Haemodynamic responses to tracheal intubation following etomidate and fentanyl for anaesthetic induction

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The haemodynamic response to anaesthetic induction and tracheal intubation was studied in 29 patients undergoing elective myocardial revascularization surgery. All patients included in the study were anaesthetized with etomidate, 0.3 mg · kg^{-1}. The patients were randomized to three groups: Group I received fentanyl, 2.5 μg · kg^{-1}; Group II received fentanyl, 5 μg · kg^{-1}; and Group III received fentanyl, 10 μg · kg^{-1}. Haemodynamic variables were measured at baseline (awake), after anaesthetic induction, and at one, three, five, and ten minutes after tracheal intubation. The number of patients with haemodynamic responses to intubation (>20% increase in heart rate or mean arterial pressure) was greater (P < 0.05) in Group I than in Groups II and III. Statistically significant, but clinically minor, decreases in mean arterial pressure and cardiac output occurred in all groups at the last three study times. The frequency of involuntary muscle movements was 14%, and all of these events occurred in patients in Group I. In conclusion, the authors recommend using fentanyl, 5–10 μg · kg^{-1} to blunt the haemodynamic response to tracheal intubation following anaesthetic induction with etomidate, 0.3 mg · kg^{-1}.

Chez 29 patients programmés pour une revascularisation chirurgicale du myocarde, on évalue la réponse hémodynamique provoquée par l'induction de l'anesthésie et de l'intubation endotrachéale. Tous les patients inclus dans l'étude sont anesthésiés à l'étomidate 0,3 m · kg^{-1}. Par randomisation, on les distribue dans un des trois groupes suivants : le groupe I reçoit du fentanyl 2,5 μg · kg^{-1}; le groupe II, 5 μg · kg^{-1}; le groupe III, fentanyl 10 μg · kg^{-1}. Les variables hémo-dynamiques de départ sont mesurées à l'état de veille, après l'induction de l'anesthésie, à une, trois, cinq et dix minutes après l'intubation endotrachéale. Le nombre de patients qui ont montré une réponse hémodynamique à l'intubation définie comme une augmentation de 20% de la fréquence cardiaque ou de la tension artérielle moyenne, est plus élevé dans le groupe I que dans les groupes II et III. Une diminution statistiquement significative mais cliniquement sans importance de la pression artérielle moyenne et du débit cardiaque survient dans les trois groupes aux trois derniers moments d'étude. La fréquence des mouvements musculaires involontaires est de 14% et tous ces épisodes surviennent chez les patients du groupe I. En conclusion, les auteurs recommandent l'utilisation de 5 à 10 μg · kg^{-1} pour atténuer la réponse hémodynamique à l'intuba-tion endotrachéal avec l'induction à l'étomidate 0,3 mg · kg^{-1}.

Key words
ANAESTHETICS, INTRAVENOUS: etomidate, fentanyl; INTUBATION, TRACHEAL: complications.

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Etomidate (Abbott Pharm, Abbott Park, IL) is an imidazole-derivative intravenous anaesthetic induction agent remarkable for its minimal cardiovascular effects and rapid onset of action.[1,2] It has, however, been associated with tachycardic and hypertensive responses to tracheal intubation.[3] These haemodynamic changes may have adverse effects on the myocardial oxygen supply versus demand ratio and may result in higher incidences of perioperative ischaemia.[4] Fentanyl is a highly lipophilic opioid often used during anaesthetic induction to attenuate the response to laryngoscopy and tracheal intubation.[5–7] The ideal dose of fentanyl for the prevention of the haemodynamic response to laryngoscopy and intubation following etomidate anaesthetic induction has not yet been determined. The administration of these drugs for induction of general anaesthesia would provide rapid achievement of conditions suitable for endotracheal intubation with minimal haemodynamic response if given in appropriate doses. A population of patients presenting for

elective myocardial revascularization was studied in order to identify how this group would respond, as these patients are in a high-risk group and are often on medications that modify cardiovascular responses.

Methods

The study protocol was approved by the Institutional Review Board and written informed consent was obtained from each patient. Thirty adult patients scheduled for elective myocardial revascularization were included in the study. Patients with left ventricular dysfunction (left ventricular ejection fraction <40%), atrial fibrillation, valvular heart disease, uncontrolled hypertension (diastolic BP > 100 mmHg), or pulmonary disease, were excluded from the study. Cardiac medications, including beta-adrenergic blockers, calcium channel blockers, and nitrates, were continued until the morning of surgery. Preanaesthetic medication consisted of morphine sulphate, 0.1 $mg \cdot kg^{-1}$, and scopolamine, 5 $\mu g \cdot kg^{-1}$ *im*, one hour before arrival in the operating suite. Monitoring included ECG leads II and V_5, and digital pulse oximetry (SpO_2). Radial arterial and rapid-response thermistor pulmonary arterial catheters were placed using local anaesthesia. After placement of the catheters, five minutes elapsed before the beginning of the study.

Assignment to three experimental groups was done using a table of random numbers. Group I received etomidate, 0.3 $mg \cdot kg^{-1}$, and fentanyl, 2.5 $\mu g \cdot kg^{-1}$ for anaesthetic induction. Group II received etomidate, 0.3 $mg \cdot kg^{-1}$ and fentanyl, 5 $\mu g \cdot kg^{-1}$. Group III received etomidate, 0.3 $mg \cdot kg^{-1}$, and fentanyl, 10 $\mu g \cdot kg^{-1}$. The study was conducted in double-blind fashion, and the fentanyl dose was diluted with bacteriostatic water so that equal volumes were administered to patients in all three groups.

Awake baseline (T_0) haemodynamic values were obtained while the patients were breathing 100% oxygen via a semi-closed circle anaesthesia circuit. All medications were given through a central venous catheter. A priming dose of vecuronium, 0.015 $mg \cdot kg^{-1}$, was administered during the completion of baseline haemodynamic measurements. The fentanyl dose was administered over 30 sec, followed immediately by the etomidate dose over 30 sec. Vecuronium, 0.085 $mg \cdot kg^{-1}$, was administered immediately after loss of consciousness. The lungs were manually ventilated with 100% oxygen prior to tracheal intubation. Asleep baseline (T_1) haemodynamic values were obtained starting one minute after the vecuronium dose. Tracheal intubation was performed two minutes after completion of the vecuronium dose. After proper endotracheal tube placement was confirmed, the lungs were ventilated mechanically with 100% oxygen and a tidal volume of 10 $ml \cdot kg^{-1}$. The ventilatory rate was adjusted to maintain $P_{ET}CO_2$ of 30–35 mmHg using a capnometer. Patients were left unstimulated for the duration of the study period (i.e., ten minutes after intubation).

Haemodynamic variables including heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), cardiac output (CO), right ventricular ejection fraction (RVEF), right ventricular end-systolic volume (RVESV), right ventricular end-diastolic volume (RVEDV) and stroke volume (SV) were measured at six different times:

T_0 – Awake baseline, prior to anaesthetic induction with the patient breathing 100% oxygen via face mask.
T_1 – One minute after anaesthetic induction, during manual ventilation, prior to tracheal intubation.
T_2 – One minute after tracheal intubation (three minutes after induction).
T_3 – Three minutes after tracheal intubation.
T_4 – Five minutes after tracheal intubation.
T_5 – Ten minutes after tracheal intubation.

Electrocardiographic and pressure tracings were recorded continously on a multi-channel recorder for subsequent analysis. All measurements were made at end-expiration. Before the inital set of measurements was made, the zero reference point of the transducers was positioned at the level of the right atrium, 5 cm posterior to the sternal angle of Louis. Intravenous fluid infusions were not started until arrival in the operating room, and were restricted to less than 500 ml of a crystalloid solution prior to anaesthetic induction.

Thermodilution data were collected using a Baxter Edwards rapid-response thermistor pulmonary arterial catheter and an American Edwards REF-1® Cardiac Output Computer (Baxter Healthcare Corp., Irvine, CA).[8] Ten ml boluses of iced 5% dextrose solution were injected until three cardiac output values within 10% of each other were obtained. (A maximum of five bolus injections was possible within a two-minute interval.) Cardiac output and RVEF were both measured from each thermodilution curve. Three CO and RVEF values were averaged for each study interval, and SV, RVESV, and RVEDV were calculated by the cardiac output computer.

Hypertension and tachycardia were defined as increases of greater than 20% from the awake baseline values. Tachycardic or hypertensive episodes were treated with esmolol, 0.5 $mg \cdot kg^{-1}$. Following the study period, the patients in all groups received an additional 50 $\mu g \cdot kg^{-1}$ of fentanyl prior to skin incision.

Contingency data were analyzed using Fisher's exact test. Repeated-measures ANOVA and Scheffe's multiple contrasts were used to evaluate changes occurring within groups. A P of less than 0.05 was considered statistically significant. All analyses were two-tailed.

Results

Twenty-nine of 30 patients that were entered in the study went on to complete the protocol. One patient was excluded because of difficult tracheal intubation, with prolonged and repeated attempts to visualize the patient's larynx. Of the remaining 29 patients, there were nine in Group I, eight in Group II, and 12 in Group III. The groups were comparable with regard to demographic data, preoperative myocardial function, and chronic medications taken. Our sample size may have been too small to identify differences in patients taking beta blockers or calcium channel blockers. Demographic data are summarized in Table I.

The number of patients that required treatment for hypertension and/or tachycardia was 5 of 9 in Group 1, 0 of 8 in Group II, and 2 of 12 in Group III. Treatment with esmolol was required with greater frequency in Group I ($P < 0.05$) than in Groups II and III combined (Table II). In each patient that required esmolol, it was needed within one minute after intubation (between T_1 and T_2). Each of these patients responded promptly, and did not require further treatment for hypertension or tachycardia.There was no electrocardiographic evidence of myocardial ischaemia during the study.

The haemodynamic changes are summarized in Table III. In Group I, CO decreased at T_1, and again at times T_3–T_5. A decrease in MAP was also present at T_5. In Group II, CO was decreased at T_1 and T_5, MAP was decreased at T_1, and T_3–T_5, PCWP was decreased at T_1–T_3, and MPAP was decreased at T_4 and T_5. In Group III, CO decreased at T_1–T_5, MAP was decreased at T_1, and T_3–T_5, HR was decreased at T_4 and T_5, and there was an isolated increase in RAP at T_4. None of the study patients complained of pain during administration of etomidate. Four patients in Group I, and none in either of the other two groups exhibited involuntary muscle movements after the administration of etomidate. This did not represent a difference among the groups. No patient suffered any adverse sequelae attributable to the study.

TABLE I Demographic data ($n = 29$)

	Group I ($n = 9$)	*Group II* ($n = 8$)	*Group III* ($n = 12$)
Age (mean ± SD)	67.6 ± 8.7	69.5 ± 6.2	63.5 ± 8.3
Sex ratio	7M:2F	7M:1F	11M:1F
Nitrates	78%	88%	67%
Beta-blockers	33%	22%	56%
Calcium entry blockers	78%	75%	58%
Anti-hypertensives	22%	0	25%

There were no significant differences among the groups.

TABLE II Incidence of hypertension/tachycardia following tracheal intubation (number of patients)

	Fentanyl		
	Group I 2.5 $\mu g \cdot kg^{-1}$	*Groups II and III* 5 or 10 $\mu g \cdot kg^{-1}$	*Total*
Hypertensive tachycardic	5	2	7
No haemodynamic response	4	18	22
Total	9	20	29

$P < 0.05$.

Discussion

Etomidate is a rapid-acting nonbarbiturate hypnotic agent. Initially, there was reluctance to use etomidate because of the adrenocortical suppression caused by continuous infusions.[9] However, subsequent work has shown that a single bolus dose of etomidate does not cause clinically important suppression of adrenocortical function,[10] although there is some controversy on this.[11,12] Etomidate has been shown to be devoid of adverse cardiovascular effects when used as an induction agent in patients with preexisting cardiovascular disease.[3] However, it does not blunt the haemodynamic response to laryngoscopy and tracheal intubation reliably and, therefore, is not ideal as a sole agent for anaesthetic induction in patients with cardiovascular disease.[14] Brief episodes of hypertension and/or tachycardia may not contribute to adverse outcomes but prolongation of these episodes most probably would.

Rapid sequence induction of general anaesthesia may precipitate undesirable haemodynamic effects. Unfortunately, there is no sole anaesthetic agent that provides haemodynamic stability during rapid sequence induction and tracheal intubation. Rapid injection of high doses of opioids is associated with chest wall rigidity.[13] Barbiturates[14] and propofol[15] are associated with dose-related myocardial depression and hypotension, and ketamine[16] is associated with tachycardia and hypertension. The use of the etomidate/fentanyl combination may provide haemodynamic stability during both induction of anaesthesia and tracheal intubation. The aim of the current study was to determine the lowest dose of fentanyl that would blunt undesirable haemodynamic responses to laryngoscopy and tracheal intubation following anaesthetic induction with etomidate.

In the present study, 29 patients presenting for coronary artery revascularization received etomidate 0.3 $mg \cdot kg^{-1}$ and were randomized to receive fentanyl in one of three doses. The patients who received fentanyl, 2.5 $\mu g \cdot kg^{-1}$ (Group I), required treatment for tachycardia and/or hypertension significantly more often than patients who received fentanyl, 5 or 10 $\mu g \cdot kg^{-1}$. Despite the high

TABLE III Haemodynamic response to etomidate/fentanyl anaesthetic induction (means ± SD)

	T_0	T_1	T_2	T_3	T_4	T_5
Group I						
HR (bpm)	62 ± 10	57 ± 11	74 ± 18	56 ± 12	57 ± 10	51 ± 8
MAP (mmHg)	103 ± 17	89 ± 15	104 ± 22	91 ± 18	86 ± 20	83 ± 17*
MPAP (mmHg)	21 ± 4	21 ± 4	26 ± 10	23 ± 11	21 ± 10	19 ± 7
PCWP (mmHg)	15 ± 4	13 ± 3	11 ± 6	11 ± 6	14 ± 7	15 ± 7
RAP (mmHg)	8 ± 3	9 ± 3	11 ± 5	10 ± 4	10 ± 3	9 ± 4
CO ($L \cdot min^{-1}$)	4.8 ± 1.3	4.1 ± 0.9†	4.5 ± 1.1	4.1 ± 1.1*	3.9 ± 1.1†	3.7 ± 1.0†
RVEF	0.51 ± 0.08	0.48 ± 0.09	0.48 ± 0.10	0.45 ± 0.10	0.48 ± 0.09	0.47 ± 0.09
RVEDV (ml)	161 ± 28	152 ± 30	156 ± 40	161 ± 52	156 ± 37	150 ± 30
RVESV (ml)	79 ± 20	79 ± 21	80 ± 22	89 ± 39	81 ± 23	79 ± 25
SV (ml)	82 ± 16	74 ± 19	77 ± 25	72 ± 22	75 ± 23	70 ± 17
SVR ($d \cdot s \cdot cm^{-5}$)	1695 ± 600	1633 ± 386	1740 ± 532	1699 ± 591	1648 ± 550	1674 ± 406
PVR ($d \cdot s \cdot cm^{-5}$)	114 ± 61	161 ± 92	189 ± 110	145 ± 89	143 ± 94	108 ± 54
Group II						
HR (bpm)	57 ± 12	50 ± 13	55 ± 14	51 ± 10	51 ± 9	48 ± 8
MAP (mmHg)	103 ± 18	76 ± 14†	91 ± 24	85 ± 19*	83 ± 23*	81 ± 14†
MPAP (mmHg)	21 ± 7	19 ± 5	20 ± 7	18 ± 6	18 ± 5*	17 ± 4†
PCWP (mmHg)	14 ± 7	11 ± 6†	11 ± 5†	11 ± 5†	12 ± 6	12 ± 6
RAP (mmHg)	9 ± 3	12 ± 5*	10 ± 5	10 ± 4	10 ± 4	10 ± 5
CO ($L \cdot min^{-1}$)	4.6 ± 1.1	3.8 ± 1.0*	4.4 ± 1.4	4.1 ± 1.2	3.8 ± 0.8	3.5 ± 0.7†
RVEF	0.46 ± 0.08	0.47 ± 0.08	0.50 ± 0.08	0.49 ± 0.08	0.50 ± 0.06	0.48 ± 0.08
RVEDV (ml)	184 ± 39	168 ± 47	154 ± 35	164 ± 29	149 ± 15	155 ± 22
RVESV (ml)	101 ± 29	91 ± 36	80 ± 29	86 ± 24	75 ± 15	82 ± 22
SV (ml)	81 ± 17	77 ± 15	75 ± 13	78 ± 9	73 ± 8	73 ± 6
SVR ($d \cdot s \cdot cm^{-5}$)	1690 ± 393	1448 ± 493	1558 ± 652	1545 ± 568	1554 ± 535	1655 ± 384
PVR ($d \cdot s \cdot cm^{-5}$)	92 ± 40	138 ± 68	119 ± 55	109 ± 48	82 ± 33	88 ± 25
Group III						
HR (bpm)	63 ± 18	56 ± 15	69 ± 19	59 ± 12	54 ± 14†	53 ± 15†
MAP (mmHg)	98 ± 10	76 ± 10†	93 ± 20	81 ± 15†	80 ± 16†	81 ± 16†
MPAP (mmHg)	21 ± 5	19 ± 4	22 ± 10	20 ± 7	19 ± 7	19 ± 5
PCWP (mmHg)	15 ± 4	13 ± 3	14 ± 5	14 ± 7	15 ± 7	13 ± 2
RAP (mmHg)	8 ± 2	11 ± 2	10 ± 3	10 ± 3	12 ± 7†	10 ± 3
CO ($L \cdot min^{-1}$)	5.3 ± 1.5	4.4 ± 1.5†	4.4 ± 1.5†	4.3 ± 1.3†	3.9 ± 1.3†	4.1 ± 1.3†
RVEF	0.52 ± 0.09	0.52 ± 0.07	0.53 ± 0.11	0.52 ± 0.09	0.50 ± 0.07	0.50 ± 0.09
RVEDV (ml)	151 ± 45	141 ± 41	133 ± 43	138 ± 38	137 ± 42	151 ± 49
RVESV (ml)	72 ± 25	70 ± 25	64 ± 29	68 ± 24	68 ± 24	76 ± 31
SV (ml)	78 ± 22	71 ± 20	68 ± 21	70 ± 20	69 ± 21	75 ± 22
SVR ($d \cdot s \cdot cm^{-5}$)	1526 ± 764	1332 ± 602	1687 ± 817	1434 ± 593	1549 ± 662	1511 ± 618
PVR ($d \cdot s \cdot cm^{-5}$)	114 ± 85	115 ± 62	146 ± 98	122 ± 53	100 ± 59	106 ± 38

*$P < 0.05$ compared with T_0. †$P < 0.01$ compared with T_0 (within-group comparisons).
(HR = heart rate, MAP = mean arterial pressure, MPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, RAP = right atrial pressure, CO = cardiac output, RVEF = right ventricular ejection fraction, RVEDV = right ventricular end diastolic volume, RVESV = right ventricular end systolic volume, SV = stroke volume, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance.)

incidence of tachycardia and/or hypertension (five of nine patients) in Group I during tracheal intubation, the statistical analysis did not detect any increases in haemodynamic variables. This was because the patients were treated as soon as the HR or MAP increased to greater than 20% above baseline values. In each case, effective treatment had been instituted before the first post-intubation study measurement time.

There were decreases in MAP and CO in all three treatment groups ten minutes after tracheal intubation. These findings are consistent with the unstimulated, anaesthetized state and were not clinically significant. The changes in PCWP (T_1–T_3) and MPAP (T_4–T_5) in Group II, and in HR (T_4–T_5) and RAP (T_4) in Group III were not clinically important. All of these values remained within acceptable limits in individual patients and did not require therapeutic intervention. Our results likely would have been altered by the adminstration of other drugs as premedications and therefore we do not recommend extrapolation of our data to patients given other premedications.

Two unpleasant side affects of etomidate are pain during injection and involuntary muscle movements.[17,18] We administered all drugs via a central venous line, and did not encounter any patient discomfort. The frequency of involuntary muscle movements was 14%. The reported frequency of involuntary muscle movements with etomidate as the sole induction agent is 15–53%.[17,19] Pretreatment with an opioid reportedly decreases this frequency,[20] which is consistent with our findings. None of the patients in groups II or III experienced involuntary muscle movements.

In previous studies, there have been variable and conflicting results with the use of etomidate and fentanyl combinations to prevent the haemodynamic changes that accompany tracheal intubation. In one study, fentanyl, 100 μg, was administered during anaesthetic induction with etomidate, 0.4 $mg \cdot kg^{-1}$.[21] The patients in that study had increases in heart rate and blood pressure after tracheal intubation. This study differs from the present one in that the patients were healthy (ASA physical status I or II), atropine was used as preanaesthetic medication, and that succinylcholine was used to facilitate tracheal intubation. In another study, patients were given fentanyl, 100–150 μg, during anaesthetic induction with etomidate, 0.3 $mg \cdot kg^{-1}$.[22] In those patients, anaesthetic induction and tracheal intubation did not alter haemodynamic values. However, the emergency coronary angioplasty patients in that study had all received lidocaine (225 mg *iv* bolus followed by 2 $mg \cdot min^{-1}$) which probably further blunted the haemodynamic response to intubation.

The present study differed from that of Inoue *et al.*, who found decreases in heart rate when etomidate, 0.3 $mg \cdot kg^{-1}$, and vecuronium (with or without fentanyl, 3 $\mu g \cdot kg^{-1}$), were used for anaesthetic induction.[23] In their series, five out of 30 patients receiving this combination of drugs required atropine treatment for heart rates below 45 beats per minute. The bradycardic responses may have been due to the timing of drug administration. They waited two minutes after the administration of fentanyl before injecting the etomidate and vecuronium, whereas, in the current study, the drugs were all injected within 60 sec. In addition, their study sample may have had a higher incidence of sinus node dysfunction.

Karliczek *et al.*, studied the effect of two doses of fentanyl in combination with etomidate infusions.[19] They found tachycardia and hypertension following 3 $\mu g \cdot kg^{-1}$ of fentanyl. However, the 6 $\mu g \cdot kg^{-1}$ dose of fentanyl was associated with hypotension. Their results do not agree with those of the current study, but this may have been due to higher etomidate levels achieved by constant infusions of etomidate.

The present study does have several limitations. Firstly, collecting three consistent sets of haemodynamic variables using the right ventricular ejection fraction pulmonary artery catheter took approximately 90 sec to complete. Thus, any transient changes in CO, SV, or SVR may have been missed. Secondly, our patients were let untouched for ten minutes after intubation. We did not allow any stimulation because we were attempting to measure the haemodynamic response to tracheal intubation alone. Thirdly, the patients in the study were premedicated with morphine and scopolamine. The heavy preanaesthetic medication could have influenced the haemodynamic responses. The last two issues make it more difficult to extrapolate these data to patients with coronary artery disease presenting for surgical procedures of shorter duration.

In conclusion, none of the previous studies[17–20,23] established a dose-response relationship between boluses of etomidate and fentanyl, and none of these investigators administered the agents in a way that would be appropriate for a rapid-sequence induction. The purpose of the current investigation was to establish the doses of etomidate and fentanyl that would provide haemodynamic stability during anaesthetic induction and tracheal intubation. The authors recommend that fentanyl, 5–10 $\mu g \cdot kg^{-1}$, be administered 60 sec before anaesthetic induction with etomidate, 0.3 $mg \cdot kg^{-1}$, when tachycardia and hypertension are undesirable. Further investigations are needed to confirm that these doses of etomidate and fentanyl provide haemodynamic stability during rapid-sequence inductions, and in patients with ventricular dysfunction.

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