Haemodynamic consequences of etomidate administration in elective cardiac surgery: a randomized double-blinded study

J. Morel1*, M. Salard1, C. Castelain1, M. C. Bayon1, P. Lambert1, M. Vola2, C. Auboyer1 and S. Molliex1

1 Département d’anesthésie réanimation and 2 Département de chirurgie cardio-vasculaire, Centre Hospitalier Universitaire de Saint Etienne, F-42055 Saint Etienne, France

* Corresponding author. E-mail: jerome.morel@chu-st-etienne.fr

Editor’s key points

- Etomidate causes suppression of adrenal function but is still used for patients undergoing cardiac surgery.
- Its effects on vasopressor use after cardiac surgery are not known.
- In this study, etomidate caused relative adrenal insufficiency in the first 24 h after operation.
- There were no differences in norepinephrine requirements; the effects on outcome in these patients remain unclear.

Background. The consequences of inhibition of cortisol synthesis by a single dose of etomidate on subsequent vasopressor drug usage and the duration of relative adrenal insufficiency (RAI) after cardiac surgery are not known.

Methods. This was a prospective, randomized, double-blinded controlled trial of 100 patients undergoing elective cardiac surgery and receiving either etomidate or propofol at induction of anaesthesia. A short corticotropin test was performed 12, 24, and 48 h after anaesthesia induction. RAI was defined as a response < 250 nmol litre⁻¹.

Results. The mean (sd) norepinephrine infusion rate during the first 48 postoperative hours was 0.11 (0.01) and 0.11 (0.01) μg kg⁻¹ min⁻¹ in the etomidate and propofol groups, respectively (P = 0.89). Time to norepinephrine withdrawal was similar between the groups. The incidence of RAI was higher in the etomidate group at 12 h (100% vs 41%, P < 0.001) and 24 h (85% vs 25%, P < 0.001).

Conclusions. A single bolus of etomidate blunts the hypothalamic–pituitary–adrenal axis response for more than 24 h in patients undergoing elective cardiac surgery, but this was not associated with an increase in vasopressor requirements.

Keywords: adrenal insufficiency; cardiac surgical procedures; etomidate cardiovascular agents, vasopressor agents

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Controversy surrounds the use of etomidate in induction of emergency anaesthesia, particularly in patients with septic shock.1–6 Although etomidate continues to be used,7 several trials suggest an association between etomidate administration, adrenal insufficiency (caused by reversible inhibition of cortisol synthesis), and increased mortality.6–8 However, confounding factors often prevent a clear interpretation of these studies, especially post hoc or subgroup analyses, and the use of etomidate in more severely ill patients.9 A recent study conducted in 655 patients requiring emergency intubation reported a lack of detrimental effect of etomidate compared with ketamine.10 Cardiac surgery constitutes a significant stimulus for the endogenous release of stress hormones.11 Although adrenal insufficiency induced by etomidate has been demonstrated in several studies of perioperative patients,12–17 surprisingly none measured the haemodynamic consequences of this inhibition. Etomidate is commonly used for induction of anaesthesia before cardiac surgery owing to its relative cardiovascular stability.18 19 Postoperative haemodynamic alterations are common after cardiac surgery, thus a functioning adrenal axis is essential. A decrease in cortisol synthesis related to etomidate administration may dramatically affect the haemodynamic status of such patients, particularly in view of the systemic inflammatory state triggered by cardiopulmonary bypass (CPB).20 21

The aim of this study was to compare norepinephrine usage over the first 48 h after cardiac surgery with CPB after a single dose of either etomidate or propofol administered for induction of anaesthesia.

Methods

This prospective, randomized, controlled, double-blinded study was performed from April 2007 to September 2008 in the cardiac surgery unit and the surgical intensive care unit (five beds) of a French teaching hospital. The study was approved by the local ethics committee (CPP Sud-Est 1) and registered with Clinical Trials.gov as NCT00451776. Written informed consent was obtained from all patients.
Adult patients undergoing coronary artery bypass grafting (CABG), valve replacement, or combined procedure, under CPB, were included. Only patients operated upon during the morning were considered due to the circadian rhythm of cortisol secretion. Exclusion criteria were pregnancy, age below 18 yr, known adrenal insufficiency, administration of any corticosteroid within the last 3 months, non-interruption of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist treatment the day before surgery, an emergency procedure, current infection, aortic stenosis, or an acute coronary syndrome (ACS) during 3 weeks before surgery.

Randomization was performed centrally on the morning of surgery by the hospital research department with allocation concealed in permuted blocks of variable size (2, 4, and 6). Stratification was performed according to the type of surgery anticipated (CABG, valve replacement, combined procedure). Patients were randomized to receive at induction of anaesthesia an i.v. bolus of either etomidate (Lipuro®), B. Braun Medical, Boulogne, France (etomidate group) or propofol (Propofol Frésénius®, Frésénius Kabi, Sévres, France) (control group). A surgical unit nurse who did not provide postoperative care for that patient prepared a 20 ml syringe containing either etomidate 2 mg ml⁻¹ or propofol 10 mg ml⁻¹ dissolved in indistinguishable lipid solutions, and handed this to the anaesthetist administering anaesthesia.

Eligibility was confirmed and consent obtained during the preoperative anaesthesia visit. Premedication consisted of oral hydroxyzine given 1 h before surgery, and midazolam (0.01–0.05 mg kg⁻¹) was administered if necessary in the operating theatre. Monitoring consisted of electrocardiography with ST-segment analysis of leads II and V5, pulse oximetry, and invasive arterial pressure. Induction of anaesthesia was performed with sufentanil (0.3–0.6 µg kg⁻¹) followed by 0.15 ml kg⁻¹ of the hypnotic drug (i.e. either propofol 0.5 mg kg⁻¹ or etomidate 0.3 mg kg⁻¹). Additional 2 ml boluses could be given to achieve loss of consciousness. A single dose of cisatracurium (0.15 mg kg⁻¹) was injected to facilitate tracheal intubation. Central venous and pulmonary artery catheters were then inserted into the right internal jugular vein. Anaesthesia was maintained with continuous infusion of sufentanil (1–2 µg kg⁻¹ h⁻¹) and desflurane (0.8 MAC) that was switched to propofol (3–4 mg kg⁻¹ h⁻¹) during CPB. Body temperature was obtained from a thermistor in the indwelling bladder catheter.

Patients in the two groups were managed identically with regard to fluid therapy and vasopressor drug administration. Normovolaemia was indicated by a central venous pressure of 8–12 mm Hg at zero positive end-expiratory pressure (ZEEP), or a pulmonary artery occlusion pressure of 12–15 mm Hg at ZEEP. If the patient required a PEEP, this was reduced to zero for these measurements. In addition, transoesophageal echocardiography was performed only for valve replacement procedure or in the case of difficult weaning from CPB. If, despite fluid challenge, arterial pressure still remained under 55 mm Hg, norepinephrine was titrated (by 0.05 µg kg⁻¹ min⁻¹ increments) to achieve a mean arterial pressure of 55–70 mm Hg. Dobutamine was titrated (by 2.5 µg kg⁻¹ min⁻¹ increments) to achieve a cardiac index of ≥2.5 litre min⁻¹ m⁻².

The bypass pump was primed with 500 ml of hydroxyethyl starch 130/0.4 and 1000 ml of normal saline solution. Unfractioned heparin was administered before CPB initiation (300 IU kg⁻¹) to obtain an activated clotting time of >400 s. Surgery was performed under mild hypothermia (35°C) with cardioplegia achieved using cold St Thomas’ hospital solution. Antifibrinolysis was initially delivered using aprotinin, stratified to haemorrhagic risk, but the protocol was later amended to tranexamic acid due to prohibition on aprotinin use.22

At the end of the operation, patients remained sedated and with mechanical ventilation, and were immediately transferred to the postoperative intensive care unit (ICU). Propofol was initiated at 2 mg kg⁻¹ h⁻¹ and titrated to reach level 3 on the Riker Sedation-Agitation Scale. Multimodal analgesia was standardized using tramadol, paracetamol, and ketoprofen. The goal-directed protocol for fluid and vasopressor drug administration used during surgery was continued after operation. Delta pulse pressure (delta PP) was measured in the first postoperative hours when patients were sedated with no spontaneous respiration and only for those with sinusual cardiac rhythm. The patient was considered hypovolaemic if delta PP <13%. Patients were transfused if their haemoglobin level decreased below 10 g dl⁻¹. Sedation was discontinued when patients were normothermic (>36.5°C) and haemodynamically stable with blood loss through mediastinal drains <50 ml h⁻¹ and a urine output exceeding 0.5 ml kg⁻¹. There was no weaning protocol in the unit, but patients were then rapidly set to pressure support ventilation to allow spontaneous breathing. Extubation criteria were checked when the patient was calm, conscious, oriented, and pain-free. Criteria for ventilator weaning included a ventilatory frequency <35 bpm, an expired tidal volume >6 ml kg⁻¹, and SpO₂ >94% under conditions of FiO₂ <40% and PEEP <5 cm H₂O.

Baseline plasma cortisol levels were sampled on the morning of surgery. A short corticotropin test was performed at 12, 24, and 48 h after etomidate injection using a 250 µg i.v. bolus of tetracosactide (Synacthène®, Ciba, Rueil-Malmaison, France). Blood samples were drawn immediately before the test (T0) and 60 min after (T60). Relative adrenal insufficiency (RAI) was defined as a cortisol response <250 nmol litre⁻¹ (9 µg dl⁻¹) (Advia Centaur™, Siemens, Berlin, Germany) after tetracosactide administration.23 Cardiac troponin I was collected on admission to the ICU, at 6 h, and on the morning of the first and second postoperative days. A postoperative ACS was defined by appearance of new Q waves or ST-segment elevation on a 12-lead electrocardiogram. Plasma concentrations of the pro-inflammatory cytokines interleukin (IL)-6 and tumour necrosis factor (TNF)α (Immulite™, Siemens, Berlin, Germany) and procalcitonin (Kryptor PCT test, Brahms Diagnostica, Berlin, Germany)
were assessed 6 h after ICU admission. A serious adverse event (SAE) was defined as any life-threatening event causing prolongation of hospital stay or resulting in permanent disability or death.

The primary study endpoint was comparison of norepinephrine usage between the two groups. A priori secondary endpoints included time to vasopressor drug withdrawal, inotropic drug use, and adrenocortical function measured at 12, 24, and 48 h after etomidate administration.

An independent data safety and monitoring committee reviewed study results and adverse events, and the incidence of ACS, ruling on study continuation after each 30 patients enrolled.

**Statistical analysis**

In a pilot study of 27 patients receiving propofol, the mean (sd) norepinephrine usage was 0.20 (0.15) μg kg⁻¹ min⁻¹ over the first 48 h after operation. Ninety-four patients were thus needed to detect a 50% increase in norepinephrine requirements between the two groups with a two-sided α-value of <5% and a power of 90% (β-value of 10%). Descriptive statistics were expressed as frequencies and percentages for categorical variables, and as means for continuous variables. Norepinephrine usage was analysed with an area under the curve (AUC) analysis for each patient. AUCs were compared between the groups using a t-test. The duration of catecholamine weaning was analysed by the Kaplan–Meier curves and log-rank test. Comparisons between the two groups used Student’s t-test for quantitative variables, the χ² test for qualitative variables, and a one-way analysis of variance followed by a post hoc Dunnett’s test as the multiple comparison method (for cortisol and troponin measurements). Statistical significance was regarded as P<0.05. Statistical analysis was performed using SAS version 9 (SAS Institute Inc., Cary, NC, USA). Patients’ data were analysed on an intention-to-treat basis.

**Results**

During the study period, 51 and 49 patients were enrolled in the etomidate and control groups, respectively. CABG was performed using the octopus stabilizer without CPB for three patients (one etomidate, two controls). In one etomidate group patient, CABG proved impossible due to coronary artery calcification.

Patient characteristics were well balanced between the two groups (Table 1). Valve replacement, CABGs, and combined procedures represented ~50%, 40%, and 10% of the cases in each group, respectively. No difference was seen in the duration of CPB or aortic clamping between groups, and aprotinin and tranexamic acid doses were similar (Table 2). Aprotinin was administered in 63% and 53% of the patients in, respectively, the etomidate and control groups (P=0.33). Tranexamic acid was administered in 37% and 47% of the patients in, respectively, the etomidate and control groups (P=0.72). Intra- and postoperative fluid requirements and blood transfusions were also similar between the groups (Tables 2 and 3). The mean (sd) duration of sedation in the ICU was 8 (4) and 9 (6) h in the etomidate and control groups, respectively (P=0.83).

Arterial pressure was not significantly different between the groups during the postoperative period (data not

### Table 1 Preoperative patient characteristics. Comparison between two groups. Values are mean (sd) or number (%)

<table>
<thead>
<tr>
<th></th>
<th>Etomidate group (n = 51)</th>
<th>Control group (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (f/m)</td>
<td>18/33</td>
<td>16/33</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66 (10)</td>
<td>68 (9)</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>26 (18)</td>
<td>26 (14)</td>
</tr>
<tr>
<td>ASA class no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>44 (86)</td>
<td>39 (80)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (14)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>EuroSCORE (points)</td>
<td>4 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59 (11)</td>
<td>58 (10)</td>
</tr>
</tbody>
</table>

### Table 2 Preoperative data expressed as mean (sd). There were no significant differences between the groups. CPB, cardiopulmonary bypass; PRBC, packed red blood cells

<table>
<thead>
<tr>
<th></th>
<th>Etomidate group (n = 51)</th>
<th>Control group (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB time (min)</td>
<td>112 (38)</td>
<td>114 (50)</td>
</tr>
<tr>
<td>Clamping time (min)</td>
<td>82 (34)</td>
<td>83 (40)</td>
</tr>
<tr>
<td>PRBC (units)</td>
<td>2.4 (0.7)</td>
<td>2.5 (1)</td>
</tr>
<tr>
<td>Fluid requirement (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>1692 (776)</td>
<td>1534 (634)</td>
</tr>
<tr>
<td>Colloid</td>
<td>633 (401)</td>
<td>706 (491)</td>
</tr>
<tr>
<td>Aprotinin (M IU)</td>
<td>3.6 (1.1)</td>
<td>3.3 (1.1)</td>
</tr>
<tr>
<td>Tranexamic acid (g)</td>
<td>3.6 (0.9)</td>
<td>4 (0.7)</td>
</tr>
</tbody>
</table>

### Table 3 Postoperative data expressed as mean (sd). There were no significant differences between the groups. PRBC, packed red blood cells; ICU, intensive care unit

<table>
<thead>
<tr>
<th></th>
<th>Etomidate group (n = 51)</th>
<th>Control group (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid requirement (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid</td>
<td>2448 (944)</td>
<td>2550 (976)</td>
</tr>
<tr>
<td>Colloid</td>
<td>564 (486)</td>
<td>567 (496)</td>
</tr>
<tr>
<td>PRBC (units)</td>
<td>1.9 (1.6)</td>
<td>1.3 (1.2)</td>
</tr>
<tr>
<td>Troponin (μg litre⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>5.9 (6.1)</td>
<td>7.3 (8.4)</td>
</tr>
<tr>
<td>6 h</td>
<td>8.2 (8.2)</td>
<td>11.4 (10.9)</td>
</tr>
<tr>
<td>24 h</td>
<td>9.2 (15.1)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>48 h</td>
<td>6 (9.8)</td>
<td>8.6 (21.1)</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>3.5 (3)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>10 (6)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Norepinephrine was administered to 17 (33%) and 20 (41%) patients in the etomidate and control groups, respectively ($P=0.44$). The median (inter-quartile range) norepinephrine requirements during the postoperative period was 0.18 (0.09–0.4) and 0.17 (0.13–0.28) µg kg$^{-1}$ min$^{-1}$ for the etomidate and control groups, respectively ($P=0.89$). The AUCs for norepinephrine use were 1.9 (0.5) and 1.1 (0.3) µg kg$^{-1}$ min$^{-1}$ for the control and etomidate groups, respectively ($P=0.2$). The time-course of norepinephrine withdrawal was similar (Fig. 1), as was the use of dobutamine, 4.9 (2.9) µg kg$^{-1}$ min$^{-1}$ (etomidate group) vs 5.6 (3.9) µg kg$^{-1}$ min$^{-1}$ (control group). The number of patients who received dobutamine was 18 (35.3%) and 16 (32.7%) in the etomidate and control groups, respectively ($P=0.83$).

The mean (sd) baseline plasma cortisol was 261 (89) nmol litre$^{-1}$ (etomidate group) and 286 (92) nmol litre$^{-1}$ (control group) ($P=0.18$). The response to corticotropin stimulation was significantly decreased at 12, 24, and 48 h in the etomidate group (Table 4). According to our definition, the incidence of RAI occurred more frequently in the etomidate group at 12 and 24 h, but this difference was no longer significant at 48 h (Fig. 2). Approximately 40% and 25% of the control group patients were corticotrophin non-responders at 12 and 24 h after propofol administration, respectively.

No significant differences were seen in the biological markers of inflammation sampled at 6 h post-ICU admission: IL-6 levels were 189 (168) ng litre$^{-1}$ in the etomidate group vs 251(193) ng litre$^{-1}$ for controls ($P=0.14$); TNF$\alpha$ levels were 16 (26) ng litre$^{-1}$ (etomidate) and 14 (10) ng litre$^{-1}$ (control) ($P=0.66$). Postoperative troponin concentrations did not differ between the two groups at any time point (Table 3). According to our definition, 4 (8%) etomidate group patients and 6 (12%) control group patients met the criteria for ACS ($P=0.27$).

The incidence of SAEs was significantly higher with 9 (18%) in the control group and 3 (6%) in the etomidate group ($P=0.04$) (Table 5). Three patients developed cardiovascular complications, all in the control group: one died in refractory cardiogenic shock while two suffered ventricular arrhythmia with cardiogenic shock and cerebral stroke. Five patients suffered from postoperative complications (mediastinitis, acute mediastinal bleeding). Outcome (hospital length of stay and hospital mortality) did not differ between groups (Table 3).
Discussion

In this study, we found that a single bolus of etomidate at induction of anaesthesia in patients undergoing elective cardiac surgery led to RAI for <48 h, but this was not associated with an increase in requirements for vasopressor drugs. Several factors can explain this lack of difference. First, the study may be underpowered as the sample size was calculated using preliminary data showing higher norepinephrine use, but this study had multiple methodological limitations. The controversy surrounding the haemodynamic consequences of adrenal insufficiency comes predominantly from either post hoc analysis of trials in patients with septic shock or retrospective subgroup analysis of cardiac surgery patients receiving hydrocortisone supplementation. In a recent retrospective study, 63 patients presenting acute circulatory failure requiring norepinephrine after cardiac surgery and etomidate administration have been studied. All patients received hydrocortisone supplementation. The authors have compared patients with and without adrenal insufficiency and did not find any increase in norepinephrine use, but this study had multiple methodological limitations.

The incidence of RAI after etomidate administration was not statistically different from control patients at 48 h. This supports the recent finding reported in 40 patients requiring emergency intubation, of whom 32 (80%) fulfilled RAI criteria at 12 h, but only 9% and 7% at 48 and 72 h, respectively. However, the response of the HPA axis to corticotrophin is probably blunter for a longer period as we found that cortisol inhibition remained significantly greater at 48 h. The inhibition of 11 β-hydroxylase by etomidate is probably incomplete as blood cortisol levels remained relatively high. Some authors suggest that the decrease in plasma cortisol concentrations was compensated by an increase in ACTH secretion.

There have been few previously published studies regarding the postoperative haemodynamic consequences of adrenal insufficiency. In colorectal surgery, catecholamine requirements were not significantly different between patients receiving hydrocortison or placebo supplementation after a single dose of etomidate; however, crystalloid administration was considerably higher in the placebo group. The anti-inflammatory effects of increasing doses of hydrocortisone in patients receiving etomidate for induction of anaesthesia in cardiac surgery have been reported. No significant differences were seen with respect to vasopressor requirements, duration of postoperative ventilation, and hospital stay between a control group receiving thiopental and an etomidate group not receiving hydrocortisone supplementation. In a recent retrospective study, 63 patients presenting acute circulatory failure requiring norepinephrine after cardiac surgery and etomidate administration have been studied. All patients received hydrocortisone supplementation. The authors have compared patients with and without adrenal insufficiency and did not find any increase in norepinephrine use, but this study had multiple methodological limitations.

The controversy surrounding the haemodynamic consequences of etomidate-related adrenal insufficiency comes predominantly from either post hoc or retrospective subgroup analysis of trials in patients with septic shock or those requiring emergency intubation in Emergency
A recent prospective randomized study compared etomidate with ketamine in 655 patients requiring emergency tracheal intubation. The authors concluded that a single bolus dose of etomidate was not associated with a significant increase in morbidity as evaluated by the maximum SOFA score over the following 3 days, even for the haemodynamic component of the score.

In conclusion, a single injection of etomidate was not associated with increased use of vasopressor agents in an elective cardiac surgical population requiring CPB. However, due to its significant inhibition of the adrenal axis, etomidate should be used with caution in high-risk cardiac surgical patients until studies determine its safety.

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**Conflict of interest**

None declared.

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