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VECURONIUM INDUCED BRADYCARDIA FOLLOWING INDUCTION OF ANAESTHESIA WITH ETOMIDATE OR THIOPENTONE, WITH OR WITHOUT FENTANYL

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SUMMARY

To define the role of vecuronium in the occurrence of bradyarrhythmia, haemodynamic changes after the induction of anaesthesia were studied in 96 patients undergoing coronary artery bypass grafting. Patients were assigned to one of six groups according to different combinations of induction agents (etomidate 0.3 mg kg^{-1} or thiopentone 3 mg kg^{-1}, with fentanyl 0.003 mg kg^{-1}; etomidate 0.4–0.5 mg kg^{-1} or thiopentone 4–6 mg kg^{-1}, without fentanyl) and neuromuscular blocking drugs (vecuronium 0.112 mg kg^{-1}, pancuronium 0.112 mg kg^{-1} or suxamethonium 1 mg kg^{-1}). Anaesthesia was maintained with enflurane and nitrous oxide in oxygen. After initial diverse changes, heart rate decreased in all groups. Thirty minutes after intubation, the reduction of heart rate showed statistically significant differences between the different combinations of drugs: fentanyl–etomidate–vecuronium (group I) (the largest reduction) > etomidate–vecuronium (II) = fentanyl–thiopentone–vecuronium (IV) > thiopentone–vecuronium (V) = fentanyl–thiopentone–suxamethonium (VI) = fentanyl–etomidate–pancuronium (III). Five patients in group I, two in group IV and one each in groups II and V had a heart rate slower than 45 beat min^{-1}, whereas a similar value was never seen in groups III and VI. These results indicate that vecuronium has a bradycardic effect. This effect is more pronounced in association with etomidate than in association with thiopentone, and is augmented by the addition of fentanyl.

Anaesthetic drugs without deleterious cardiovascular effects are considered ideal, and are preferred in patients with poor cardiovascular reserve. Etomidate is gaining popularity in clinical anaesthesia, primarily because it has fewer cardiovascular effects compared with the barbiturates [1]. Vecuronium is often preferred to pancuronium because of its shorter duration of action and, importantly, because of its non-vagolytic effects [2]. Consequently, it has been routine in our clinic to induce anaesthesia in cardiac patients with etomidate preceded by a small dose of fentanyl, and to facilitate tracheal intubation with vecuronium.

Recently, reports have appeared which described asystole or severe bradyarrhythmia in connection with the use of vecuronium, when associated with severe vagal stimulation, or the administration of a large dose of opioid [3–8]. This was attributed to the non-vagolytic action, or the cardiovascularly "clean" effect of vecuronium. In addition, our own experience in cardiac anaesthesia suggests that vecuronium may, occasionally, cause severe bradyarrhythmia, even in association with minimal vagal stimulation, when it is combined with etomidate and a small dose of fentanyl [9]. Furthermore, some investigators have reported an increase in the requirement for atropine when vecuronium is used—even in the absence of vagal stimulation [10, 11].

Thus there are data which suggest that there may be an association between vecuronium and the occurrence of bradyarrhythmia. However, as yet, it has not been defined whether vecuronium is a primary causative agent or whether it acts merely as a cardiovascularly "clean" agent, such that the vagomimetic action of other drugs, or the bradyarrhythmic responses to vagal stimulation, appear unopposed. Furthermore, it is not known

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if, besides a large dose of opioid, a combination of any other agents predisposes to bradyarrhythmia when combined with vecuronium. Therefore, we designed the following study to clarify the role of vecuronium in the occurrence of bradyarrhythmia and the interactions of etomidate, thiopentone and a small dose of fentanyl with vecuronium.

PATIENTS AND METHODS

Once informed consent had been obtained, 96 patients (aged 38–72 yr) scheduled for coronary artery bypass grafting and classified as Montreal Heart Institute class 0 (normal risk [12]; exceptionally class I, if age over 65 yr was the only factor) were allocated to one of six groups according to the different combinations of induction agents (table I). Patients who had myocardial infarction within the last 3 months were excluded from the study. β-Adrenoceptor blocking drugs (acebutolol, atenolol, metoprolol or sotalol) were discontinued 24–72 h before surgery; other medication was continued until the day before the operation. Characteristics of the patients are summarized in table II.

Patients were premedicated with diazepam 10 mg by mouth and morphine sulphate 0.15 mg kg^{-1} i.m. approximately 1 h before the induction of anaesthesia. In the induction room a large-bore i.v. cannula and a radial artery catheter were inserted under local anaesthesia. Direct arterial pressure (Medex Novatrans MX800) and heart rate via ECG were monitored with a digital display (Siemens Sirecust).

Once the patients were observed to be in a stable condition, the induction of anaesthesia was started with a priming dose of vecuronium or pancuronium (except group VI). The priming dose was given to permit intubation sooner after induction, and timed to coincide with the maximum effects of etomidate or thiopentone. Patients in groups I, III and IV received fentanyl 2 min

TABLE I. *Combinations of induction agents and neuromuscular blocking drugs*

Group	Priming	Induction agents		Neuromuscular blocker
I ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	Fentanyl 0.003 mg kg^{-1}	Etomidate 0.3 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
II ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	—	Etomidate 0.4–0.5 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
III ($n = 16$)	Pancuronium 0.012 mg kg^{-1}	Fentanyl 0.003 mg kg^{-1}	Etomidate 0.3 mg kg^{-1}	Pancuronium 0.1 mg kg^{-1}
IV ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	Fentanyl 0.003 mg kg^{-1}	Thiopentone 3 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
V ($n = 16$)	Vecuronium 0.012 mg kg^{-1}	—	Thiopentone 4–6 mg kg^{-1}	Vecuronium 0.1 mg kg^{-1}
VI ($n = 16$)	—	Fentanyl 0.003 mg kg^{-1}	Thiopentone 3 mg kg^{-1}	Suxamethonium 1 mg kg^{-1}

TABLE II. *Characteristics of the patients studied*

	Group I	Group II	Group III	Group IV	Group V	Group VI
Male/female	15/1	14/2	14/2	14/2	16/0	12/4
Age (yr)	62±2.2	54±2.3	58±2.1	60±2.2	58±1.7	59±1.8
Weight (kg)	75±2.2	75±2.7	72±1.7	76±2.1	76±1.7	70±2.3
Number of diseased vessels						
3	8	10	10	11	9	8
2	7	5	6	3	6	8
1	1	1	0	2	1	0
Preoperative medication						
β-blocker	2	3	4	4	3	5
Digitalis	2	0	2	1	2	0

after the priming dose, were preoxygenated and 2 min later received etomidate or thiopentone. Patients in group VI received fentanyl and thiopentone as above, but without the pretreatment with a neuromuscular blocking drug.

In groups II and V, etomidate or thiopentone was administered 4 min after the priming dose. In the groups without pretreatment with fentanyl, the doses of etomidate and thiopentone were increased to attenuate the circulatory reactions to intubation. In this regard, the doses of both induction agents were comparable. Etomidate or thiopentone was injected slowly over 20 s via a rapidly running infusion of lactated-Ringer's solution. Following the injection of the etomidate or thiopentone, vecuronium, pancuronium or suxamethonium was administered. Commencing with the loss of consciousness, the lungs were ventilated via an anaesthetic face mask with 100% oxygen, and up to 3% inspiratory concentration of enflurane at the discretion of the anaesthetist.

Intubation of the trachea was performed 60 s after the injection of suxamethonium or at least 90 s after the injection of vecuronium or pancuronium. Arterial pressure and heart rate were recorded during the control, 2 min after the injection of fentanyl, 1 min after the injection of etomidate or thiopentone, and 2, 5, 10, 20 and 30 min after intubation of the trachea. Anaesthesia was maintained with enflurane and 50% nitrous oxide in oxygen. Various concentrations of enflurane (0.4–3%) were administered according to the value of the arterial pressure (systolic arterial pressure was to be kept between 90 and 130 mm Hg). Ventilation was adjusted to provide an end-expiratory carbon dioxide concentration of about 4.5% measured by a capnograph (Datex Normocap).

Surgery was not started until 30 min after tracheal intubation; that is, there was no surgical stimulation during the observation period. If episodes of hypertension (systolic arterial pressure greater than 180 mm Hg) or tachycardia (more than 120 beat min^{-1}) developed in association with the induction of anaesthesia or the intubation of the trachea, and if additional doses of fentanyl or injections of nitroglycerin were required, the patient was excluded from the study. If the heart rate decreased to less than 45 beat min^{-1}, incremental doses of atropine 0.5 mg were given. In this situation, the heart rate before the injection of atropine (44 beat min^{-1}) was used also for the postinjection period in statistical analysis. If atropine was required before intubation of the trachea, the study was terminated.

The data are presented as mean ± SEM. The comparability of the groups before injections of drugs was assessed by analysis of variance. The statistical significance of the changes within each group was evaluated with the Student's t test for paired samples. The Student's t test for unpaired samples was used to compare the post-injection values between the groups. Differences were considered statistically significant when $P < 0.05$.

RESULTS

The six groups of patients were comparable in respect of age, weight and number of diseased coronary vessels (table II). There were no statistically significant differences in control heart rate or systolic arterial pressure (tables III, IV).

TABLE III. *Heart rate (beat min^{-1}) (mean ± SEM).* n = *16 for each group. ns = Not significant;* *P < *0.05;* **P < *0.01;* ***P < *0.001*

Group	Control	After fentanyl	1 min after induction	Time after intubation (min) 2	5	10	20	30
I	77 ± 3.0	73 ± 4.2 *	63 ± 3.5 ***	65 ± 3.6 ***	60 ± 2.8 ***	54 ± 2.6 ***	51 ± 2.1 ***	50 ± 1.6 ***
II	77 ± 3.2	—	68 ± 1.9 **	75 ± 2.4 ns	69 ± 2.4 *	62 ± 2.1 ***	57 ± 2.0 ***	53 ± 1.6 ***
III	78 ± 4.2	80 ± 4.8 ns	77 ± 3.7 ns	81 ± 4.2 ns	77 ± 4.1 ns	72 ± 3.9 ns	70 ± 3.5 **	67 ± 3.2 **
IV	78 ± 2.9	72 ± 2.8 **	78 ± 2.3 ns	74 ± 2.7 *	67 ± 2.3 ***	59 ± 2.1 ***	58 ± 1.9 ***	56 ± 1.9 ***
V	73 ± 3.6	—	82 ± 3.8 **	81 ± 3.9 **	75 ± 3.4 ns	66 ± 3.1 **	62 ± 2.6 **	58 ± 2.2 ***
VI	74 ± 4.0	72 ± 4.6 ns	79 ± 3.5 ns	75 ± 3.8 ns	66 ± 3.1 **	62 ± 2.6 ***	60 ± 2.4 ***	60 ± 2.2 ***

TABLE IV. *Systolic arterial pressure (mm Hg) (mean ± SEM). n = 16 for each group. ns = Not significant; *P < 0.05; **P < 0.01; ***P < 0.001*

Group	Control	After fentanyl	1 min after induction	Time after intubation (min) 2	5	10	20	30
I	143±4.3	141±4.4 ns	117±3.9 ***	129±3.2 **	128±3.3 **	121±3.7 ***	112±3.2 ***	115±2.7 ***
II	141±3.5	—	123±5.1 ***	124±3.1 ***	127±3.6 **	115±3.1 ***	112±2.0 ***	111±2.7 ***
III	138±5.1	138±4.9 ns	116±4.5 ***	126±4.7 **	124±4.3 *	115±3.1 ***	113±2.5 ***	112±1.9 ***
IV	140±3.3	141±4.8 ns	117±4.6 ***	126±6.2 *	116±3.9 ***	104±3.1 ***	101±2.5 ***	104±2.4 ***
V	142±3.2	—	128±5.2 *	121±3.4 ***	113±3.5 ***	108±2.8 ***	99±1.7 ***	99±3.0 ***
VI	134±2.6	131±3.8 ns	109±9.0 ***	120±4.7 **	110±3.2 ***	101±2.3 ***	99±2.3 ***	104±3.0 ***

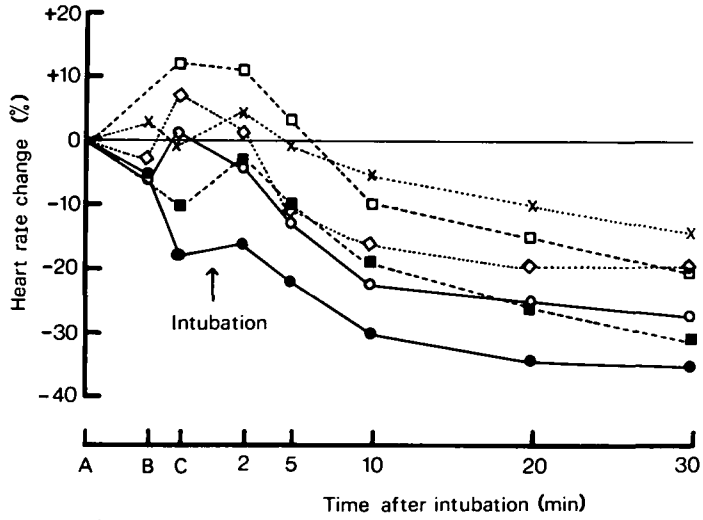

FIG. 1. Time course of heart rate changes in the six groups. Changes are expressed as mean percent reduction from the control (n = 16 for each group). A = Control; B = 2 min after fentanyl; C = 1 min after induction; thereafter, time after intubation. ●——● = Group I; ■---■ = group II; x...x = group III; ○——○ = group IV; □---□ group V; ◇...◇ = group VI.

After initial and varied changes in heart rate caused by the induction of anaesthesia and the subsequent intubation of the trachea, heart rate decreased in all groups, but to different degrees (fig. 1, table III). It is noteworthy that the heart rate was lowest in group I during the entire course of the study. In actual fact, mean heart rate would have been even less if atropine had not been given to these patients. In five out of 16 patients in group I, heart rate decreased to less than 45 beat min^{-1} between 5 and 30 min after intubation, and incremental doses of atropine were injected. In other groups, atropine was given sparingly but two patients in group IV, and one each in groups II and V received atropine 0.5–1.5 mg (mean 0.78 mg). In contrast, no patient in groups III and VI received atropine. We could not find any causal relation between the injection of atropine and preoperative medications. Of the 96 patients studied, 21 were receiving β-adrenoceptor blocker in the preoperative period (discontinued 24–72 h before surgery) and seven were receiving digitalis. Only two out of nine patients who received atropine had been receiving β-blocker and one out of nine was receiving digitalis. The injection of atropine frequently caused a junctional rhythm: in three patients in group I and all patients in groups II and IV, junctional rhythm, which

TABLE V. *Decreases in heart rate at 30 min after tracheal intubation (% reduction from control) and comparison between two groups at a time. ns = Not significant, *P < 0.05; **P < 0.01; ***P < 0.001*

	Group I	Group II	Group IV	Group V	Group VI	Group III
Decrease (%)	35.9±1.7	29.1±2.3	27.4±2.2	20.4±2.4	18.1±2.6	12.4±3.6
Group I	—	*	**	***	***	***
Group II	—	—	ns	*	**	***
Group IV	—	—	—	*	*	**
Group V	—	—	—	—	ns	ns
Group VI	—	—	—	—	—	ns

lasted 5–15 min, developed immediately after the injection.

Although the degree of the change was different, the heart rate in each group reached its lowest value between 20 and 30 min after intubation. Therefore, the differences in the changes of heart rate between the groups were compared 30 min after intubation (table V). Heart rate decreased to different extents in association with the different combinations of drugs: fentanyl–etomidate–vecuronium (group I) (the largest reduction) > etomidate–vecuronium (II) = fentanyl–thiopentone–vecuronium (IV) > thiopentone–vecuronium (V) = fentanyl–thiopentone–suxamethonium (VI) = fentanyl–etomidate–pancuronium (III).

The following comparisons are of particular interest:

(1) The reduction in heart rate in group IV was greater than that in group VI; that is, because suxamethonium only has a brief period of action, vecuronium itself has a bradycardic effect.

(2) The reduction in heart rate in group I was greater than that in group IV. The same applies to groups II and V. This means that bradycardia associated with the use of vecuronium was more pronounced when etomidate, as compared with thiopentone, was used.

This comparison also showed, as expected, that the addition of fentanyl decreased heart rate—as seen in the difference of heart rate responses between groups I and II as well as between groups IV and V. As the large difference in the decrease in heart rate between groups I and III shows, the substitution of pancuronium for vecuronium attenuated greatly the decrease in heart rate.

In contrast to the varied changes in heart rate, changes in systolic arterial pressure were similar in all groups. There were no statistically significant differences between the groups (table IV).

Three patients were excluded from the analysis. Two patients who had relatively high initial heart rates (93 and 98 beat min^{-1}) developed tachycardia and hypertension before intubation after having received thiopentone and vecuronium (group V) and required the administration of fentanyl and nitroglycerin. One patient in group I was given atropine 0.5 mg before intubation because of a decrease in heart rate.

DISCUSSION

The induction of anaesthesia with different combinations of drugs caused different patterns and degrees of change in heart rate, whereas the patterns and degrees of change in arterial pressure were similar.

The combination of etomidate, vecuronium and a small dose of fentanyl led to the slowest heart rate. When thiopentone was substituted for etomidate, or when pancuronium was used instead of vecuronium, the decrease in heart rate was significantly less.

The vagomimetic effects of fentanyl [13] and the vagolytic [14] and sympathomimetic [15, 16] effects of pancuronium are well established. Therefore, the bradycardic effect of fentanyl and the bradycardia-attenuating effect of pancuronium, which we demonstrated here, were not unexpected. In our view the present study demonstrates that vecuronium has a bradycardic effect, and that this effect is more pronounced when vecuronium is administered along with etomidate than when it is given in association with thiopentone.

To reach this conclusion, we compared the patients receiving fentanyl, thiopentone and vecuronium (group IV) with those receiving fentanyl, thiopentone and suxamethonium (group VI), because group VI constitutes a control for group IV as a result of the brief action of suxamethonium. At present we have no explanation for the mechanism of the observed bradycardic effect of vecuronium. Nor are there

experimental data which confirm this observation. Obviously, it would have been of interest to compare the haemodynamic effects of vecuronium and suxamethonium in patients receiving etomidate and fentanyl. However, we chose thiopentone as an induction agent because we had noted previously several cases of severe bradycardia and asystole after a single injection of suxamethonium, when combined with etomidate and a small dose of fentanyl [17]. As a result, we considered the inclusion of this combination to be unjustifiable.

In many of the previous studies in which bradycardia was documented after the injection of vecuronium, a large dose of fentanyl or sufentanil had been used for the maintenance of anaesthesia [10, 18]. Clinically insignificant decreases in heart rate were reported when vecuronium was used along with thiopentone or with thiopentone and a small dose of fentanyl [19, 20]. However, in contrast, no changes in heart rate or in haemodynamic stability have been recorded after the injection of vecuronium with or without the concomitant use of fentanyl [21–25].

In those studies in which there were only minor or no changes in heart rate, the haemodynamic responses were studied for up to between a few minutes and 10 min after the injection of vecuronium. As the development of the changes in heart rate in the present study shows, the decrease in heart rate became evident only at least 10 min after intubation (see the difference in the changes in heart rate between groups IV and VI (fig. 1): significant difference starting at 10 min). Moreover, occasional episodes of asystole or severe bradycardia have been reported to occur about 20 min after the injection of vecuronium [3, 5, 26]. Therefore, it is possible that the bradycardic effect of vecuronium does not always become evident immediately after the injection. More importantly, however, the type of induction agent plays an important role in the differences between the heart rate responses. In the present study, the use of etomidate led to more pronounced bradycardia than the use of thiopentone. On occasions, we observed marked bradycardia or asystole during induction in response to vagal stimulation, and when vecuronium was combined with etomidate and a small dose of fentanyl. This kind of arrhythmia was never observed when thiopentone or methohexitone was used instead of etomidate [9]. Similarly, etomidate does not protect against bradyarrhythmias induced by a second injection of suxamethonium, although thiopentone does [27]. Furthermore, the first injection of suxamethonium caused bradyarrhythmia relatively frequently in adult patients when etomidate and a small dose of fentanyl were used for the induction of anaesthesia [17].

The mechanism for these different responses in heart rate with either etomidate or thiopentone may be explained by the different actions of etomidate and barbiturates on vagal activity. In animal studies, etomidate was shown either to have minimal effects on vagal activity or, on occasions, to enhance it, whereas methohexitone was shown to inhibit vagal activity and cause a tachycardia [28]. Thus barbiturates seem to protect against vagal stimulation, whereas etomidate does not.

Although thiopentone has been used as a sole agent for the induction of anaesthesia in patients with coronary artery disease [29, 30], our experience with thiopentone as a sole agent was not satisfactory. We saw two cases of tachycardia and hypertension before intubation and immediately after the injection of thiopentone. The common feature in both patients was a relatively high heart rate before induction, which might indicate inadequate premedication. Such patients may show a response to thiopentone quite different from that of normal well-sedated patients in whom thiopentone causes a decrease in arterial pressure as a result of its inhibitory action on sympathetic activity [31, 32].

A problem arises with the attempt to treat bradycardia with atropine because, as we found, a junctional rhythm develops fairly often [11]. This finding is not too surprising; in moderate doses (0.4–1.2 mg i.v.), atropine may cause junctional rhythm, A–V dissociation and ventricular arrhythmia [33–35]. In a larger dose (3 mg i.v.), the occurrence of arrhythmia was reported to be rare [36]. It was postulated that atropine inhibits the influence of the vagus on the A–V node before the sinus node [33]. In this situation, the A–V node can escape and establish itself as the pacemaker. Therefore, it can be argued that this imbalance in the effects of atropine may become more marked in a situation in which the heart rate has been decreased markedly by strong vagal stimulation. This may explain the frequent occurrence of junctional rhythm in the present study. Interestingly, when atropine 0.5 mg i.v. is administered at the time of induction, a junctional rhythm follows only rarely and the occurrence of

bradycardia is prevented (unpublished observation).

Enflurane, which was used as a maintenance anaesthetic, is not devoid of chronotropic effects. It may increase or decrease heart rate depending on the initial heart rate [37–39]. If a patient's heart rate while awake is high, heart rate tends to decrease, and *vice versa*. In the present study the induction of anaesthesia caused, after the initial varied changes, a decrease in heart rate in all groups—even in those in which fentanyl was not administered. Anaesthesia probably abolished preanaesthetic excitement and led to the decrease in heart rate. Unfortunately, it was not possible for us to administer the same concentration of enflurane to all patients. However, because different concentrations resulted mainly from the fact that fentanyl was or was not used for induction, comparisons between the groups with fentanyl-pretreatment or between the groups without fentanyl can be considered to be valid even in the presence of enflurane.

β-Adrenoceptor blocking drugs were discontinued 24–72 h before surgery in the present study. However, since the cardiovascular effects of a short-acting β-adrenoceptor blocker, propranolol, have been shown to persist for 72 h after discontinuation [40], one may ask whether the preoperative use of β-adrenoceptor blockers influenced our results. As the number of patients who were receiving β-blockers and required the injection of atropine shows, the preoperative use of β-blocker did not appear to modify the changes in heart rate.

In conclusion, our results indicate that vecuronium has a bradycardic effect, and that this effect is pronounced in combination with etomidate and a small dose of fentanyl. When thiopentone is substituted for etomidate or pancuronium is used instead of vecuronium, the decrease in heart rate is attenuated.

REFERENCES

1. Arndt JO, Zindler M. Effect of intravenous anesthetics on the circulation and its control; in *Hemodynamic Changes in Anesthesia*, Proceedings of the 5th European Congress of Anesthesiology. Paris: Académie Européere D'Anesthésiologie, 1978; **3**: 1069–1095.
2. Lee Son S, Waud BE, Waud DR. A comparison of the neuromuscular blocking and vagolytic effects of Org NC 45 and pancuronium. *Anesthesiology* 1981; **55**: 12–18.
3. Kirkwood I, Duckworth RA. An unusual case of sinus arrest. *British Journal of Anaesthesia* 1983; **55**: 1273.
4. Milligan KR, Beers HT. Vecuronium-associated cardiac arrest. *Anaesthesia* 1985; **40**: 385.
5. May JR. Vecuronium and bradycardia. *Anaesthesia* 1985; **40**: 710.
6. Pollok AJP. Cardiac arrest immediately after vecuronium. *British Journal of Anaesthesia* 1986; **58**: 936–937.
7. Clayton D. Asystole associated with vecuronium. *British Journal of Anaesthesia* 1986; **58**: 937.
8. Starr NJ, Sethna DH, Estafanous FG. Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. *Anesthesiology* 1986; **64**: 521–523.
9. Inoue K, Reichelt W. Combination of fentanyl, etomidate and vecuronium may cause severe vagotonic state. *British Journal of Anaesthesia* 1988; (in press).
10. Salmenperä M, Peltola K, Takkunen O, Heinonen J. Cardiovascular effects of pancuronium and vecuronium during high-dose fentanyl anesthesia. *Anesthesia and Analgesia* 1983; **62**: 1059–1064.
11. Conzanitis DA, Pouttu J, Rosenberg PH. Vecuronium-induced bradycardia. A comparison with pancuronium with and without glycopyrolate premedication. *Anesthesiology* 1986; **65**: A117.
12. Paiement B, Pelletier C, Dyrda I, Maillé JG, Boulanger M, Taillefer J, Sahab P, Delorme M, Dupont E. A simple classification of the risk in cardiac surgery. *Canadian Anaesthetists Society Journal* 1983; **30**: 61–68.
13. Inoue K, Samodelov LF, and Arndt JO. Fentanyl activates a particular population of vagal efferents which are cardioinhibitory. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1980; **312**: 57–61.
14. Lee Son S, Waud DR. Effects of non-depolarizing neuromuscular blocking agents on the cardiac vagus nerve in the guineapig. *British Journal of Anaesthesia* 1980; **52**: 981–987.
15. Domenech JS, Garcia RC, Sasiain JMR, Loyola AO, Oroz JS. Pancuronium bromide: An indirect sympathomimetic agent. *British Journal of Anaesthesia* 1976; **48**: 1143–1148.
16. Salt PJ, Barnes PK, Conway CM. Inhibition of neuronal uptake of noradrenaline in the isolated perfused rat heart by pancuronium and its homologues, Org 6368, Org 7268 and NC 45. *British Journal of Anaesthesia* 1980; **52**: 313–317.
17. Inoue K, Reichelt W. Asystole and bradycardia in adult patients after a single dose of suxamethonium. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 571–573.
18. Gravlee GP, Ramsey FM, Roy RC, Angert KC, Rogers AT, McConville JF, Royster RL, Pauca AL, Thomas K. Pancuronium is hemodynamically superior to vecuronium for narcotic/relaxant induction. *Anesthesiology* 1986; **65**: A46.
19. Barnes, PK, Smith GB, White WD, Tennant R. Comparison of the effects of Org NC 45 and pancuronium bromide on heart rate and arterial pressure in anaesthetized man. *British Journal of Anaesthesia* 1982; **54**: 435–439.
20. Robertson EN. Booij LHDJ, Fragen RJ, Crul JF. Clinical comparison of atracurium and vecuronium. *British Journal of Anaesthesia* 1983; **55**: 125–129.
21. Gregoretti SM, Sohn YS, Sia RL. Heart rate and blood pressure changes after Org NC 45 (vecuronium) and pancuronium during halothane and enflurane anesthesia. *Anesthesiology* 1982; **56**: 392–395.
22. Morris RB, Canalan MK, Miller RD, Wilkinson PL,

Quasha AL, Robinson SL. The cardiovascular effects of vecuronium (Org NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; **58**: 438–440.
23. Starr NJ, Sethna DH, Samonte AF, Estafanous FG. Hemodynamic comparison of non-depolarizing muscle relaxants: a randomized prospective study. *Anesthesia and Analgesia* 1985; **64**: 287.
24. Baraka A, Ghaya L. Hemodynamic effects of vecuronium in patients with coronary artery disease. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 28–29.
25. Gallo JA, Cork RC, Kobayashi H, Puchi P. Hemodynamic effects of atracurium versus vecuronium in cardiac surgical patients. *Anesthesia and Analgesia* 1986; **65**: S54.
26. Mirakhur RK, Ferres CJ, Clarke RSJ, Bali IM, Dundee JW. Clinical evaluation of Org NC 45. *British Journal of Anaesthesia* 1983; **55**: 119–124.
27. Sears DH, Abdul-Rasool IH, Katz RL. Succinylcholine-induced arrhythmias following anesthetic induction with etomidate and midazolam. *Anesthesiology* 1986; **65**: A120.
28. Inoue K, Arndt JO. Efferent vagal discharge and heart rate in response to methohexitone, Althesin, ketamine and etomidate in cats. *British Journal of Anaesthesia* 1982; **54**: 1105–1116.
29. Tarnow J, Hess W, Klein W. Etomidate, Alfathesin, and thiopentone as induction agents for coronary artery surgery. *Canadian Anaesthetists Society Journal* 1980; **27**: 338–344.
30. Lunn JJ, Raimundo HS. Anesthetic management of the patient undergoing coronary artery bypass grafting. In: Tarhan S, ed. *Anesthesia and Coronary Artery Surgery* 1st edn. Chicago: Year Book Medical Publishers, 1986; 134–161.
31. Millar, RA, Warden J, Cooperman LH, Price HL. Further studies of sympathetic actions of anaesthetics in intacts and spinal animals. *British Journal of Anaesthesia* 1970; **42**: 366–378.
32. Skovsted P, Price MI, Price HL. The effects of short-acting barbiturates on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. *Anesthesiology* 1970; **33**: 10–18.
33. Averill KH. Less commonly recognized actions of atropine on cardiac rhythm. *American Journal of Medical Sciences* 1959; **237**: 304–318.
34. Gravenstein JS, Ariet M, Thornby JI. Atropine on the electrocardiogram. *Clinical Pharmacology and Therapeutics* 1969; **10**: 660–666.
35. Valentin N, Lomholt BS, Andersen GW. Atropine before enflurane anaesthesia: Effects of cardiac rhythm, pulse rate, blood pressure and airway secretion. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 156–161.
36. Carrow DJ, Aldrete JA, Masden RR, Jackson D. Effects of large doses of intravenous atropine on heart rate and arterial pressure of anesthetized patients. *Anesthesia and Analgesia* 1975; **54**: 262–266.
37. Dobkin AB, Heinrick RG, Israel JS, Levy AA, Neville JF jr, Ounkasem K. Clinical and laboratory evaluation of new inhalation agent: compound 347 (CHF_2-O-CF_2-CHFCl). *Anesthesiology* 1968; **29**: 275–287.
38. Calverley RK, Smith NT, Prys-Roberts C, Eger EI II, Jones CW. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. *Anesthesia and Analgesia* 1978; **57**: 619–628.
39. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. *Anesthesiology* 1981; **54**: 390–398.
40. Bruncin T, Edhag O, Lundman T. Effects remaining after withdrawal of long-term beta-receptor blockade. *British Heart Journal* 1976; **38**: 1065–1072.