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EFFECTS OF ALFENTANIL ON THE PRESSOR AND CATECHOLAMINE RESPONSES TO TRACHEAL INTUBATION

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SUMMARY

The effects of alfentanil (given during induction of anaesthesia) on the haemodynamic and catecholamine responses to tracheal intubation were studied in 44 adult patients who received alfentanil 10 μg kg^{-1} or 40 μg kg^{-1}, or saline placebo. Alfentanil 10 μg kg^{-1} and 40 μg kg^{-1} prevented any increase in heart rate and arterial pressure after tracheal intubation. Alfentanil 40 μg kg^{-1} produced profound hypotension and bradycardia. The use of alfentanil in both doses was associated with a decrease in plasma adrenaline concentrations after tracheal intubation.

Laryngoscopy and intubation are associated with increases in arterial pressure, heart rate and plasma catecholamine concentrations (Derbyshire et al., 1983)—haemodynamic responses which may be accompanied by myocardial ischaemia and increased myocardial oxygen demand (Prys-Roberts et al., 1971). The pressor response can be blocked by high doses of opioids (Lunn et al., 1979) given during the induction of anaesthesia, and attenuated by low doses of fentanyl (Martin et al., 1982), volatile anaesthetics (Bedford and Marshall, 1984), local anaesthetics (Stoelting, 1978; Dohi et al., 1982), α-adrenoceptor blockers (Curran, Crowley and O'Sullivan, 1980), β-adrenoceptor blockers (Prys-Roberts et al., 1971) and drugs with vasodilating properties (Stoelting, 1979). The catecholamine response is modified by the use of large doses of opioids (Delange et al., 1983), and a number of neuromuscular blocking drugs (Cummings, Russell and Frewin, 1983). Although the most reliable method for preventing the catecholamine and haemodynamic responses appears to be the use, during induction, of large doses of opioids, any technique using fentanyl in excess of 10 μg kg^{-1} at induction may lead to postoperative ventilatory depression.

The introduction of the ultra short-acting opioid, alfentanil, permitted the use of a high-dose opioid induction technique without the concomitant risk of postoperative ventilatory depression. Black, Kay and Healy (1984) showed that alfentanil 15 μg kg^{-1} i.v. modified the haemodynamic changes and that 30 μg kg^{-1} abolished the pressor response in healthy patients undergoing elective surgery.

In the present study, alfentanil 10 μg kg^{-1} and 40 μg kg^{-1} were administered i.v. as part of the anaesthetic induction sequence, and the effects on the sympathoadrenal response to tracheal intubation were studied. These doses were chosen to equate with low (2–3 μg kg^{-1}), or medium (10 μg kg^{-1}) dose fentanyl in the ratio alfentanil : fentanyl of 4 : 1 (Rucquoi and Camie, 1983).

PATIENTS AND METHODS

Forty-four patients were studied, during major vascular, head and neck or thoracoabdominal surgery where direct arterial monitoring was planned as part of the anaesthetic technique. District Ethical Committee approval was obtained and each patient gave informed consent.

Patients were allocated randomly to receive i.v. over 30 s (as part of the anaesthetic induction sequence) a 10-ml bolus containing either alfen-

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tanil 10 μg kg^{-1} (A10), alfentanil 40 μg kg^{-1}, (A40) or saline placebo (S).

Each patient was premedicated with diazepam 10 mg orally, given 90 min before operation. In the anaesthetic room, arterial and i.v. cannulae were inserted under local anaesthesia. Direct arterial pressure monitoring was commenced, and the ECG (lead II) was displayed. After a 10-min stabilization period arterial blood was drawn for catecholamine analysis, and arterial pressure and heart rate were recorded simultaneously by an independent observer.

Induction of anaesthesia was achieved with sufficient thiopentone (3–5 mg kg^{-1}) to obtund the eyelash reflex, given i.v. over 1 min and was immediately followed by vecuronium 0.1 mg kg^{-1}. After 30 s the study drug was administered. Ventilation was assisted, then controlled, using an anaesthetic face mask and a coaxial Mapleson D breathing system with a fresh gas flow of 33% oxygen in nitrous oxide 70 ml kg^{-1} to maintain an end-expired carbon dioxide concentration of approximately 5% (Gould capnograph). One minute after the administration of the study drug, heart rate and arterial pressure were recorded and arterial blood drawn for catecholamine analysis. Ninety seconds after the administration of the study drug the patient's trachea was intubated with the aid of a standard Macintosh laryngoscope blade, and anaesthesia was continued with nitrous oxide in oxygen and positive pressure ventilation—which was adjusted, if necessary, so as to maintain normocapnia.

Further samples and measurements were taken at 1, 3 and 5 min after intubation. Throughout the study period, both observer and anaesthetist were unaware of the nature of the study drug. The anaesthetist was permitted to use increments of thiopentone to treat clinically inadequate anaesthesia or to increase the rate of the i.v. infusion to correct unacceptable degrees of hypotension. At the end of the study period, anaesthesia and surgery continued using additional anaesthetic agents as appropriate.

Arterial blood for measurement of plasma concentrations of adrenaline and noradrenaline was collected in lithium heparin tubes and centrifuged within 1 h at 0 °C. Plasma was separated and stored at −70 °C before assay was peformed by HPLC using a method described previously (Derbyshire et al., 1983).

Statistical analysis was by a two-way analysis of variance and Student's t test (paired within groups and unpaired between groups). A P value of less than 0.05 was deemed significant.

TABLE I. *Demographic data (mean ± SEM)*

	Control	A10	A40
n	15	14	15
Age (yr)	66.1 (2.8)	67.0 (2.2)	65.7 (2.3)
M:F	12:3	10:4	11:4
Wt (kg)	70.0 (3.1)	63.0 (4.2)	67.0 (2.1)
MAP (mm Hg)	100.7 (4.1)	108.5 (4.7)	103.5 (4.8)
HR (beat min^{-1})	84.2 (3.9)	78.5 (4.5)	75.7 (3.6)

RESULTS

The three groups were comparable in respect of age, weight and gender (table I). There were no significant differences between the three groups in the baseline (preinduction) values for mean arterial pressure (MAP) or heart rate (HR). Twenty-two patients were receiving concurrent

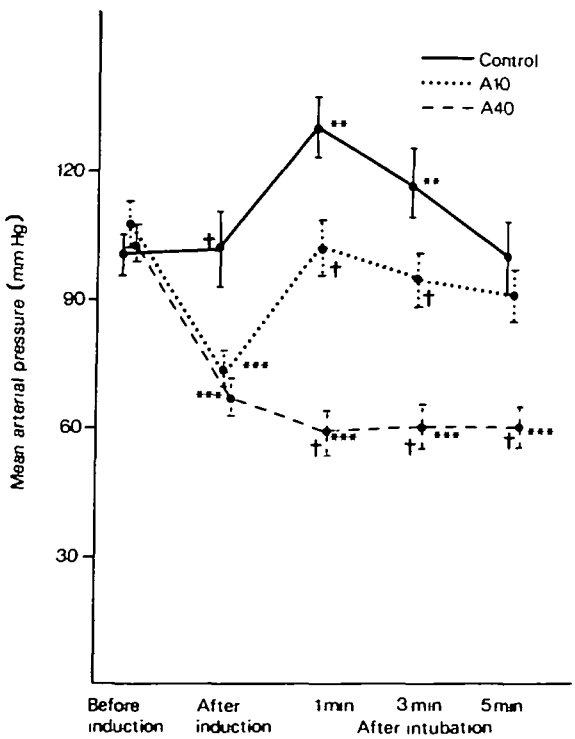

FIG. 1. Mean arterial pressure. $^{**}P < 0.01$ within group in comparison with value before induction; $^{***}P < 0.001$ within groups in comparison with value before induction; $\dagger P < 0.05$ between group comparison.

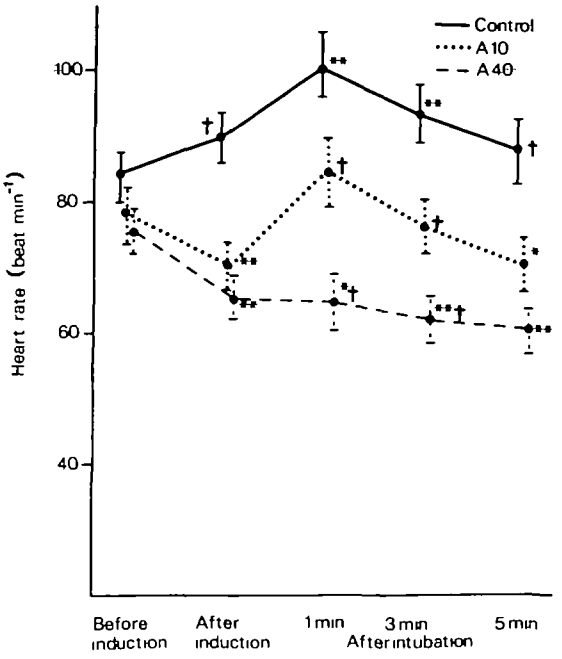

FIG. 2. Heart rate. *$P < 0.05$ within group in comparison with value before induction; **$P < 0.01$ within group in comparison with value before induction; †$P < 0.05$ between group comparison.

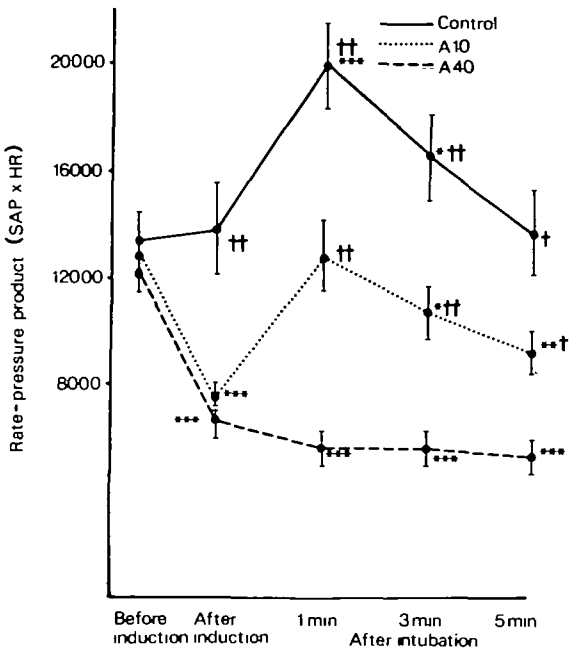

FIG. 3. Rate–pressure product. *$P < 0.05$ within group in comparison with value before induction; **$P < 0.01$ within group in comparison with value before induction; ***$P < 0.001$ within group in comparison with value before induction; †$P < 0.05$ between group comparison; ‡$P < 0.001$ between group comparison.

medication with β-adrenoceptor blockers or other antihypertensive agents; they were evenly distributed between the three groups.

The results for mean arterial pressure (MAP) are shown in figure 1. In the control group (S), there was a significant increase above preinduction values at 1 and 3 min after intubation ($P < 0.01$). In both treatment groups, MAP decreased significantly on induction ($P < 0.001$). After intubation in the A10 group, MAP returned to preinduction values, whereas in the A40 group MAP decreased further to 59 mm Hg (±4.5) ($P < 0.05$). This value was significantly lower than that for both control and A10 groups ($P < 0.001$). Eleven patients in the A40 group received more than 750 ml of fluids i.v. to maintain mean arterial pressure at 60 mm Hg.

Heart rate increased in the control group 1 min after intubation ($P < 0.01$) (fig. 2). In the A10 group there was a decrease in heart rate after the induction of anaesthesia ($P < 0.01$), and at 5 min after intubation ($P < 0.05$). Heart rates in the A40 group were significantly lower than the preinduction heart rate in this group after induction and intubation ($P < 0.05$).

Heart rates in the two treatment groups were significantly slower than those of patients in the control group at all times after induction, and differed between the two alfentanil groups at 1 and 3 min after intubation. Five patients in the A40 group received atropine i.v. in response to bradycardia associated with hypotension.

Figure 3 shows the values for rate–pressure product (RPP) in the three groups. RPP was increased in the control group at 1 and 3 min after intubation. In the treatment groups there were significant decreases after induction ($P < 0.001$). In the A10 group RPP was significantly less than that before induction at 3 and 5 min. In the A40 group there was a further decline in RPP after intubation and the RPP remained lower than the preinduction value throughout the study period ($P < 0.001$). Following the induction of anaesthesia, the two treatment groups demonstrated a significantly lower RPP than that of the control group and the RPP differed significantly between the three groups after intubation.

Plasma noradrenaline concentrations were determined in blood samples from 17 patients (fig. 4).

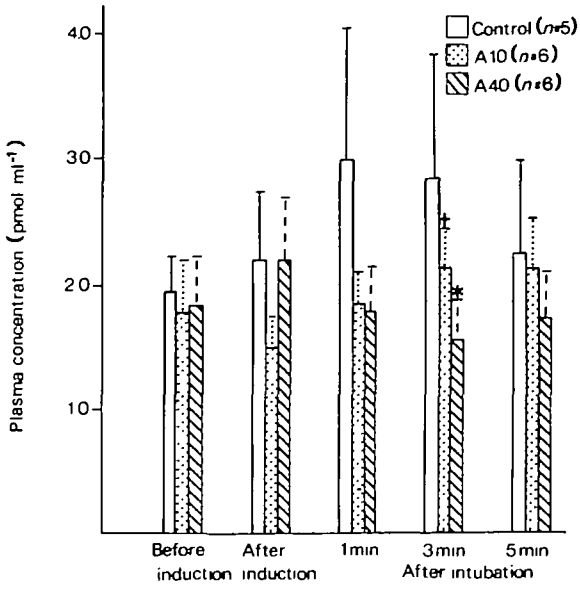

FIG. 4. Plasma noradrenaline concentrations. *$P < 0.05$ within group comparison with value after induction; †$P < 0.01$ within group in comparison with values after induction.

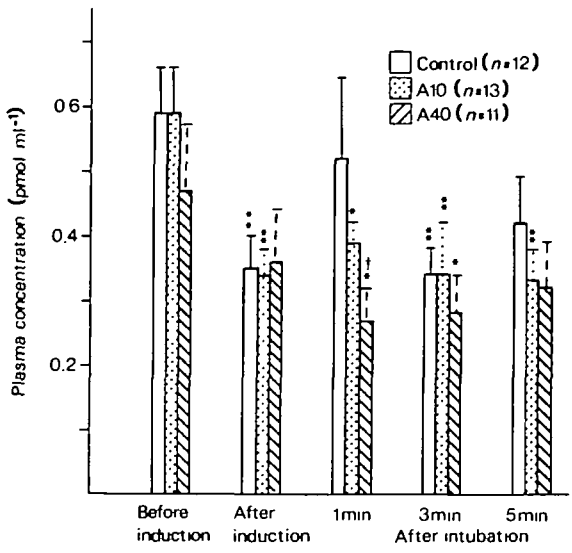

FIG. 5. Plasma adrenaline concentrations. *$P < 0.05$ within group in comparison with value before induction; **$P < 0.01$ within group in comparison with value before induction; †$P < 0.05$ in comparison with the A10 group.

There was a 50% increase (from preinduction) in noradrenaline concentration in the control group 1 min after intubation, but this was not statistically significant. In the A10 group, there was an increase in plasma noradrenaline between the sample taken after induction and the one taken 3 min after intubation ($P < 0.01$) while in the A40 group, noradrenaline concentration declined at 3 min in comparison with that after induction ($P < 0.05$). There were no significant differences between the three groups.

Figure 5 depicts the changes in the plasma adrenaline concentrations determined in samples from 36 patients. In both treatment groups plasma adrenaline concentration decreased at 1 and 3 min after intubation ($P < 0.05$). The value at 1 min was significantly lower in the A40 group than the A10 group ($P < 0.05$).

Six patients in the control group and one patient in the A10 group each required one increment of thiopentone. Four patients in the control group and one patient in the A10 group exhibited ECG arrhythmias, but none required treatment. No patients displayed ECG signs of ischaemia.

There was no morbidity attributable to anaesthesia and no patient in the A40 group required naloxone at the end of surgery despite liberal use of other opioid drugs during surgery.

DISCUSSION

This study has confirmed previous work that intubation of the trachea following thiopentone and a neuromuscular blocking drug is associated with significant increases in heart rate and mean arterial pressure (Derbyshire et al., 1983). Alfentanil in doses of 10 μg kg^{-1} and 40 μg kg^{-1} prevented the increases in mean arterial pressure and heart rate, in contrast to results from other authors where alfentanil 15 μg kg^{-1} failed to obtund the tachycardia (Black, Kay and Healy, 1984). In the present study, this may result from the use of a non-depolarizing myoneural blocking drug with stable cardiovascular properties (vecuronium) rather than the shorter acting suxamethonium which may have led to an increase in heart rate as spontaneous ventilation recommenced.

The decreases in mean arterial pressure demonstrated in both treatment groups after the induction of anaesthesia were maintained after intubation in the group who received the larger dose of alfentanil, and were unacceptably low to the "blind" anaesthetist. Much of the previously published work demonstrating the cardiostability of alfentanil has used alfentanil or etomidate as the induction agent, with oxygen-enriched air, ventilation and pancuronium as the myoneural blocking drug, and this may account for the apparent

discrepancy between that and the present results obtained during the use of the non-vagolytic drug, vecuronium.

A decrease in mean arterial pressure has been reported previously after alfentanil 150 $\mu g\ kg^{-1}$ (Moldendenhaur et al., 1983), 120 $\mu g\ kg^{-1}$ (Rucquoi and Camie, 1983), 70 $\mu g\ kg^{-1}$ (Spiss et al., 1984) and 30 $\mu g\ kg^{-1}$ (Black, Kay and Healy, 1984). The magnitude of the decrease in MAP (40%) observed in the present study has not been reported previously and may reflect our use of ASA grade III patients. The resistance of the hypotension to treatment with i.v. fluids or atropine, or both, would tend to support the work of Moldenhaur and colleagues (1983), who suggested that alfentanil produced a degree of direct myocardial depression.

Despite evidence in animals that cerebral blood flow is preserved in the presence of alfentanil-induced hypotension (McPherson et al., 1985) and the lack of reports of anaesthetic morbidity, the results of our study suggest that it may be inappropriate to use a high dose technique in patients with potential atheromatous cerebrovascular disease.

In contrast to the high-dose group, patients receiving alfentanil 10 $\mu g\ kg^{-1}$ demonstrated a restoration of mean arterial pressure after intubation to values similar to those obtained before induction. In addition, the increase in rate–pressure product seen in the control group after intubation was obtunded by the smaller dose of alfentanil (fig. 3). Thus alfentanil 10 $\mu g\ kg^{-1}$ has been shown (in this study) to exert a stabilizing effect upon these indices of the haemodynamic response to tracheal intubation.

Catecholamine responses to intubation have not previously been documented in association with the use of vecuronium, but various studies have shown differing plasma concentrations of noradrenaline with suxamethonium (Russell et al., 1981), pancuronium (Derbyshire et al., 1983), alcuronium (Cummings, Russell and Frewin, 1983) and tubocurarine (Cummings et al., 1983). The failure in this study to demonstrate any significant change in plasma noradrenaline concentrations may well result from the fact that, for technical reasons, samples were obtained from only a relatively small number of patients. If vecuronium is associated with smaller changes in noradrenaline concentration in contrast to those observed when pancuronium is used, it may be necessary to study catecholamine concentrations in central venous blood samples, since these could be expected to exhibit a greater change than arterial samples—as it is known that noradrenaline is selectively taken up by the lungs (Ginn and Vane, 1968).

The data relating to plasma adrenaline concentrations agree with the suggestion of Russell and colleagues (1981) that the induction of anaesthesia causes a significant decrease in adrenaline concentration. In the present study the change was more marked in the high-dose alfentanil group in comparison with the low-dose group immediately after intubation. This decrease in adrenaline concentration was sustained for up to 3 min after intubation in both treatment groups, and up to 5 min in the low-dose alfentanil group, a pattern which was not mirrored by the haemodynamic data. However, immediately after intubation, concentrations in the control group returned to preinduction values, in contrast to those for the two treatment groups. This contrasts with earlier work from this Department which demonstrated an increase in plasma noradrenaline concentration with suxamethonium but not with pancuronium, again stressing the variation in catecholamine concentrations seen with various neuromuscular blockers (Derbyshire et al., 1983).

In conclusion, this study has shown that alfentanil 40 $\mu g\ kg^{-1}$ in combination with an anaesthetic technique comprising thiopentone, nitrous oxide and vecuronium, prevented the haemodynamic and catecholamine responses to intubation. However, this dose produced profound hypotension and bradycardia which were resistant to volume replacement and atropine. Alfentanil 40 $\mu g\ kg^{-1}$ cannot, therefore, be recommended for use in patients in whom a cardiostable induction is desirable. However, alfentanil 10 $\mu g\ kg$ produced a more stable cardiovascular system and we would recommend this dose since, in the present investigation, it prevented haemodynamic variables from increasing above their baseline values immediately after intubation, whilst both doses were associated with a reduction in plasma adrenaline concentrations. It should be emphasized, however, that such recommendations relate to patients who have not received atropine but to whom a non-vagolytic neuromuscular blocking drug has been administered.

REFERENCES

Bedford, R. F., and Marshall, W. K. (1984). Cardiovascular responses to endotracheal intubation during four anaesthetic techniques. *Acta Anaesthesiol. Scand.*, **28**, 563.

Black, T. E., Kay, B., and Healy, T. E. J. (1984). Reducing the haemodynamic responses to laryngoscopy and intubation. *Anaesthesia*, **39**, 883.

Cummings, M. F., Russell, W. J., and Frewin, D. B. (1983). Effects of pancuronium and alcuronium on the changes in arterial pressure and plasma catecholamine concentrations during tracheal intubation. *Br. J. Anaesth.*, **55**, 619.

—— —— —— Jonssons, J. R. (1983). The effects of suxamethonium and d-tubocurarine on the pressor and plasma catecholamine responses to tracheal intubation. *Anaesth. Intens. Care*, **11**, 103.

Curran, J., Crowley, M., and O'Sullivan, G. (1980). Droperidol and endotracheal intubation. *Anaesthesia*, **35**, 290.

DeLange, S., Stanley, T. H., Boscoe, M. K., Bruijn, N., Berman, L., Green, O., and Robertson, D. (1983). Catecholamine and cortisol responses to sufentanil O_2 and alfentanil O_2 anaesthesia during coronary artery surgery. *Can. Anaesth. Soc. J.*, **30**, 248.

Derbyshire, D. R., Chmielewski, A., Fell, D., Vater, M., Achola, K., and Smith, G. (1983). Plasma catecholamine responses to tracheal intubation. *Br. J. Anaesth.*, **55**, 855.

Dohi, S., Nishikawa, T., Ukuke, Y., and Mayumi, T. (1982). Circulatory responses to airway stimulation and cervical epidural blockade. *Anesthesiology*, **57**, 359.

Ginn, R., and Vane, J. R. (1968). Disappearance of catecholamines from the circulation. *Nature (Lond.)*, **219**, 740.

Lunn, J. K., Stanley, T. H., Gisele, J., Webster, L., and Woodward, A. (1979). High dose fentanyl anesthesia for coronary artery surgery. Plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. *Anesth. Analg.*, **58**, 390.

McPherson, R. W., Krempasanka, E., Eimeri, D., and Traystman, R. J. (1985). Effects of alfentanil on cerebrovascular reactivity in dogs. *Br. J. Anaesth.*, **57**, 1232.

Martin, D. E., Rosenberg, H., Aukburg, S. J., Bartkowski, R. R., McIver, W. E., Greenhow, D. E., and Lkineberg, P. L. (1982). Low dose fentanyl blunts the circulatory responses to tracheal intubation. *Anesth. Analg.*, **61**, 680.

Moldenhaur, C. C., Griesemer, R. W., Hug, C. C., and Holbrook, G. W. (1983). Haemodynamic changes during rapid induction of anesthesia with alfentanil. *Anesth. Analg.*, **62**, 276.

Prys-Roberts, C., Greene, L. T., Meloche, R., and Foëx, P. (1971). Studies of anaesthesia in relation to hypertension II. Haemodynamic consequences of induction and endotracheal intubation. *Br. J. Anaesth.*, **43**, 531.

Rucquoi, M., and Camie, F. (1983). Cardiovascular responses to large doses of alfentanil and fentanyl. *Br. J. Anaesth.*, **55**, 223S.

Russell, W. J., Morris, R. G., Frewin, D. B., and Drew, S. E. (1981). Changes in plasma catecholamine concentrations during endotracheal intubation. *Br. J. Anaesth.*, **53**, 837.

Spiss, C. K., Coraim, F., Haider, W., and White, P. F. (1984). Haemodynamic effects of fentanyl or alfentanil as adjuvants to etomidate for induction of anaesthesia in cardiac patients. *Acta Anaesthesiol. Scand.*, **28**, 554.

Stoelting, R. K. (1978). Blood pressure and heart rate changes during short duration laryngoscopy for tracheal intubation. Influence of viscous or intravenous lidocaine. *Anesth. Analg.*, **57**, 197.

—— (1979). Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesth. Analg.*, **58**, 116.