Effects of fentanyl, nitrous oxide, or both, on baroreceptor reflex regulation in the cat

Ö. LENNANDER, B-Å. HENRIKSSON, J. MARTNER AND B. BIBER

Summary
We have investigated the effects of fentanyl, nitrous oxide, or both, on carotid sinus baroreceptor reflexes in cats during basal chloralose anaesthesia. The bilaterally isolated carotid sinuses were perfused at prevailing systemic arterial pressure or at predetermined levels of pump-controlled pulsatile pressures of 50–200 mm Hg in steps of 25 mm Hg. Other major baroreceptor sites were denervated by bilateral vagotomy. Fentanyl decreased arterial pressure dose-dependently when the carotid sinuses were perfused at prevailing systemic arterial pressure and when the perfusion pressure was controlled artificially. High-dose fentanyl reduced significantly baroreceptor reflex responses in the sinus perfusion pressure range 50–125 mm Hg. Nitrous oxide increased arterial pressure in the carotid sinus perfusion range 75–125 mm Hg. There was no interaction between nitrous oxide and fentanyl for baroreceptor reflex responses. Our results indicated that baroreceptor reflexes, with and without nitrous oxide, were well preserved by moderate doses of fentanyl while high doses of fentanyl depressed baroreceptor reflexes. (Br. J. Anaesth. 1996;77:399–403)

Key words

The baroreflex is very important for short-term cardiovascular homeostasis. Halogenated inhaled anaesthetics decrease arterial pressure in a dose-dependent manner by interaction with both central and peripheral mechanisms. There is evidence also that halogenated inhaled anaesthetics depress the baroreceptor reflex1. In contrast, balanced anaesthesia with nitrous oxide and fentanyl is characterized by more stable peroperative haemodynamic conditions. One reason for this might be that this type of anaesthesia blunts baroreceptor reflexes to a lesser degree.

The aim of this study was to investigate the effects of nitrous oxide alone or in combination with fentanyl on the carotid sinus baroreceptor reflex. The study was performed in an experimental model in cats allowing analysis of the carotid sinus open loop gain, that is the impact on systemic arterial pressure of changes in perfusion pressure to the bilaterally isolated carotid sinuses.

Materials and methods
The study was performed on eight cats, weighing 3.2–4.9 kg. The animals had been deprived of food for 12 h but had free access to water. The study was approved by the National Swedish Animal Experiment Ethics Committee.

Anaesthesia was induced with enflurane and 70% nitrous oxide in oxygen and continued with chloralose 50 mg kg⁻¹ i.v. as basal anaesthesia. Supplementary doses of chloralose 50 mg were given when necessary during the experiment. After tracheotomy, the lungs were ventilated with air at a frequency of 20 bpm with a Harvard 661 small animal ventilator. Tidal volume was adjusted to maintain an arterial Pco₂ of 3.5–4.5 kPa, as verified by repeated arterial blood-gas analyses (ABL-2, Radiometer, Copenhagen).

Hydration and avoidance of metabolic acidosis was accomplished by a continuous infusion (10 ml kg⁻¹ h⁻¹ during preparation and 5 ml kg⁻¹ h⁻¹ during experiment) of Ringer’s–glucose with the addition of 20 ml of sodium bicarbonate 0.6 mol litre⁻¹ per 100 ml. Core temperature was maintained at 37–38 °C by means of a heating pad. Cardiopulmonary and aortic baroreceptors were denervated by bilateral sectioning of the vagal nerves.

The carotid sinuses were bilaterally partly isolated by ligation of the external and sometimes also the internal carotid arteries, and all other arterial branches that could be ligated without endangering the integrity of the sinus nerves by dissection. After administration of heparin 5000 IE i.v., catheters were inserted bilaterally into the common carotid arteries and femoral arteries, allowing the carotid sinuses to be perfused with blood from the femoral arteries, either at systemic arterial pressure by a direct bypass or at any desired level of pulsatile pressure using a rotor pump. To allow adjustments of carotid sinus perfusion pressure without changes in pump frequency, an arteriovenous shunt was inserted between the carotid sinuses and an external jugular vein. The carotid sinus perfusion pressure was recorded from a side branch of the tubing system. This preparation has been described in detail previously².

ÖRJAN LENNANDER, MD, Department of Anaesthesia, Näl, S-461 85 Trollhättan, Sweden. BENGTÅKE HENRIKSSON, MD, PHD, JAN MARTNER, MD, PHD, Department of Anaesthesia, University of Göteborg, Sahlgrenska Hospital, S-413 85 Gothenburg, Sweden. BJÖRN BIBER, MD, PHD, Department of Anaesthesia, University of Umeå, S-901 85 Umeå, Sweden. Accepted for publication: April 4, 1996.

Correspondence to Ö. L.
infusion of fentanyl 4 μg kg⁻¹ h⁻¹; (6) ventilation with air. Bolus injection of fentanyl 40 μg kg⁻¹ followed by an infusion of fentanyl 16 μg kg⁻¹ h⁻¹; (7) ventilation with 70% nitrous oxide in oxygen. Continued infusion of fentanyl 16 μg kg⁻¹ h⁻¹; and (8) ventilation with air. At steady state, 15 min after (7), naloxone 30 μg kg⁻¹ was injected i.v.

STATISTICAL ANALYSIS
Data were analysed by repeated analysis of variance and Duncan’s multiple range test. *P<0.05 was considered significant. All data are presented as mean (SEM).

Results

CAROTID SINUSES PERFUSED AT SYSTEMIC ARTERIAL PRESSURE

Fentanyl decreased arterial pressure in a dose-dependent manner during air ventilation. Although no significant changes in HR from baseline were induced by fentanyl, HR was significantly lower after the high dose than after the low dose of the drug (*P<0.01, table 1).

Fentanyl-induced changes in DAP and HR were reversed by naloxone, while SAP and MAP were increased above baseline values (*P<0.01 and **P<0.05, respectively, table 1).

Administration of nitrous oxide in oxygen compared with ventilation with air did not induce any significant changes in arterial pressures or HR during basal chloralose anaesthesia with or without the addition of fentanyl (table 2).

CAROTID SINUS PERFUSION PRESSURES CONTROLLED ARTIFICIALLY

Fentanyl decreased MAP throughout the range of carotid sinus perfusion pressures (50–200 mm Hg; ANOVA main effects *P<0.001 for both fentanyl doses). At sinus perfusion pressures of 50, 75 and 100 mm Hg, fentanyl caused a dose-related decrease in MAP (fig. 1). Baroreflex gain was not changed by fentanyl, while high-dose fentanyl reduced the gain for sinus perfusion pressure intervals of 50–75, 75–100 and 100–125 mm Hg (fig. 1).

Although no significant changes in HR from baseline were induced by fentanyl, HR was significantly lower after high-dose compared with low-dose fentanyl (ANOVA main effects; *P<0.05, table 3).

Fentanyl-induced decreases in MAP and baroreflex gain were reversed by naloxone. At carotid sinus pressures of 50, 75 and 100 mm Hg, MAP was increased significantly above baseline (fig. 1).

When air was replaced by nitrous oxide in oxygen before administration of fentanyl, MAP increased at carotid sinus perfusion pressures of 75, 100 and 125

Table 1 Systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures and heart rate (HR) at baseline and after administration of two different doses of fentanyl and naloxone (mean (SEM)). *P<0.05. **P<0.01 compared with baseline. ††P<0.01 compared with low-dose fentanyl

<table>
<thead>
<tr>
<th></th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beat min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>164.8 (4.8)</td>
<td>129.3 (7.2)</td>
<td>141.1 (3.2)</td>
<td>243.1 (11.5)</td>
</tr>
<tr>
<td>Low fentanyl</td>
<td>144.4 (8.9)*</td>
<td>105.0 (10.2)**</td>
<td>118.2 (9.4)**</td>
<td>263.6 (8.1)</td>
</tr>
<tr>
<td>High fentanyl</td>
<td>116.1 (5.1)**</td>
<td>81.6 (7.5)**</td>
<td>93.1 (6.4)**</td>
<td>226.6 (11.6)††</td>
</tr>
<tr>
<td>Naloxone</td>
<td>189.4 (11.2)**</td>
<td>146.3 (10.1)</td>
<td>160.6 (10.3)*</td>
<td>237.6 (6.5)</td>
</tr>
</tbody>
</table>
Baroreceptor reflex and fentanyl–nitrous oxide

Table 2  Systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures and heart rate (HR) at baseline and after administration of two different doses of fentanyl during ventilation with air and ventilation with nitrous oxide (N2O) and oxygen (O2) (mean (SEM))

<table>
<thead>
<tr>
<th></th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beat min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air</td>
<td>N2O–O2</td>
<td>Air</td>
<td>N2O–O2</td>
</tr>
<tr>
<td>Baseline</td>
<td>167.9 (4.4)</td>
<td>175.0 (4.5)</td>
<td>133.1 (4.1)</td>
<td>139.8 (6.6)</td>
</tr>
<tr>
<td>Low fentanyl</td>
<td>144.4 (8.9)</td>
<td>149.3 (7.1)</td>
<td>105.0 (10.2)</td>
<td>114.0 (9.5)</td>
</tr>
<tr>
<td>High fentanyl</td>
<td>116.1 (5.1)</td>
<td>120.5 (6.4)</td>
<td>81.6 (7.5)</td>
<td>85.5 (7.7)</td>
</tr>
</tbody>
</table>

Figure 2  Baroreflex responses (systemic mean arterial pressure (MAP) vs carotid sinus perfusion pressure) in animals receiving either air (open symbols, interrupted lines) or nitrous oxide (filled symbols, solid lines) (mean, SEM). Panels show the following stages: baseline; low-dose fentanyl; high-dose fentanyl. *P<0.05.

Discussion

The aim of this study was to investigate the effect of generally used components of balanced anaesthesia, namely nitrous oxide and fentanyl, on high pressure baroreceptor reflex function. We used an animal experimental model which merits some comments on methodology.

First, we cut the vagus nerves to avoid secondary influences from cardiopulmonary low pressure reflexes. As this procedure also denervates the baroreceptors of the aortic arch, only carotid baroreflex responses were evaluated. However, aortic baroreceptors primarily modulate high pressure responses and thus are less likely to be significant for the overall cardiovascular reflex response to lowered arterial pressure, the object of this study. Second, the degree of baroreceptor activation depends on the carotid sinus perfusion pressure level and the velocity of the pulsatile pressure change. In our model, the profile of the pump-generated carotid pressure wave differed from pressure waves normally produced by the pumping heart. This implies different baroreceptor activation compared with the intact animal at similar arterial pressure levels. However, the pulsatile characteristics of the pump-generated carotid pressure wave were essentially similar at each phase of the experiment, as pump rate was kept constant. Changes in carotid

Table 3  Heart rate (HR) at different carotid sinus perfusion pressures at baseline and after administration of fentanyl, nitrous oxide (N2O) and naloxone (mean (SEM))

<table>
<thead>
<tr>
<th>Carotid sinus perfusion pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Nitrous oxide</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Low fentanyl</td>
</tr>
<tr>
<td>Low fentanyl + N2O</td>
</tr>
<tr>
<td>High fentanyl</td>
</tr>
<tr>
<td>High fentanyl + N2O</td>
</tr>
<tr>
<td>Naloxone</td>
</tr>
</tbody>
</table>
Nitrous oxide has been shown previously to increase systemic vascular resistance in combination with 1% halothane in humans and in combination with pentobarbitone in dogs. These findings, and other data in humans, indicate that nitrous oxide induces an increase in efferent sympathetic nervous activity (SNA). We observed circulatory effects (increased MAP) of nitrous oxide only when the carotid sinuses were perfused at pressures in the medium range (75–125 mm Hg). We suggest this reflects efficient baroreflex suppression of adrenergic nitrous oxide effects during intense baroreceptor activity (sinus perfusion pressure ≥150 mm Hg) and a background of pre-existing intense sympathetic outflow in the face of maximal baroreceptor unloading (sinus perfusion pressure <75 mm Hg). At these two extremes in sinus pressure, it is conceivable that nitrous oxide, although having sympatomimetic effects, adds only minimally to the prevailing degree of sympathetic discharge. These findings are in agreement with those of Bagshaw and Cox in the dog during light halothane anaesthesia.

Fentanyl has been shown to reduce sympathetic and increase vagal neural tone. These effects may depend on facilitation of impulse transmission at the dorsal nucleus of the vagus nerve and nucleus tractus solitarii of the baroreflex pathway. However, the reduction in MAP produced by fentanyl throughout the sinus perfusion pressures used in our study, with vagotomized animals, indicated reduced sympathetic output or direct cardiovascular organ effects, or both. At low sinus perfusion pressures, we observed a dose-dependent effect of fentanyl on MAP, probably reflecting the effects of fentanyl on the baroreflex as a dose-dependent reduction in baroreflex gain was observed at perfusion pressure increments of 50–125 mm Hg.

The effect of fentanyl on the baroreflex represents dose-dependent depression of baroreceptor arterial pressure control, as also shown in newborn infants. Despite the fact that nitrous oxide attenuates the baroreflex reflex, it did not further depress reflex control of arterial pressure when added to fentanyl at any of the infusion rates.

Data from this study support findings from other studies in humans where resetting of the baroreflex has been found after fentanyl and after the combination of fentanyl, diazepam and nitrous oxide. Kortly and co-workers also found that baroreflex control of heart rate was attenuated after lower doses of fentanyl (7.5 mg kg⁻¹). However, in their study and at higher doses of fentanyl (10 and 12.5 mg kg⁻¹) there was a discrepancy between baroreflexmediated tachycardia and bradycardia induced by lowered and increased arterial pressures compared with lower doses of fentanyl. This was postulated to be the result of enhanced vagal efferent activity mediated by fentanyl. In our study we did not find this difference in systemic arterial pressures or heart rate after low and high carotid sinus pressures, probably because we used vagotomized animals.

However, species differences cannot be excluded. Furthermore, differences between human and non- erect walking animals in baroreceptor reflexes seem to apply mainly to low pressure cardiopulmonary receptors. In our model these were excluded by vagotomy thus allowing for selective analysis of the high pressure carotid sinus part of the baroreceptor reflexes.

Naloxone was given to reverse the circulatory effects of fentanyl. After administration of naloxone, arterial pressure was not only restored but exceeded baseline arterial pressure. It is not clear from our study if this overshoot in arterial pressure reflected the central or peripheral effects of naloxone. Similar effects with naloxone have been observed in other studies. For example, in a study in conscious rabbits, naloxone increased arterial pressure both before and after sinoaortic barodenervation, but the increase was more pronounced after denervation. This indicates that the baroreceptor reflex buffers an increase in arterial pressure. In other studies, naloxone has been shown to increase baroreflex sensitivity.

Acknowledgements
This study was supported by grants from the Swedish Medical Research Council (project No. 6575).

References


