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ALFENTANIL OBTUNDS THE CARDIOVASCULAR AND SYMPATHOADRENAL RESPONSES TO SUXAMETHONIUM-FACILITATED LARYNGOSCOPY AND INTUBATION

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SUMMARY

Alfentanil 75 μg kg^{-1} or saline (control group) was given 1 min before induction of anaesthesia in 20 healthy patients premedicated with diazepam 0.14 mg kg^{-1} and pethidine 1 mg kg^{-1}. Anaesthesia was induced with a sleep dose of thiopentone preceded by glycopyrrolate. Suxamethonium 1 mg kg^{-1} was used to facilitate laryngoscopy (which lasted 10 s) and tracheal intubation. Arterial pressure, heart rate and noradrenaline concentration in mixed venous plasma increased significantly after suxamethonium, and increased further after laryngoscopy and intubation in the control group (n = 10). The QT interval of the ECG was prolonged after the administration of suxamethonium, and was prolonged further after laryngoscopy and intubation. All these changes were attenuated in patients pretreated with alfentanil (n = 10), but four patients had chest wall rigidity. Changes in the QT interval correlated directly with the changes in plasma noradrenaline concentration (r = 0.67). Plasma adrenaline concentrations decreased during induction of anaesthesia in both groups.

Tracheal intubation is associated with increases in arterial pressure, heart rate [1, 2] and plasma catecholamine concentrations [1–9], in addition to prolongation of the QT interval of the ECG and cardiac arrhythmias in some patients [10].

Fentanyl 6 μg kg^{-1} has been found to abolish these cardiovascular responses to intubation [11]. Alfentanil also offers protection against the increases in arterial pressure and heart rate which occur during tracheal intubation [8, 12]. Alfentanil 250 μg kg^{-1} has been given to healthy patients without untoward cardiovascular effects [13], whereas alfentanil 40 μg kg^{-1} caused hypotension and bradycardia in a group of patients, some of whom were receiving β-blockers or other antihypertensive drugs [8].

The aim of the present study was to investigate the cardiovascular and sympathoadrenal responses to suxamethonium-facilitated laryngoscopy and intubation, in addition to the relationship between plasma catecholamine concentrations and ECG changes in healthy patients given either alfentanil 75 μg kg^{-1} or saline before induction of anaesthesia.

PATIENTS AND METHODS

Clinical procedure

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients. We studied 20 patients (ASA I) scheduled for elective surgery (table I); patients receiving any drug therapy were excluded from the study.

All patients were premedicated with diazepam 0.14 mg kg^{-1} by mouth and pethidine 1 mg kg^{-1} i.m., and the skin over the basilic vein in the antecubital fossa was covered with local anaesthetic cream (prilocaine–lignocaine cream, EMLA). One hour later, a venous catheter was inserted on the dorsum of the hand and glycopyrrolate 3 μg kg^{-1} was injected i.v. A 70-cm

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TABLE I. *Demographic data (mean values (SD))*

	Control group	Alfentanil group
No. patients	10	10
Sex (M/F)	3/7	3/7
Age (yr)	44 (9)	40 (12)
Weight (kg)	65 (11)	71 (11)

catheter was inserted via the basilic vein on the contralateral arm pretreated with EMLA. The position of the catheter tip was shown to be in the right atrium or ventricle, either by the pressure wave form or by postoperative chest x-ray. An automatic sphygmomanometer (BP-103N Mark III, Nippon Colin Ltd, Tokyo, Japan) was used on the catheterized arm for monitoring of arterial pressure.

The ECG–aVR lead was displayed on an oscilloscope and recorded continuously. The QT intervals were retrospectively measured manually from the onset of the QRS-complex to the end of the T-wave. The mean QT interval of four successive beats was calculated. A heart rate correction ($QT_{corr.}$) was made according to the formula:

$$QT_{corr.} = \frac{QT}{\sqrt{R\text{–}R'}}$$

where the R–R interval is expressed in seconds [14].

The patients were allocated randomly to receive either alfentanil ($n = 10$) or saline ($n = 10$). When the monitoring equipment had been attached, the patient was allowed to rest for 20 min. Cardiovascular recordings were made and the first blood samples obtained. A coded 20-ml syringe containing either alfentanil 75 $\mu g\ kg^{-1}$ in saline or, in the control group, saline only, was injected as a rapid bolus via the peripheral cannula. One minute later, a sleep dose of thiopentone 3–7 $mg\ kg^{-1}$ was injected at a rate of 5 $mg\ s^{-1}$ to obtund the eyelash reflex, followed by suxamethonium 1 $mg\ kg^{-1}$. The patient's lungs were ventilated with 100% oxygen for 1 min with the end-tidal carbon dioxide concentration maintained at 5% throughout the study (Datex, Normocap). Laryngoscopy which lasted 10 s was performed with a MacIntosh laryngoscope and the trachea was intubated. Ventilation of the lungs with 100% oxygen continued for 5 min after tracheal intubation. If needed, supplementary doses of thiopentone 50 mg were added to treat inadequate depth of anaesthesia as indicated by signs such as lachrymation. All patients were anaesthetized by the same anaesthetist (L.L.). The code was not broken until the study was completed.

Blood from the right ventricle of the heart was sampled simultaneously with recording of the QT interval of the ECG and heart rate and the sphygmomanometer was restarted for recording arterial pressures at the following times:

1 = after 20 min rest, before induction of anaesthesia.
2 = after the administration of a sleep dose of thiopentone.
3 = 45 s after the end of injection of suxamethonium.
4 = after 10 s of laryngoscopy.
5 = 10 s after tracheal intubation.
6 = 5 min after intubation.

The blood samples were collected into prechilled polypropylene tubes containing EDTA, and immediately placed on ice. The blood was centrifuged at 0 °C, and the plasma stored in polypropylene tubes at −70 °C until required for analysis.

Plasma concentrations of catecholamines and the catecholamine metabolite 3,4-dihydroxyphenylglycol (DHPG) were measured using HPLC with electrochemical detection [15]. Slight reduction of the mobile phase methanol content allowed the concomitant separation and quantitation of DHPG, together with the amines. The method in its present form has intra-assay coefficients of variation of approximately 2% for noradrenaline, 4% for DHPG and 10% for adrenaline in the physiological concentration ranges.

Statistical analysis was performed using analysis of variance (ANOVA) for repeated measurements, with one between-factor (drug) and one within-factor (time), computed with BMDP2V and BMDP4V programs (BMDP Statistical Software Inc., U.S.A.). When pooled orthogonal components showed non-sphericity, Greenhouse–Geisser probability values were used and further tests, if required, were carried out with contrasts using separate error terms [16]. In other instances, traditional probability values and contrasts with a common error term were applied [17]. Student's paired and unpaired *t*-tests and the Chi-square-test were used, as appropriate.

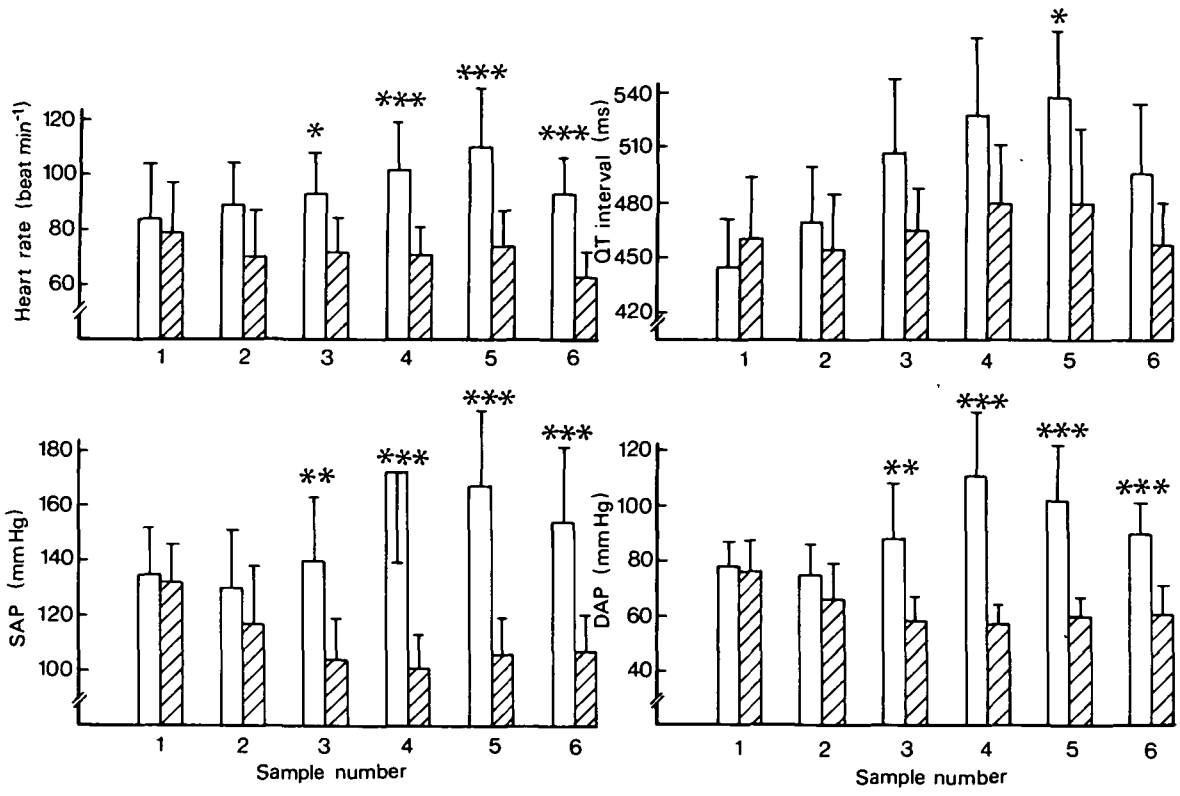

FIG. 1. Cardiovascular responses during induction of anaesthesia. Mean value (SD). □ = Control group; ▨-alfentanil group. 1 = Before anaesthetic; 2 = after thiopentone and alfentanil or saline; 3 = 45 s after injection of suxamethonium; 4 = after 10 s of laryngoscopy; 5 = 10 s after intubation; 6 = 5 min after intubation. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ between groups (Bonferroni corrected P values).

RESULTS

The average sleep dose of thiopentone was 6.5 (SEM 0.3) mg kg^{-1} in the control group, and 4.1 (0.3) mg kg^{-1} in the alfentanil group ($P < 0.001$, t test). In the control group, eight of 10 patients received additional doses of thiopentone (50–150 mg) during the 5-min period after tracheal intubation, while none of the patients in the alfentanil group required more thiopentone. Chest wall rigidity occurred in four patients in the alfentanil group.

In the control group there was a significant prolongation of the QT interval after injection of suxamethonium and an increase in arterial pressure and heart rate. Laryngoscopy and intubation were associated with further increases in heart rate (31 % average increase from baseline), systolic and diastolic arterial pressure (21 % and 42 % increases), and the QT interval of the ECG (21 % increase) (fig. 1; see tables II and III for statistical evaluation). Four of these patients had significant cardiac arrhythmia; at laryngoscopy, ventricular ectopic beats were seen in two patients and multiple ectopics in bigeminy in one patient. A 33-yr-old woman developed ventricular ectopic beats followed by ventricular tachycardia after suxamethonium. The cardiac arrhythmias subsided spontaneously. The pre-anaesthetic mean QT interval for all patients was 450 (9) ms and 440 (5) ms (ns) in those who later developed arrhythmia. The QT interval increased to 537 (18) ms during the period of arrhythmia.

Cardiovascular responses to suxamethonium, laryngoscopy and intubation were abolished almost totally in the patients receiving alfentanil as pretreatment (fig. 1, tables II, III). Injection of alfentanil and a sleep dose of thiopentone was followed by decreases in heart rate (11 %) and

TABLE II. *Analysis of variance with one between- and one within-factor: effects of drug (alfentanil/saline) and time. Because of unequal variances, the following transformations were used: logarithmic (adrenaline), square-root (noradrenaline), reciprocal (arterial pressure)*

		Factor 1: drug	Factor 2: time	Interaction: drug × time
Heart rate	*F*	16.38	6.97	7.53
	P	0.0008	0.0026	0.0017
Systolic arterial pressure	*F*	31.31	3.58	18.42
	P	< 0.0001	0.030	< 0.0001
Diastolic arterial pressure	*F*	38.42	3.98	22.41
	P	< 0.0001	0.013	< 0.0001
QT-interval	*F*	6.33	22.46	8.27
	P	0.022	< 0.0001	< 0.0001
Noradrenaline	*F*	18.24	6.24	8.30
	P	0.0005	0.0016	0.0002
Adrenaline	*F*	7.57	24.28	1.26
	P	0.013	< 0.0001	0.30
DHPG	*F*	1.23	8.15	2.85
	P	0.28	0.0002	0.048

arterial pressure (maximal average decrease of 23% in systolic and 25% in diastolic pressures). The QT interval increased only minimally in the alfentanil group and no ECG abnormalities were observed ($P < 0.02$ compared with control, Chi-square test).

The mean concentration of noradrenaline in mixed venous plasma decreased similarly in both groups after thiopentone. In the control group the average concentrations of noradrenaline increased by 35% after suxamethonium, by a further 46% after laryngoscopy and further still, by 25%, after tracheal intubation (145% total increase) (fig. 2, tables II and III). Plasma concentrations of noradrenaline decreased slightly in the alfentanil group.

The mean preoperative concentration of noradrenaline in patients with cardiac arrhythmia during anaesthetic induction was 0.8 (0.2) nmol litre^{-1} and this increased to 1.6 (0.2) nmol litre^{-1}

TABLE III. *Significance levels (P values) from pairwise statistical tests of differences between the groups at the various time points, and for the different time points v. baseline within the groups (Bonferroni-corrected P values). ns = Not significant (P ≥ 0.05). NA = Noradrenaline; HR = heart rate; SAP, DAP = systolic, diastolic arterial pressures; $QT_{corr.}$ = heart rate correction*

Sample	NA	DHPG	HR	SAP	DAP	$QT_{corr.}$
Control *v.* alfentanil						
1	ns	ns	ns	ns	ns	ns
2	ns	ns	ns	ns	ns	ns
3	< 0.05	ns	< 0.05	< 0.01	< 0.01	ns
4	< 0.001	ns	< 0.001	< 0.001	< 0.001	ns
5	< 0.001	ns	< 0.001	< 0.001	< 0.001	< 0.05
6	< 0.01	ns	< 0.001	< 0.001	< 0.001	ns
Control group						
1 *v.* 2	ns	ns	ns	ns	ns	ns
1 *v.* 3	ns	ns	ns	ns	ns	< 0.001
1 *v.* 4	ns	< 0.001	< 0.05	< 0.001	< 0.001	< 0.001
1 *v.* 5	< 0.05	< 0.001	< 0.01	< 0.001	< 0.001	< 0.001
1 *v.* 6	ns	< 0.05	ns	< 0.05	< 0.01	< 0.001
Alfentanil group						
1 *v.* 2	ns	ns	< 0.05	< 0.01	< 0.01	ns
1 *v.* 3	ns	ns	ns	< 0.001	< 0.001	ns
1 *v.* 4	ns	ns	ns	< 0.001	< 0.001	ns
1 *v.* 5	ns	ns	ns	< 0.001	< 0.001	ns
1 *v.* 6	ns	ns	< 0.05	< 0.001	< 0.001	ns

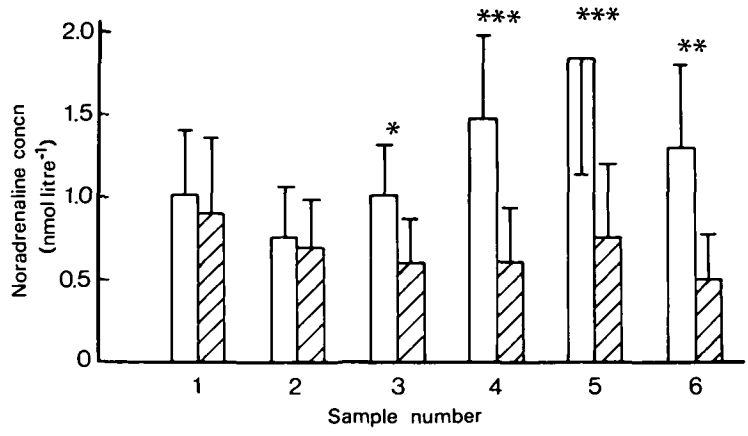

FIG. 2. Concentrations of noradrenaline in plasma from right heart ventricle during anaesthetic induction. Symbols as in figure 1. (For statistics, see tables II and III.)

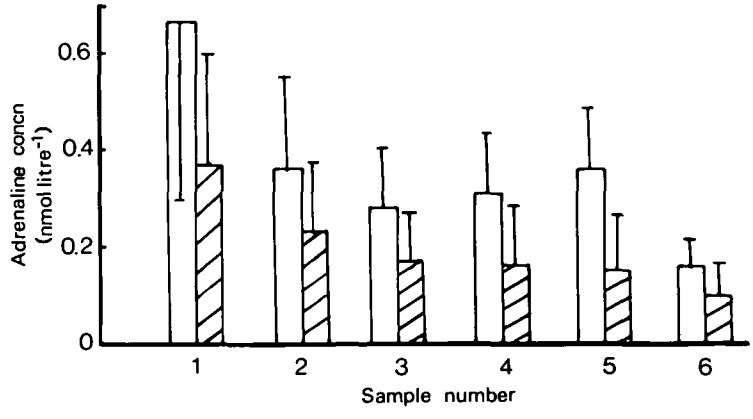

FIG. 3. Concentrations of adrenaline in plasma from right heart ventricle during anaesthetic induction. Symbols as in figure 1. (For statistics see table II.)

during arrhythmia. In all patients the mean preanaesthetic noradrenaline value was 0.95 (0.1) nmol litre^{-1}. The plasma concentrations of noradrenaline were significantly higher in the control group after administration of suxamethonium and thereafter, when compared with the alfentanil group (fig. 2).

The plasma concentration of adrenaline at baseline was greater in the control group than in the group receiving alfentanil, but both groups showed a similar, decreasing trend throughout the study (fig. 3). DHPG in plasma increased significantly (by 25%, on average) in the control group during the procedure, and was unaltered in the alfentanil group (tables II–IV). The changes in the QT interval were directly proportional to the changes in plasma noradrenaline concentrations in the control group during induction (fig. 4). Linear regression analysis gave the equation $y = 52x + 7$ with $r = 0.67$ ($P < 0.001$).

TABLE IV. *Mean (SD) concentrations (nmol litre^{-1}) of DHPG in plasma from right heart ventricle during induction of anaesthesia*

	Sample number					
	1	2	3	4	5	6
Control group	4.91 (0.74)	4.59 (0.93)	5.30 (0.94)	5.63 (0.74)	5.73 (0.89)	5.41 (0.90)
Alfentanil group	4.79 (0.60)	4.80 (0.56)	4.91 (0.88)	5.01 (0.77)	5.13 (0.83)	4.86 0.69)

DISCUSSION

We have found that pretreatment with alfentanil totally obtunded the cardiovascular and catecholamine responses to tracheal intubation in healthy patients. In the control group receiving saline, plasma concentrations of noradrenaline and its metabolite, DHPG, increased after administration of suxamethonium and increased further at laryngoscopy and intubation. Changes in the QT interval on the ECG correlated directly with the changes in plasma concentrations of noradrenaline.

Increases in arterial pressure and heart rate observed in the control group in our study were similar to those reported in numerous earlier studies with patients not receiving an opioid as part of the anaesthetic medication [4, 5, 8, 18]. The incidence of cardiac arrhythmia in association with laryngoscopy was of the same order as that observed elsewhere in healthy patients [10, 19]. Our data are also consistent with the results obtained by Prys-Roberts and others [5] and by Shribman and others [7].

There is evidence that suxamethonium stimulates cardiac sympathetic ganglia [20, 21]. Increases in arterial pressure and heart rate after suxamethonium have been demonstrated previously in normotensive patients [18]. In our control group, the plasma concentrations of noradrenaline and DHPG, and heart rate and arterial pressures tended to increase after administration of suxamethonium. Nigrovic and others [22] found a significant increase in arterial plasma concentration of noradrenaline after suxamethonium. This increase may have been overestimated, as they also used halothane, which decreases the pulmonary uptake of noradrenaline [23] and may also liberate noradrenaline from sympathetic nerves [24]. Catecholamines, especially noradrenaline, are taken up selectively by the lungs to a significant extent [25, 26]. Therefore, we sampled venous blood from the right ventricle of the heart for determination of plasma catecholamine concentrations. Thus even small increases in plasma concentrations of noradrenaline could be detected in the present study as was found also by Derbyshire and others [4], who observed higher concentrations of catecholamines in central venous than in arterial or peripheral venous blood.

Plasma DHPG was measured as an indicator of intraneuronal metabolism of noradrenaline [27], and it followed a temporal pattern similar to that of changes in plasma noradrenaline. Thus in-

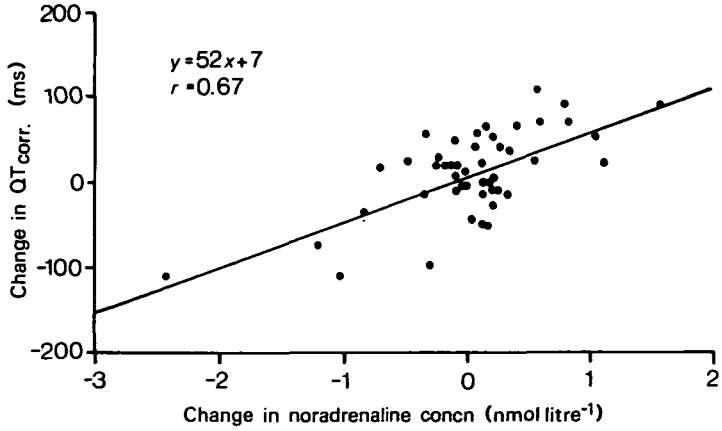

FIG. 4. Relationship between changes in mixed venous plasma noradrenaline concentrations and in the heart rate-correlated QT interval on the ECG in patients not receiving alfentanil during anaesthetic induction. Regression line for 48 points: $y = 52x + 7$; $r = 0.67$ ($P < 0.001$).

creases in plasma DHPG appear to reflect augmented release of noradrenaline from sympathetic nerves. The greater increase in diastolic than in systolic arterial pressure in this study also indicates the predominance of noradrenaline with a pronounced α-mimetic activity. Pretreatment with alfentanil inhibited these cardiovascular and noradrenaline responses related to suxamethonium.

In the present study, the concentration of adrenaline in plasma decreased during induction of anaesthesia, as was documented by Russell and others [3]. In their study, patients were premedicated with morphine and atropine, and in the present study we used diazepam combined with pethidine and glycopyrrolate. Increased concentrations of adrenaline after tracheal intubation have been demonstrated in normotensive [4, 6–8] and hypertensive [5] patients. However, in all the studies showing increases of adrenaline the patients were premedicated without an opioid. Thus it may be suggested that premedication with an opioid, even in low doses, prevents the increase of adrenaline, but not that of plasma noradrenaline, after laryngoscopy and intubation.

In a group of patients, 50% of whom received β-adrenoceptor blockers or other antihypertensive therapy, alfentanil in doses of 10 μg kg^{-1} or 40 μg kg^{-1} was shown to obtund cardiovascular responses to intubation [8], but alfentanil 40 μg kg^{-1} was associated with profound hypotension and bradycardia. In healthy patients, alfentanil 10 μg kg^{-1} was not sufficient to obviate the cardiovascular response to intubation [28]. In contrast, doses of alfentanil 100–250 μg kg^{-1} produced no hypotension or bradycardia in unpremedicated young adults [13]. In the present study, alfentanil 75 μg kg^{-1} and a sleep dose of thiopentone produced a significant although not clinically important decrease in arterial pressure. The hypotension and bradycardia observed after alfentanil [8] may have been a result of the lack of anticholinergic premedication.

Suxamethonium was used in the present study and also in that by McDonnel and others [13]. The lack of hypotension and bradycardia after alfentanil in our study was possibly related to the use of suxamethonium, which has a sympathomimetic activity, as demonstrated in the present study. Our patients also received an anticholinergic, which protected against bradycardia.

We wanted to use a relatively high dose of alfentanil in order to prevent the cardiovascular response to laryngoscopy. Fentanyl 6 μg kg^{-1} blunts this response [11]; the analgesic potency ratio between fentanyl and alfentanil has been stated as 1:3 [29], but also 1:13 [30]. Four of 10 of our patients treated with alfentanil 75 μg kg^{-1} developed chest wall rigidity, which made ventilation of the lungs difficult during induction of anaesthesia. A smaller dose of alfentanil (30 μg kg^{-1}) may be ideal to prevent the sympathoadrenal response to tracheal intubation as reported by Black and others [31].

In our control group, the QT interval was prolonged significantly after the administration of suxamethonium and further after laryngoscopy and intubation, thereby confirming earlier reports [10, 19, 32, 33]. The changes in QT interval correlated directly with the changes in plasma concentration of noradrenaline. There is evidence that the QT interval is prolonged in the presence of high plasma concentrations of catecholamines and that this prolongation is a predictor of cardiac arrhythmia [32]. The QT interval was prolonged during serious ventricular arrhythmia after myocardial infarction [34, 35] and increased concentrations of catecholamines have been observed in patients with myocardial infarction during arrhythmia immediately before cardiac arrest [36]. To our knowledge, there have been no studies in which prolongation of the QT interval and catecholamine concentrations in plasma have been measured simultaneously. The present data show that, in healthy persons, the prolongation of the QT interval closely reflects the increase in plasma concentrations of noradrenaline.

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