RESTORATION OF BAROREFLEX CONTROL OF HEART RATE DURING RECOVERY FROM ANAESTHESIA

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Carotid sinus and aortic arch baroreflexes are important acute cardiovascular control mechanisms which influence venous capacitance, systemic vascular resistance, myocardial contractility and heart rate. A change of heart rate, in response to an increase in systolic arterial pressure, is a measure of the gain or sensitivity of the overall baroreflex which can be evaluated readily in patients (Smyth, Sleight and Pickering, 1969; Bristow et al., 1969).

The sensitivity of the baroreflex control of heart rate has been shown to be altered by both i.v. (Bristow et al., 1969; Jones and Prys-Roberts, 1983) and inhalation anaesthetic agents (Bristow et al., 1969; Duke, Fownes and Wade, 1977; Duke and Trosky, 1980; Morton, Duke and Ong, 1980; Kotryl et al., 1984). Brief barbiturate anaesthesia and halothane–nitrous oxide anaesthesia have both been shown to cause at least a 40% depression of baroreflex sensitivity in man (Bristow et al., 1969). Such depression of homeostatic cardiovascular reflexes may have important consequences following postural changes or sudden loss of circulating blood volume, as may occur during and on recovery from anaesthesia. As there have been no previous studies on the return of the baroreflex to normal during recovery from anaesthesia, we have studied the return of the baroreflex control of heart rate in man after i.v. or inhalation anaesthesia.

Methohexitone has a short elimination half-life and a high metabolic clearance (Breimer, 1976; Hudson, Stanski and Burch, 1982), and has been shown to be a suitable agent for administration by infusion (Hunter, 1972; Prys-Roberts et al., 1983). The Minimum Infusion Rate for methohexitone under the conditions of this study was established previously as 48.8 µg kg⁻¹ min⁻¹ (95% confidence limits 38.7–61.5) (Sear et al., 1983), and in a previous study we reported the haemodynamic effects of methohexitone infused at 60 and 120 µg kg⁻¹ min⁻¹ during anaesthesia with nitrous oxide in oxygen (Prys-Roberts et al., 1983). These infusion rates were used in our present study and their effects on the baroreflex were compared with those of halothane–nitrous oxide anaesthesia.

SUMMARY

The effects on baroreflex control of heart rate of halothane or methohexitone used to supplement 67% nitrous oxide in oxygen have been studied in 21 patients. Stable anaesthesia with either agent caused depression of baroreflex sensitivity by more than 50%. The set point of the reflex was also changed by both agents, but in opposite directions. Halothane administration resulted in slower heart rates at lower arterial pressures, whereas the infusion of methohexitone caused faster heart rates at lower arterial pressure. During recovery from anaesthesia, there was a rapid return of baroreflex sensitivity to normal and this was achieved before the patients regained consciousness, with no difference between the two groups. The reflex was reset rapidly and repeatedly during the recovery phase.

PATIENTS AND METHODS

Twenty-one patients (ASA I) aged 21–57 yr undergoing elective surgery to the body surface were studied. All patients had normal cardiovascular systems on clinical examination. All gave informed consent to take part in the study, and were premedicated with morphine 0.15 mg kg⁻¹ i.m. 1 h before the start of the definitive investigation. No atropine or other vagolytic drugs were administered. Eleven of the patients (mean
age 34 yr, mean weight 74 kg) received an infusion of methohexitone to supplement nitrous oxide anaesthesia (group 1); the other 10 patients (mean age 38 yr, mean weight 68 kg) received halothane as a supplement to nitrous oxide anaesthesia (group 2) following the induction of anaesthesia with methohexitone.

In all patients, intra-arterial and central venous cannulae were placed under local analgesia before the induction of anaesthesia, and the electrocardiogram (CM5) was monitored continuously. All variables were recorded on a Mingograph EM81 ink jet recorder.

Baroreflex activity was assessed by measuring the response of the heart rate to an increase in systolic arterial pressure (SAP) induced by the rapid administration of phenylephrine 1–2 μg kg⁻¹ through the central venous catheter (Smyth, Sleight and Pickering, 1969; Bristow et al., 1969). The dose of phenylephrine was selected to increase SAP by 25–30 mm Hg over a 20–30-s period. The relationship between the pulse interval and the SAP was evaluated quantitatively during the time from injection of the phenylephrine to the peak of its pressor effect, by plotting the R–R interval as a function of the SAP for the preceding beat. Pulse intervals occurring during inspiration were excluded to minimize the influence of sinus arrhythmia. SAP decreased to pre-injection values within 3 min of each dose of phenylephrine. Two indices of this relationship, the baroreflex slope and the pulse interval at reference arterial pressure (set point) were calculated as described previously (Bristow et al., 1969). The slope of the R–R interval/systolic arterial pressure function (baroreflex slope) represents the gain of the negative feedback system for regulation of arterial pressure. The change in heart rate is only one component of the complete regulatory system (Prys-Roberts, 1980). Resetting of the reflex is recognized as a shift of the mid-point of the normal curve, and implies a change in the balance of sympathetic and parasympathetic control of heart rate independent of the gain of the control system.

Pressor tests were performed with the patient awake and lying supine, and were repeated during anaesthesia and recovery. Anaesthesia was induced in all patients with methohexitone 1.5 mg kg⁻¹ given i.v. over 30 s. If intubation of the trachea was required it was facilitated by suxamethonium 1 mg kg⁻¹ and topical analgesia to the larynx and trachea using 4% lignocaine. Anaesthesia was maintained using 67% nitrous oxide in oxygen breathed spontaneously through a Magill breathing system and supplemented by either methohexitone as an infusion of 10 mg ml⁻¹ (group 1 patients) or halothane delivered from a recently calibrated Flutec Mk.3 vaporizer (group 2 patients).

The methohexitone infusion (group 1) was set at a rate of 60 μg kg⁻¹ min⁻¹ for 30 min before surgery, increasing to 120 μg kg⁻¹ min⁻¹, at which rate it was maintained for the duration of surgery (between 60 and 120 min).

The concentration of halothane (group 2) was adjusted to maintain an end-tidal concentration of 1.2% as measured by an Engstrom multigas monitor (EMMA) sensor inserted to the Magill system between the mask and angle piece, or tracheal tube and connector. This concentration was maintained for 30 min before surgery and continued throughout surgery—which lasted between 65 and 128 min.

A pressor test was performed 30 min after the induction of anaesthesia before any surgical stimulus had been applied, and again at the end of surgery before the end of anaesthesia. Anaesthesia was then discontinued by stopping the infusion of methohexitone (group 1) or discontinuing the administration of halothane (group 2) and simultaneously turning off the nitrous oxide. Further pressor tests were then performed at 2, 5, 10, 15, 30, 60, 90 and 120 min after the end of anaesthesia. The time from the end of anaesthesia until the patients opened their eyes in response to command was noted.

The baroreflex slopes and the time for arousal from anaesthesia showed a skewed distribution and were evaluated statistically after logarithmic transformation of the data. All other variables showed a normal distribution. Results within groups were evaluated using paired Student’s t test with Yates’ correction for small numbers. Comparisons between the groups were analysed using unpaired Student’s t test.

RESULTS

The two groups of patients were comparable in respect of age, weight and awake haemodynamic variables (table I). The duration of anaesthesia was longer ($P < 0.05$) in group 2 (halothane), but all patients had between 90 and 160 min total anaesthesia. The mean time to awakening was the same in each group, but there was a more consistent awakening time (narrower confidence limits) in group 2 (halothane).
RECOVERY OF BAROREFLEX CONTROL AFTER ANAESTHESIA

TABLE I. Patient details, anaesthetic and recovery times, and awake haemodynamic variables in group 1 (methohexitone) and group 2 (halothane) patients. *P < 0.05. †Geometric mean and 95% values; all other values mean ± SD

| Group 1 | Methohexitone (n = 11) | | Group 2 | Halothane (n = 10) | |
|---------|------------------------|-----------------|-----------|-------------------|
| Age (yr) | 34 (±5.6) | 37.9 (±11) | | Weight (kg) | 73 (±12.8) | 67.5 (±13) | |
| Duration of anaesthesia (min) | 104.4 (±18.6) | 124 (±21) | | Time to eyes open (min)† | 18.9 (4.4–81.4) | 18.4 (9.8–34.4) | |
| Awake arterial pressure | | | | Systolic (mm Hg) | 121 (±23.4) | 125 (±14.9) | |
| | | | | Diastolic (mm Hg) | 62.5 (±11.6) | 60 (±9.5) | |
| | | | | Awake pulse interval (ms) | 998 (±139) | 891 (±176) | |

TABLE II. Haemodynamic variables and baroreflex responses in group 1 patients (methohexitone). †Geometric mean and 95% values; all other values mean ± SD. By comparison with awake values: *P < 0.05; **P < 0.01; ***P < 0.001. By comparison with group 2 values: $P < 0.05; $$P < 0.01; $$$P < 0.001

<table>
<thead>
<tr>
<th>Group 1 Methohexitone (n = 11)</th>
<th>R–R interval (ms)</th>
<th>Heart rate (beat min⁻¹)</th>
<th>Arterial pressure</th>
<th>Baroreflex slope (ms mm Hg⁻¹)†</th>
<th>Pulse interval at reference arterial pressure (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>996 (±136)</td>
<td>60 (±8)</td>
<td>124 (±24)</td>
<td>64 (±11)</td>
<td>10.1 (2.8–35.7)</td>
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<td>30 min Anaesthesia</td>
<td>785 (±187)</td>
<td>$76 (±17)</td>
<td>94 (±22)</td>
<td>54 (±15)</td>
<td>4.5 (1–21.2)</td>
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<tr>
<td>End of surgery</td>
<td>715 (±152)</td>
<td>$$$84 (±18)</td>
<td>97 (±18)</td>
<td>58 (±13)</td>
<td>2.7 (0.4–17.9)</td>
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<td>Recovery (min)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>740 (±104)</td>
<td>$81 (±10)</td>
<td>102 (±17)</td>
<td>58 (±10)</td>
<td>3.3 (0.7–15.8)</td>
</tr>
<tr>
<td>5</td>
<td>863 (±130)</td>
<td>$70 (±12)</td>
<td>115 (±17)</td>
<td>61 (±11)</td>
<td>9.2 (1.3–64.8)</td>
</tr>
<tr>
<td>10</td>
<td>849 (±187)</td>
<td>71 (±16)</td>
<td>116 (±18)</td>
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<tr>
<td>15</td>
<td>860 (±227)</td>
<td>70 (±20)</td>
<td>115 (±20)</td>
<td>61 (±14)</td>
<td>8.1 (0.9–73.1)</td>
</tr>
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<td>72 (±16)</td>
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<tr>
<td>90</td>
<td>902 (±233)</td>
<td>67 (±18)</td>
<td>122 (±18)</td>
<td>61 (±10)</td>
<td>11.4 (2.8–46.4)</td>
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Group 1 (methohexitone) (table II)

The infusion of methohexitone at 60 μg kg⁻¹ min⁻¹ was associated with a 24% decrease in SAP compared with the awake state (P < 0.05), and heart rate increased by 21% (P < 0.01). Baroreflex sensitivity was diminished by 55% compared with the awake value (P < 0.01) and the set point (pulse interval at reference arterial pressure) had changed in all patients. The sequential baroreflex responses of a typical patient in group 1 are shown in figure 1. In eight patients the changes in the set point resulted in faster heart rates at the reference SAP, whilst slower heart rates were observed in the other three patients.

Doubling the infusion rate of methohexitone to 120 μg kg⁻¹ min⁻¹ during surgery resulted in a further increase (9%) in heart rate (ns), but there was no significant change in baroreflex sensitivity. There was no further change in the resetting of the reflex as the heart rate at the reference SAP remained 19% faster than the awake values (P < 0.05).

Five minutes after stopping the infusion of methohexitone, the SAP had returned to the awake value, but the heart rate continued to be significantly more rapid until the 10-min values were recorded. The sensitivity of the baroreflex increased towards the awake value by 5 min following the termination of anaesthesia, but then fluctuated, being decreased at 10 min into recovery (P < 0.05), with subsequent restoration of sensitivity towards the awake value. A change in the set...
Fig. 1. Baroreflex responses of one patient in group 1 (methohexitone) during anaesthesia and recovery from anaesthesia. Responses show depression of baroreflex sensitivity during anaesthesia with rapid recovery after termination of anaesthesia. (Responses at 10, 60 and 90 min have been excluded in the interest of clarity.) Baroreflex responses were reset during anaesthesia to allow faster heart rates at lower arterial pressures than awake which persisted, in this patient, into the recovery period. 30A = During anaesthesia, 30 min after induction; ES = during anaesthesia, at the end of surgery. Figures beside the individual slopes refer to time (min) from end of anaesthesia.

Group 2 (halothane) (table III)

There was a 31% decrease in SAP after 30 min of halothane–nitrous oxide anaesthesia, compared with the awake value ($P < 0.001$), and a 21% decrease in heart rate ($P < 0.05$). The sensitivity of the baroreflex decreased by 55% from the awake value ($P < 0.01$), and resetting occurred, resulting in a greater than 40% decrease in heart rate at the reference SAP ($P < 0.001$). The sequential baroreflex responses of a typical patient in group 2 are shown in figure 2. At the end of surgery, before anaesthesia had been discontinued, SAP had increased slightly compared with the value observed before surgery, but there was no significant difference in the mean values. The heart rate had increased, and was not significantly different from the awake value. Baroreflex sensitivity had decreased further (ns) by comparison with the pre-surgery value and, although the set point was restored partially towards the awake value, it was still significantly different ($P < 0.05$).

SAP was restored to awake values by 5 min after the termination of anaesthesia, and there was a rapid return of baroreflex sensitivity, with no

| Table III. Haemodynamic variables and derived baroreflex responses in group 2 patients (halothane). † Geometric mean and 95% values; all other values mean (± SD). By comparison with awake values: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. By comparison with group 1 values: $\dollar P < 0.05$; $\dollar\dollar P < 0.01$; $\dollar\dollar\dollar P < 0.001 |
significant difference between the 2-, 5- and 10 min values and the preoperative awake value. As in group 1 patients, this initial recovery was followed by a brief decline in sensitivity at 15 min after cessation of anaesthesia ($P < 0.05$). During recovery from anaesthesia resetting of the reflex was inconsistent, resulting in both faster and slower heart rates within individual patients, but with no significant difference in the means, from the awake value.

**Group 1 and group 2**

There were no significant differences between the two groups in either SAP or baroreflex sensitivity at the various times during anaesthesia or during recovery from anaesthesia (fig. 3). There was a significant difference between the heart rates after 30 min anaesthesia for the two groups ($P < 0.001$) which was still significant at the end of surgery ($P < 0.01$) and at 2 min into recovery ($P < 0.05$). The set point of the reflex was also significantly different between the two groups during anaesthesia ($P < 0.001$ before surgery, and $P < 0.05$ after surgery), but there were no significant differences during recovery from anaesthesia because of the large variability in the values for R–R interval at the reference pressure for both groups.
DISCUSSION

In patients breathing 67% nitrous oxide in oxygen, in the absence of surgery, baroreflex control of heart rate was depressed to a similar degree by either an infusion of methohexitone 60 μg kg⁻¹ min⁻¹ or by halothane, administered to an end-tidal concentration of 1.2%. The reflex was also reset by both agents, but in opposite directions. The resetting that occurred during halothane anaesthesia resulted in slower heart rates at lower arterial pressures than when awake. This has been demonstrated before with halothane (Bristow et al., 1969; Duke et al., 1977; Duke and Trosky, 1980) and with infusions of Althesin (Jones and Prys-Roberts, 1983) and may be the result of either an increase in vagal activity or a decrease in sympathetic activity. As these changes persist during surgical stimulation, it would appear that an increase in vagal activity is the more likely explanation. Methohexitone, in contrast to volatile agents or infusions of Althesin, resulted in faster heart rates at lower arterial pressures than when awake. This effect has also been reported previously, but only immediately following the induction of anaesthesia with Althesin (Jones and Prys-Roberts, 1983) or thiopentone (Bristow et al., 1969). This could be the result of either a central release of vagal activity (Greene and Bachand, 1971) or an increase in sympathetic activity. However, as there is no evidence of increased plasma catecholamine concentrations after the induction of anaesthesia in the absence of surgery (Russell et al., 1981; Derbyshire et al., 1983), the evidence would suggest that methohexitone inhibits central vagal activity.

At the end of surgery, while anaesthesia continued, baroreflex activity was reduced to less than 40% of the awake values for both groups, and further resetting had occurred, resulting in slightly faster (methohexitone) or slower (halothane) heart rates than at the pre-surgical anaesthetized value. In the patients who received an infusion of methohexitone, this effect could be attributed to the increase in sympathetic activity which would be expected following surgery. Baroreflex sensitivity recovered rapidly after the end of anaesthesia in both groups, with a transient return to awake values before most patients had awoken. There was a significant reduction in baroreflex sensitivity in both groups after this initial recovery (fig. 3) (as measured from the awake value), although this was not a significant change from the preceding recovery value. This change occurred before most patients recovered consciousness, and subsequent values showed no significant differences from the awake values for both groups.

Resetting of the reflex occurred repeatedly during recovery from anaesthesia in the two groups, resulting in both faster and slower heart rates at various times within individual patients. These changes were consistent with those seen at various depths during normal sleep (Smyth, Sleight and Pickering, 1969), and resulted in large variability in the resetting values for both groups which made comparisons between the two groups difficult to interpret.

Changes in PaCO₂ during spontaneous ventilation are unlikely to have had much effect on either the sensitivity or resetting of the baroreflex. Hypercapnia alone has been shown to have only minimal effects on baroreflex sensitivity (Bristow et al., 1968) and, although resetting occurs with hypercapnia in the same direction as with methohexitone, it is only to a very minor degree, considering that the degree of hypercapnia caused by infusions of methohexitone (Prys-Roberts et al., 1983) has been shown to be less than that studied by Bristow and colleagues (1968), and so would be expected to have even less effect.

The results of the present study have important implications for those responsible for postoperative care, in that the return of baroreflex control of heart rate occurred before the return of consciousness in the majority of patients. Only a small percentage of patients, anaesthetized with either halothane or methohexitone to supplement nitrous oxide, showed a delayed recovery of baroreflex control. Although we have not studied the heart rate response to decreasing arterial pressure in this study, it seems reasonable to assume, on the basis of the studies by Kotrly and co-workers (1984), that the positive chronotropic response to hypovolaemia, or to any other cause of postoperative arterial hypotension, would be restored within a few minutes of the end of anaesthesia.

REFERENCES


