CIRCULATORY RESPONSES TO KETAMINE: DEPENDENCE ON RESPIRATORY PATTERN AND BACKGROUND ANAESTHESIA IN THE RABBIT

J. C. McGrath, J. E. MacKenzie and R. A. Millar

SUMMARY

In rabbits which were initially conscious or lightly anaesthetized with pentobarbitone, ketamine respectively increased or did not change arterial pressure, whereas in mechanically ventilated animals there was prolonged depression of both pressure and preganglionic sympathetic activity. Although respiratory rate slowed during spontaneous ventilation, blood-gas changes were not responsible for these differences. Following bilateral division of the carotid sinus and aortic nerves, a depressor response to ketamine occurred during spontaneous respiration. When respiratory rate was slowed coincidentally with ketamine injection during mechanical ventilation, the circulatory responses were similar to those during spontaneous respiration; this did not occur after carotid and aortic denervation. These variations in the circulatory effects of ketamine, according to respiratory pattern and background anaesthesia, are discussed.

In a recent study (McGrath, MacKenzie and Millar, 1975) in rabbits given pentobarbitone and gallamine and ventilated mechanically with 100% oxygen, ketamine was found consistently to decrease arterial pressure. This appears to contrast with the published findings of a pressor effect of the drug in animals and man.

In laboratory experiments, ketamine has been reported to cause pressor or depressor responses according to the species, experimental methods or dose employed (McCarthy et al., 1965; Virtue et al., 1967; Dowdy and Kaya, 1968; Chang, Chan and Ganendran, 1969; Traber and Wilson, 1969).

Ketamine has been shown to cause respiratory depression in animals (McCarty et al., 1965; Gassner et al., 1974; Wong and Jenkins, 1974) and man (Domino, Chodoff and Corssen, 1965; Virtue et al., 1967; Dillon, 1971; Savege et al., 1973). The question arises, therefore, whether a pressor response to the drug is influenced by accompanying respiratory depression or by the type of pulmonary ventilation employed.

In the clinical studies referred to above, pressor effects appeared to occur when respiration was spontaneous, whereas during investigations employing mechanical ventilation no hypertensive responses were noted (Oyama, Matsumoto, and Kudo, 1970; Meer, Downing and Coleman, 1973; Johnston, Miller and Way, 1974); indeed the last group of authors described a hypotensive effect of ketamine in man.

Variations in "sympathetic tone" during ketamine anaesthesia, attributed by Zimmerman and Liao (1973) to species differences between the cat and dog, could also be accounted for by the use of mechanical ventilation in the latter species.

The present investigation attempts to determine whether a pressor response to ketamine is influenced by ventilation, or other respiratory factors, or by the presence of a background anaesthetic.

METHODS

Male New Zealand white rabbits, 2.9-3.5 kg, were studied. When pentobarbitone anaesthesia was employed, 30 mg/kg was given initially via the marginal ear vein, followed by supplements of 4 mg/kg administered through a femoral vein cannula. A tracheal cannula was inserted soon after induction of anaesthesia, and arterial pressure was recorded from the femoral artery. Heart rate was obtained from the pressure recording using a Devices instantaneous ratemeter. In conscious animals, the central ear artery was used for pressure measurement.

The end-tidal carbon dioxide concentration was monitored with a Beckman LB-2 carbon dioxide analyser. For mechanical ventilation, a Harvard apparatus Model 613, with air or 100% oxygen, was used to maintain the end-tidal carbon dioxide
concentration at approximately 4%. Heart rate, arterial pressure, electronically meaned arterial pressure and end-tidal carbon dioxide were displayed on a Devices MX-4 four-channel recorder. In animals given pentobarbitone, rectal temperature was maintained at 38.5 ± 0.5 °C by means of a Palmer homeothermic blanket. pH, Pco₂ and Po₂ of arterial samples were measured immediately after withdrawal, using an IL Model 213 blood-gas analyser.

Neuromuscular blockade was produced with gallamine, 1 mg/kg, given i.v. at intervals of approximately 40 min.

Several series of investigations were performed. Conscious rabbits were given a single injection of ketamine 5 mg/kg i.v. (an effective anaesthetic dose in this species). The experimental conditions were then altered, as indicated in the separate groups below, until finally the rabbits were anaesthetized with pentobarbitone, mechanically ventilated with 100% oxygen, paralysed with gallamine, and subjected to bilateral aortic depressor nerve section. The results from this series thus relate to the following experimental conditions:

- **Group I**—Conscious, unanaesthetized rabbits, breathing room air
- **Group II**—Light pentobarbitone anaesthesia, spontaneous respiration (air)
- **Group III**—Pentobarbitone anaesthesia, mechanical ventilation (air)
- **Group IV**—Pentobarbitone anaesthesia, mechanical ventilation (air), gallamine injection
- **Group V**—Pentobarbitone anaesthesia, mechanical ventilation (100% oxygen), gallamine injection
- **Group VI**—Pentobarbitone anaesthesia, mechanical ventilation (100% oxygen), gallamine injection, depressor nerves divided.

The effects on the response to ketamine of bilateral division of the aortic depressor or carotid sinus nerves, or both, were investigated in animals anaesthetized with pentobarbitone. Before giving ketamine, fine silk thread was looped round both carotid sinus nerves so that control responses could be obtained before baroreceptor/chemoreceptor denervation.

In mechanically ventilated rabbits under background pentobarbitone anaesthesia and given gallamine, the arterial Pco₂ was increased by administering 5% carbon dioxide in oxygen, control responses having been obtained using a gas mixture of 95% oxygen and 5% nitrogen. Also, in four animals, the rate of mechanical ventilation was reduced by 50% in an attempt to mimic the respiratory depressant action of ketamine, the stroke volume being held constant.

In other rabbits anaesthetized with pentobarbitone, preganglionic sympathetic activity was recorded both while the animals were breathing spontaneously and after they had been given gallamine and were being ventilated mechanically. Multifibre strands were dissected from the cut central end of the left cervical sympathetic nerve. The nerve impulses, recorded with bipolar platinum electrodes, were amplified by a Tektronix Type 122 low-level preamplifier and displayed on a Tektronix Type D12 oscilloscope, whence they were carried to a pulse height selector and a Panax ratemeter for counting of the integrated discharge rate. This was displayed on the Devices recorder, using a time constant of 1-3 sec. In all experiments involving sympathetic recording, 2 μg of adrenaline was given i.v. to establish that the multifibre preparation was under baroreceptor control; studies were undertaken only if nerve activity was reduced by the resulting increase in arterial pressure.

Results were analysed using Student's t test.

The drugs used were: adrenaline acid tartrate (Macarthys), gallamine triethiodide (Flaxedil, May & Baker), pentobarbitone sodium (Nembutal, Abbott) and ketamine hydrochloride (Ketalar, Parke-Davis).

**RESULTS**

**Group I.** In the conscious rabbit, ketamine 5 mg/kg produced an initial transient decrease, followed by a small increase, in mean arterial pressure. Heart rate was increased. The data are shown in tables I and II. Respiratory rate was slowed by 59% (SEM ± 5) at 2 min after injection, but there was no significant change in arterial Pco₂, Po₂ or pH (table III). The effects of a larger dose of ketamine (10 mg/kg) are illustrated in figure 1.

**Group II.** In the presence of light background anaesthesia with pentobarbitone, ketamine 5 mg/kg did not change mean arterial pressure significantly at 2 min (table I). The transient reduction in pressure following the injection was similar to that in conscious rabbits (fig. 1). There was a smaller increase in heart rate than in the conscious animal (table II). Respiratory rate was reduced by 29 ± 5%. There was a small increase in PaO₂ and a decrease in PaCO₂ (table III).

**Group III.** The effects of ketamine differed when given to rabbits with a background of pentobarbitone anaesthesia and mechanical ventilation (fig. 1). Mean arterial pressure was markedly depressed (table I),
CIRCULATORY RESPONSES TO KETAMINE

TABLE I. Respiratory influences on the response of mean arterial pressure (MAP) to ketamine 5 mg/kg

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Basal anaesthesia</th>
<th>Ventilation</th>
<th>Inspired gas</th>
<th>Depressor nerves</th>
<th>Pre-ketamine control MAP (mm Hg)</th>
<th>Δ MAP (mm Hg)</th>
<th>MAP % control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7</td>
<td>None</td>
<td>Spontaneous</td>
<td>Air</td>
<td>Intact</td>
<td>97.0 ± 3.6</td>
<td>+7.4 ± 2.9</td>
<td>107.3 ± 2.9</td>
<td>*</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>Pentobarbitone</td>
<td>Spontaneous</td>
<td>Air</td>
<td>Intact</td>
<td>99.4 ± 7.3</td>
<td>-2.1 ± 5.9</td>
<td>100.4 ± 3.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Pentobarbitone</td>
<td>Mechanical</td>
<td>Air</td>
<td>Intact</td>
<td>85.0 ± 5.9</td>
<td>-25.9 ± 4.5</td>
<td>66.5 ± 5.9</td>
<td>**</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical (gallamine)</td>
<td>Air</td>
<td>Intact</td>
<td>91.2 ± 5.4</td>
<td>-30.6 ± 4.8</td>
<td>70.5 ± 5.8</td>
<td>**</td>
</tr>
<tr>
<td>V</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical (gallamine)</td>
<td>100% O₂</td>
<td>Intact</td>
<td>93.4 ± 8.4</td>
<td>-29.7 ± 9.9</td>
<td>77.0 ± 10.1</td>
<td>*</td>
</tr>
<tr>
<td>VI</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical (gallamine)</td>
<td>100% O₂</td>
<td>Cut</td>
<td>89.0 ± 11</td>
<td>-29.9 ± 6.7</td>
<td>66.0 ± 3.7</td>
<td>*</td>
</tr>
</tbody>
</table>

* 0.05 > P > 0.01; ** 0.01 > P > 0.001; n.s. = not significant.

TABLE II. Respiratory influences on the response of heart rate (HR) to ketamine 5 mg/kg

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Basal anaesthesia</th>
<th>Ventilation</th>
<th>Inspired gas</th>
<th>Depressor nerves</th>
<th>Pre-ketamine control HR min⁻¹</th>
<th>Δ HR min⁻¹</th>
<th>HR % control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>None</td>
<td>Spontaneous</td>
<td>Air</td>
<td>Intact</td>
<td>244 ± 5</td>
<td>+32.5 ± 8.1</td>
<td>111.0 ± 3.2</td>
<td>*</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>Pentobarbitone</td>
<td>Spontaneous</td>
<td>Air</td>
<td>Intact</td>
<td>276 ± 20</td>
<td>+14.4 ± 4.1</td>
<td>103.3 ± 1.6</td>
<td>**</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical</td>
<td>Air</td>
<td>Intact</td>
<td>283 ± 21</td>
<td>-11.9 ± 9.1</td>
<td>90.4 ± 2.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical (gallamine)</td>
<td>Air</td>
<td>Intact</td>
<td>295 ± 10</td>
<td>-7.0 ± 6.6</td>
<td>92.0 ± 4.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>V</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical (gallamine)</td>
<td>100% O₂</td>
<td>Intact</td>
<td>291 ± 10</td>
<td>-6.0 ± 8.9</td>
<td>96.3 ± 2.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>VI</td>
<td>5</td>
<td>Pentobarbitone</td>
<td>Mechanical (gallamine)</td>
<td>100% O₂</td>
<td>Cut</td>
<td>304 ± 18.4</td>
<td>-8.0 ± 6.0</td>
<td>97.6 ± 1.9</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* 0.05 > P > 0.01; ** 0.01 > P > 0.001; n.s. = not significant.

TABLE III. Arterial blood-gas changes produced by ketamine 5 mg/kg (groups as in tables I and II)

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Pre-ketamine control (mm Hg)</th>
<th>Δ PaCO₂</th>
<th>P</th>
<th>PaCO₂</th>
<th>Ketamine + 2 min</th>
<th>Δ PaCO₂</th>
<th>P</th>
<th>PaCO₂</th>
<th>Ketamine + 2 min</th>
<th>Δ PaCO₂</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>5</td>
<td>31.8 ± 1.7</td>
<td>+2.2 ± 1.7</td>
<td>n.s.</td>
<td>90.5 ± 1.7</td>
<td>-2.8 ± 6.1</td>
<td>n.s.</td>
<td>7.462 ± 0.028</td>
<td>-0.063 ± 0.047</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>34.5 ± 4.2</td>
<td>+4.0 ± 1.2</td>
<td>*</td>
<td>85.9 ± 5.4</td>
<td>-15.3 ± 3.1</td>
<td>**</td>
<td>7.465 ± 0.027</td>
<td>-0.055 ± 0.012</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>28.7 ± 1.5</td>
<td>-5.1 ± 1.5</td>
<td>*</td>
<td>95.4 ± 4.9</td>
<td>+3.2 ± 2.4</td>
<td>n.s.</td>
<td>7.409 ± 0.036</td>
<td>+0.021 ± 0.020</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>28.3 ± 2.4</td>
<td>-3.8 ± 0.7</td>
<td>**</td>
<td>90.6 ± 7.6</td>
<td>+2.8 ± 0.86</td>
<td>n.s.</td>
<td>7.360 ± 0.016</td>
<td>+0.021 ± 0.022</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>5</td>
<td>30.0 ± 3.3</td>
<td>-5.3 ± 1.0</td>
<td>**</td>
<td>&gt;280</td>
<td>---</td>
<td>---</td>
<td>7.421 ± 0.024</td>
<td>+0.040 ± 0.020</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 0.05 > P > 0.01; ** 0.01 > P > 0.001; n.s. = not significant.

while heart rate showed a more variable reduction (table II). The blood-gas data (table III) show that PaCO₂ was reduced and PaO₂, although increased, was subject to great variation.

Group IV. In the presence of gallamine, the effects of ketamine were similar to those described in Group III above (tables I, II and III). Mean arterial pressure was reduced, and heart rate was decreased.
Fig. 1. Effects of ketamine 10 mg/kg, i.v. on arterial pressure. Upper trace: response in conscious rabbit; middle trace: following pentobarbitone anaesthesia with spontaneous respiration; lower trace: during mechanical ventilation after gallamine injection. 90 min elapsed between doses.

variably. The blood-gas changes show mainly a reduction in $P_{aCO_2}$ (table III).

Group V. When rabbits which were given gallamine were ventilated with 100% oxygen, the effects of ketamine were similar to those obtained using air, with or without gallamine. The mean arterial pressure was reduced (table I), heart rate was not significantly affected (table II), and $P_{aCO_2}$ decreased (table III).

Group VI. After the aortic depressor nerves had been divided bilaterally in the presence of pentobarbitone, gallamine and mechanical ventilation with 100% oxygen, the effects of ketamine were similar to the above groups (III, IV and V) in which mechanical ventilation was employed. The mean arterial pressure was reduced (table I) and heart rate was reduced variably (table II).

Within each of the above groups the effects of ketamine were reproducible, and variations were not the result of tachyphylaxis.

Aortic depressor and carotid sinus denervation

The effects of ketamine in the spontaneously breathing rabbit, subsequent to baroreceptor/chemoreceptor denervation, were similar to those observed during mechanical ventilation in intact animals. Thus, mean arterial pressure was depressed, and remained so for 15–30 min, in contrast to the pattern in intact spontaneously breathing rabbits where control values were re-established after less than 2 min (fig. 2). Section of the depressor nerves alone was associated with a response to ketamine which was intermediate between that with all baroreceptors intact and that after additional carotid sinus denervation (fig. 3).

Fig. 2. Effect of ketamine 5 mg/kg, i.v. on arterial pressure in a rabbit with background anaesthesia of pentobarbitone. (A) Spontaneous respiration. (B) Mechanical ventilation without gallamine. (C) Return to spontaneous respiration. (D) Following bilateral aortic depressor nerve section. (E) After bilateral section of carotid sinus and depressor nerves.

Fig. 3. Effect of division of the baroreceptor afferents on the arterial pressure response to ketamine 5 mg/kg, i.v. in four rabbits breathing spontaneously and anaesthetized with pentobarbitone. Open columns: control (C) mean arterial pressure (MAP) before administration of ketamine. Striped columns: mean arterial pressure 2 min after ketamine (K). I-bars indicate SEM.
Effect of increasing Pa\textsubscript{CO}\textsubscript{2} on the circulatory responses to ketamine during mechanical ventilation

When three rabbits were ventilated mechanically for 2 min with 5% carbon dioxide in oxygen, Pa\textsubscript{CO}\textsubscript{2} was increased by 13.4 ± 4.0 mm Hg and mean arterial pressure by 10 ± 3.0 mm Hg. When ketamine 5 mg/kg was given simultaneously with 5% carbon dioxide, 2 min later Pa\textsubscript{CO}\textsubscript{2} was increased by 18.4 ± 5.5 mm Hg, but mean arterial pressure was decreased by 29 ± 3 mm Hg (fig. 4). Despite the increase in Pa\textsubscript{CO}\textsubscript{2}, therefore, the changes following ketamine were similar to those found in the mechanically ventilated animals without an increase in Pa\textsubscript{CO}\textsubscript{2} (groups III–VI, table I).

Effect of altered respiratory rate on the response to ketamine

When the respiratory rate was reduced by 50%, while maintaining stroke volume constant, in mechanically ventilated rabbits anesthetized with pentobarbitone, mean arterial pressure was increased after 2 min by 20 ± 4.6 mm Hg (P < 0.01). In the same animals, when ketamine was administered simultaneously with the reduction of respiratory rate, after 2 min the mean arterial pressure was not significantly different from the pre-ketamine value (+3.1 ± 9.2 mm Hg). Administration of ketamine to these rabbits without alteration of the respiratory rate resulted in a reduction in arterial pressure at 2 min of 18 ± 6.1 mm Hg (P < 0.01). This suggests that the depression of arterial pressure which ketamine itself produces during mechanical ventilation can be prevented by changing artificially the pattern of respiration, in a manner analogous to that produced by ketamine in spontaneously breathing animals.

In the same group of animals, after the aortic depressor and carotid sinus nerves had been divided bilaterally, reducing respiratory rate by 50% for 2 min produced a smaller increase in arterial pressure (5.5 ± 1.5 mm Hg; P < 0.05). Under the same circumstances, this reduction in respiratory rate simultaneous with the administration of ketamine made no difference to the depressor response produced by the drug (fig. 5). Baroreceptor denervation per se had increased the mean arterial pressure to 129 ± 8.7 mm Hg, and ketamine produced a depressor response which was proportionately larger than before denervation, but the value to which the pressure decreased was similar (fig. 5).
Relationship of preganglionic cervical sympathetic activity to changes in arterial pressure

A comparison was made of the effects of ketamine on sympathetic discharge in spontaneously breathing and mechanically ventilated rabbits. In the spontaneously breathing animal, sympathetic activity decreased transiently following the injection of ketamine, then recovered to the control values within 2 min. During mechanical ventilation, sympathetic activity and arterial pressure were depressed in parallel (fig. 6).

![Graph showing the comparison of the effects of ketamine 5 mg/kg, i.v. on mean arterial pressure (MAP) and preganglionic cervical sympathetic activity (CSA) in three rabbits during spontaneous (S) and mechanical (M) ventilation (background anaesthesia, pentobarbitone). Measurements, expressed as a percentage of the pre-ketamine values, relate to 2 min after injection. I-bars indicate SEM.](image)

**DISCUSSION**

These studies have demonstrated variability in the circulatory responses to ketamine, in an animal species, related apparently to whether respiration is spontaneous or controlled, and to the presence of background anaesthesia with pentobarbitone. The main findings are summarized thus: in conscious rabbits ketamine caused a transient reduction in arterial pressure followed within 2 min by a secondary increase; when the animals were anaesthetized with pentobarbitone and allowed to breathe spontaneously, the secondary pressor phase was absent, the arterial pressure returning by 2 min to the control value; during mechanical ventilation and pentobarbitone anaesthesia, the response to ketamine was entirely depressor, reaching a maximum at 2 min and lasting for 15–30 min, this occurring in the presence or absence of gallamine, and when ventilation was with air or 100% oxygen. A second factor which was associated with a depressor response to ketamine, whatever the experimental conditions, was bilateral division of the carotid sinus and aortic nerves. These findings point to an interaction of circulatory and respiratory reflex mechanisms of some complexity.

It should be emphasized that carotid and aortic denervation, by removing both baroreceptor and chemoreceptor input to the central nervous system, distorts normal circulatory and respiratory regulation; invariably it has been shown to change the normal responses of arterial pressure to those inhalation anaesthetic agents which increase sympathetic activity (Millar and Bischoe, 1965; Price et al., 1969; Skovsted and Price, 1970). It is uncertain whether such effects are specific in all circumstances.

Baroreceptor desensitization by ketamine, suggested by Dowdy and Kaya (1968), cannot be related easily to the present experiments, since a prolonged reduction in arterial pressure occurred during mechanical ventilation when the baroreceptor/chemoreceptor afferents were intact. Also, in order to exclude chemoreceptor discharge and to demonstrate unequivocal changes in the sensitivity of baroreceptor afferents, direct recording from single nerve fibres is required.

In the doses which produced the greatest changes in arterial pressure, ketamine also depressed respiration in rabbits breathing spontaneously, periods of apnoea of up to 10–20 sec being followed by a slowed respiratory rate. From this, two possible reflex mechanisms have been considered: systemic chemoreceptor stimulation secondary to an increase in $\text{Pa}_{\text{CO}_2}$ or to a reduction in $\text{Pa}_{\text{O}_2}$, or more subtle changes resulting from an interaction of afferent baroreceptor activity and respiratory rate.

The magnitude of the change in blood-gases was small when ketamine 5–10 mg/kg was given to rabbits breathing spontaneously. Also, when $\text{Pa}_{\text{CO}_2}$ was increased by the addition of carbon dioxide to the inspired gas during mechanical ventilation, the cardiovascular depression induced by ketamine was not reversed. Thus, chemoreceptor stimulation does not appear to account for a reflex increase of arterial pressure during ketamine anaesthesia.

Total afferent baroreceptor input is modulated as a result of changes in arterial pressure, and its rhythmic oscillations, which are associated with variations in respiratory rate and intrathoracic pressure (Angell James, 1968; Angell James and Daly, 1970). The implication of such modulations...
to the circulatory action of ketamine is hypothetical, and was tested crudely by reducing the respiratory rate in mechanically ventilated animals to mimic the slowing induced by ketamine, which is by about 50% over the first 2 min after injection. When carried out simultaneously with the administration of ketamine, however, this manoeuvre eliminated the depressor response to the drug, whereas after carotid sinus and aortic denervation it failed to reverse the reduction in arterial pressure. Thus, alteration of afferent baroreceptor input secondary to respiratory changes may be involved in the circulatory responses to ketamine. The absence of an inhibitory effect of ketamine on central baroreceptor pathways, other than those involved in control of heart rate (McGrath, MacKenzie and Millar, 1975), permits this reasoning.

Such comparisons, based on changes in respiratory rate in spontaneously breathing and mechanically ventilated animals, are complicated by the widely differing intrathoracic pressures associated with the two patterns. Intermittent positive pressure ventilation in the rabbit can be associated with a lower mean arterial pressure, and with wider respiratory oscillations, than occur during spontaneous respiration. Such differences in arterial pressure between the two respiratory patterns were minimized in the present studies, by avoiding large stroke volumes and by maintaining relatively fast rates of mechanical ventilation; also, an artificial pneumothorax did not change the findings in one mechanically ventilated animal.

Another relevant factor could be a change in systemic vascular resistance resulting from alterations in lung volume through an afferent vagosympathetic reflex (Daly, Hazzledine and Ungar, 1967). Also, an influence of afferent chemoreceptor activity, other than from changes in mean arterial gas tensions, is not excluded.

These findings show that the circulatory effects of ketamine differ in the spontaneously breathing and mechanically ventilated rabbit, and that this difference may be related to afferent baroreceptor or other reflexes regulating the cardiovascular system; overall, also, that the pressor effect of ketamine is based on subtler mechanisms than the generalized sympathetic stimulation shown by the inhalation anaesthetic agents cyclopropane and diethyl ether.

The results may help to explain the pressor response to ketamine which occurs in spontaneously respiring patients (Domino, Chodoff and Corssen, 1965; Virtue et al, 1967; Dillon, 1971; Savege et al., 1973) but apparently not during mechanical ventilation (Oyama, Matsumoto and Kudo, 1970; Meer, Downing and Coleman, 1973; Johnston, Miller and Way, 1974). They suggest that the pattern of respiration must be characterized during circulatory studies of ketamine.

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KREISLAUFREAKTIONEN AUF KETAMIN: ABHÄNGIGKEIT VON ATMUNGSWEISEN UND VORLÄUFIG NARKOSE BEIM KANINCHEN


RESPUESTAS CIRCULATORIAS A LA QUETAMINA: DEPENDENCIA SOBRE LAS MODALIDADES RESPIRATORIAS Y EL ANTECEDENTE ANESTESICO EN EL CONEJO

La ketamina aumentó o no varió la presión arterial, respectivamente, en conejos que estaban inicialmente conscientes o ligeramente anestesiados con pentobarbitona, mientras que en animales ventilados mecánicamente se produjo una depresión prolongada de la presión y la actividad simpática pregangliónica. Aunque el ritmo respiratorio se retardó durante la ventilación espontánea, los cambios en el contenido de gas sanguíneo no fueron los responsables de esas diferencias. Se produjo una respuesta depresora a la quetamina, durante la respiración espontánea, siguiendo a la división bilateral del seno carotídeo y los nervios aurícos. Cuando el ritmo respiratorio se retardó al mismo tiempo con una inyección de quetamina durante la ventilación mecánica, las respuestas circulatorias fueron similares a las producidas durante la respiración espontánea; esto no sucedió después de la denervación carotídea y auricular. Se reseñan esas variaciones en los efectos circulatorios de la quetamina, según el ritmo respiratorio y el antecedente anestésico.