulmonary shunt sources may have decreased. Although a decreased $P_{A\text{O}_2}$ does not alter anatomical shunt (Aviado et al., 1961) it may decrease bronchial flow, which may reduce bronchial venous $P_{O_2}$. Increased oxygen extraction by the myocardium would also result in a decrease in the $P_{O_2}$ of the Thebesian vein blood.

Increased carbon dioxide tensions have been shown to increase venous admixture, but only by a non-significant amount and at carbon dioxide tensions far greater than those achieved in the present study (Finlay, Wightman and Sykes, 1970). The results of this study do not, therefore, help elucidate the cause of the increased venous admixture observed.

Cardiovascular measurements

The magnitude of the changes in cardiac output observed are comparable to those of Vatner, McRitchie and Braunwald (1974) who showed a 43% increase in cardiac output of conscious dogs with an infusion of $20\mu g kg^{-1} min^{-1}$ of dobutamine and an 80% increase of cardiac output with an infusion rate of $40\mu g kg^{-1} min^{-1}$. However, these workers found a minimal increase in arterial pressure, whereas the present study showed a significant decrease of arterial pressure during the infusion of $30\mu g kg^{-1} min^{-1}$ of dobutamine. The present decrease in $P_{A\text{O}_2}$ may be a result of either the systemic dilator action of a decreased pH or the $\beta$-agonist effects of dobutamine on the systemic vasculature (Vatner, McRitchie and Braunwald, 1974). Tinker and others (1976) also found that dobutamine $5\mu g kg^{-1} min^{-1}$ and $10\mu g kg^{-1} min^{-1}$ given i.v. to cardiac patients recovering from surgery increased mean arterial pressure by 12%. However, dobutamine also increased cardiac output significantly.

The inotropic effects of dobutamine have been well documented (Glynne and Lucas, 1978), as have its peripheral adrenergic agonist effects (Robie,
O2 Consumption
O2 Supply
O2 Supply
O2 Consumption

Dobutamine (µg kg\(^{-1}\) min\(^{-1}\))

![Graph showing oxygen consumption, supply, and consumption:supply ratio during the infusion of dobutamine.](https://academic.oup.com/bja/article/54/6/673/239873)

**Fig. 3.** Oxygen consumption (mean ± SEM), oxygen supply and oxygen consumption: supply ratio during the infusion of dobutamine. S = saline infusion during control periods.

Nutter and McNay, 1973; Robie et al., 1974; Vatner, McRitchie and Braunwald, 1974). From the present study, it appears that the overall cardiorespiratory effect will be a balance of several different factors and may vary between individuals depending on their initial condition.

**REFERENCES**


