Cardiovascular effects of etilefrine hydrochloride during abdominal aortic surgery

L. W. RETIEF, J. A. ROELOFSE, B. H. MEYER

Summary

To counteract the decrease in blood pressure after release of the aortic cross-clamp, 2 mg etilefrine hydrochloride (Effortil; Boehringer Ingelheim) was administered intravenously to 13 patients undergoing aortofemoral bypass operations. It caused a statistically significant increase in mean arterial pressure, cardiac index, pulmonary capillary wedge pressure and left and right ventricular stroke work index. No significant changes were found in total peripheral resistance.

Aortic or aortofemoral transplant surgery consists of suturing a synthetic graft into position to replace a ruptured, dilated or obstructed abdominal aorta. During surgery a clamp is applied to the aorta. Release of the clamp after completion of the suturing is frequently followed by a decrease in blood pressure.1 Pharmacological intervention is not always necessary, but since almost all these patients also have an ischaemic myocardium2-5 cardiovascular manipulation requires caution. It could be argued that, where hypotension does occur, the use of a β1,stimulant would be more advantageous than an α-stimulant, since the former would not cause as large an increase in afterload, thereby limiting myocardial oxygen requirements.3

Etilefrine hydrochloride (Effortil; Boehringer Ingelheim) is a sympathomimetic amine with low β1,- and α-receptor affinities, but high β2-receptor affinity (Table 1).4 This drug has been shown to have a positive inotropic and chronotropic effect on the heart, causing an increase in cardiac output.5

Patients and methods

The study was approved by the Ethics Committee of the Faculty of Medicine at the University of the Orange Free State. Informed consent was obtained from 13 unselected patients scheduled for elective repair of abdominal aneurysms of the aorta or of aortofemoral occlusion. Their ages ranged from 48 years to 78 years, with a mean age of 60 years. Two patients had a decreased creatinine clearance. Clinical examination and lung function tests showed chronic obstructive airway disease in 11 patients, while the same number had a history and/or ECG signs of myocardial ischaemia; 6 had a history of hypertension. One male patient had had carcinoma of the breast and 1 patient had had an episode of pericarditis 16 years previously. Drugs taken which could interfere with cardiac action were propranolol (6 patients), nifedipine (2 patients) and nitrates (2 patients).

The same anaesthetic technique was used for all patients. Premedication consisted of morphine (0,15 mg/kg) to a maximum of 10 mg and promethazine hydrochloride (12,5 mg) given intramuscularly 1 hour pre-operatively. Anaesthesia was induced with etomidate (0,3 mg/kg) and fentanyl (10 μg/kg). Pancuronium bromide (0,1 mg/kg) was used for muscle relaxation; 2 patients required an additional 2 mg during the course of surgery. The patients were mechanically ventilated, at a frequency of 10 ventilations/min and a tidal volume of 10 ml/kg, with a mixture of 50% oxygen in N2O. For maintenance of anaesthesia 0,5 - 1% halothane was used, with increments of fentanyl (0,5 μg/kg) as necessary. Ventilation was monitored by serial blood gas analysis. Approximately 10 minutes before release of the cross-clamp, the halothane concentration was decreased to 0,25% until the restoration of an adequate blood pressure after unclamping.

One patient received a bolus of dihydralazine (2,5 mg) intraoperatively for hypertension. A hypertensive episode was regarded as a period of sustained mean arterial blood pressure (MAP) of more than 100 mmHg not reversed by deepening anaesthesia or analgesia and with no evidence of hypercarbia or hypoxia. For the same reason 3 other patients received an infusion of sodium nitroprusside which was terminated 15 minutes before release of the cross-clamp.

Before induction, 500 ml 5% dextrose in water was administered intravenously. This was followed by Ringer's lactate or Plasmalyte B in sufficient amounts to keep the pulmonary capillary wedge pressure at not less than 15 mmHg and to ensure a urine output of at least 1 ml/kg/h. The mean amount of fluid infused totalled 5.1 l of Ringer's lactate or Plasmalyte B per patient, while 7 patients received 200 ml 4% albumin and 1 patient received 400 ml. Blood was given only if the hematocrit decreased to below 35%; 3 patients received 500 ml whole blood each.

Before induction, a radial artery cannula and an ECG monitor (lead II) were set up. After induction and intubation a central venous catheter was inserted via the right internal jugular vein. A flow-directed thermodilution pulmonary artery catheter (model 93A-131-7F; Edwards Laboratories) was threaded into position.

<p>| TABLE I. RELATIVE AFFINITIES OF ETILEFRINE, ADRENALINE AND NORADRENALINE TO ADRENERGIC RECEPTORS, WITH NORADRENALINE TAKEN AS STANDARD4 |</p>
<table>
<thead>
<tr>
<th>Compound</th>
<th>α</th>
<th>β1</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline</td>
<td>1,0</td>
<td>1,0</td>
<td>1,0</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>2,5</td>
<td>5,0</td>
<td>12,5</td>
</tr>
<tr>
<td>Etillefrine</td>
<td>0,1</td>
<td>31,0</td>
<td>0,4</td>
</tr>
</tbody>
</table>

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via the right subclavian vein and connected to a cardiac output computer (model 9520; Edwards Laboratories) for registration of cardiac output and core temperature. A bladder catheter was inserted and blood gases, acid-base status, electrolyte levels and hematocrit were serially determined. Blood loss and intravascular fluid intake were also monitored.

The surgeon was asked to announce when, in his opinion, he was about 15 minutes from releasing the cross-clamp. Systolic, diastolic and MAPs, central venous pressure, pulmonary capillary wedge pressure (PCWP) and cardiac output were measured at this stage and again immediately after release of the cross-clamp. Etilerfine 2 mg was administered intravenously if the MAP decreased by more than 20% of the reading obtained before unclamping. These measurements were repeated 2 and 5 minutes after the administration of the drug.

Results

Eleven of the 13 patients required only 2 mg etilerfine to restore a satisfactory MAP, while 1 patient required an additional 2 mg 2 minutes after the first dose. Another patient required the second dose as well as an additional 2 mg 2 minutes after the second dose, i.e. 6 mg etilerfine in all. Changes induced by the injections of etilerfine were evaluated for statistical significance by means of the Student’s t-test (Tables II and III).

No dysrhythmias developed after injections of etilerfine. One patient died 6 days postoperatively from causes unrelated to the anaesthesia.

Discussion

Both patients who needed additional doses of etilerfine had myocardial ischaemia and 1 had a previous myocardial infarction, but apart from this common condition (i.e. for patients undergoing this type of surgery) no other reason could be found for the weak response to the initial 2 mg dose. Various explanations have been put forward for the decrease in blood pressure after release of the cross-clamp. It has been suggested that hypotension at this point can be minimized by infusing enough fluid to keep the PCWP at 3 - 4 mmHg above pre-anaesthetic values.1 In this study the pre-anaesthetic PCWP values were not known, but the mean value before unclamping was 17.9 mmHg, which is above the upper limit of normal. The initial PCWP readings taken when the catheter was inserted after induction showed high or high-normal wedge pressures in all but 3 patients. Since no patient developed oliguria during the operation and the fluid regimen was apparently adequate, the decrease in MAP to 59.9 mmHg (with a mean systolic pressure of 84 mmHg) must be ascribed at least in part to impaired cardiac function, since the contractile function of the myocardium may be lost or decreased in any area of ischaemia even in the absence of infarction and necrosis.2 The low concentrations of halothane (0.25%) the patients were receiving at the time may also have played a role. The decrease in total peripheral resistance (TPR) after release of the clamp, without a concomitant increase in cardiac output, may also be of importance. It must be pointed out that, although the MAPs of all the patients in this study decreased by at least 20% after release of the clamp (as demanded by the study protocol) the blood pressures of individual patients did not cause concern in every case.

In caring for the patient undergoing abdominal aortic surgery, the anaesthetist often finds himself between the devil and the deep blue sea: should hypotension develop, it must be corrected, but not at the cost of placing too large a load on the ischaemic myocardium which most of these patients have. Furthermore, adequate flow through the prosthesis must be ensured, particularly in patients in whom the outflow tract distal to the prosthesis is already impaired.

No ideal agent for use under such circumstances exists, since it is inevitable that myocardial oxygen consumption must be increased in order to improve blood pressure and flow through the prosthesis. The most that can be done is to minimize the increased oxygen demand and maximize supply.

Factors relevant to this situation which will decrease myocardial oxygen supply are tachycardia, diastolic hypotension and increased preload, while oxygen demand will be increased by tachycardia, increased preload, increased afterload and increased contractility.3,4

### TABLE II. STATISTICAL EVALUATION OF CARDIOVASCULAR PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>Pulse rate</th>
<th>MAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>CI (l/m²/min)</th>
<th>LVSWI (g/m²)</th>
<th>RVSWI (g/m²)</th>
<th>TPR (dyn/s/cm²)</th>
<th>PVR (dyn/s/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Before unclamping</td>
<td>74 (147)</td>
<td>86 (9)</td>
<td>17,9 (5,3)</td>
<td>2.3 (0,9)</td>
<td>29 (8,2)</td>
<td>3.5 (2,4)</td>
<td>1349 (490)</td>
<td>152 (118)</td>
</tr>
<tr>
<td>B. After unclamping</td>
<td>81 (15,2)</td>
<td>59,9 (8,8)</td>
<td>14,2 (4)</td>
<td>2.1 (0,8)</td>
<td>16.6 (7,4)</td>
<td>1.9 (1,3)</td>
<td>1044 (392)</td>
<td>127 (101)</td>
</tr>
<tr>
<td>P (v. A)</td>
<td>&lt; 0,05</td>
<td>&lt; 0,001 NS</td>
<td>&lt; 0,001 NS</td>
<td>&lt; 0,01 NS</td>
<td>&lt; 0,01 NS</td>
<td>&lt; 0,01 NS</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>C. 2 min after etilerfine</td>
<td>78 (16,1)</td>
<td>69,9 (10,8)</td>
<td>16,3 (4,7)</td>
<td>2,7 (0,5)</td>
<td>23,6 (10,5)</td>
<td>3,2 (2,4)</td>
<td>967 (447)</td>
<td>132 (105)</td>
</tr>
<tr>
<td>P (v. B)</td>
<td>&lt; 0,05</td>
<td>&lt; 0,01</td>
<td>&lt; 0,05</td>
<td>&lt; 0,001</td>
<td>&lt; 0,001</td>
<td>&lt; 0,05</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>D. 5 min after etilerfine</td>
<td>85 (17,5)</td>
<td>81 (13,1)</td>
<td>18,1 (9)</td>
<td>3 (1,1)</td>
<td>28,1 (10,1)</td>
<td>4,9 (3)</td>
<td>1065 (580)</td>
<td>148 (96)</td>
</tr>
<tr>
<td>P (v. C)</td>
<td>NS</td>
<td>&lt; 0,001</td>
<td>&lt; 0,01</td>
<td>&lt; 0,001</td>
<td>&lt; 0,01 NS</td>
<td>&lt; 0,10 NS</td>
<td>NS NS NS</td>
<td></td>
</tr>
</tbody>
</table>

*Mean data from 11 patients only since 2 required additional doses of etilerfine before the 5-minute values could be read.

FIGURES IN BRACKETS REPRESENT THE STANDARD DEVIATIONS.

### TABLE III. CARDIOVASCULAR PARAMETERS IN THE 2 PATIENTS REQUIRING MORE THAN 2 mg ETILERFINE

<table>
<thead>
<tr>
<th>Pulse (l/min)</th>
<th>MAP (mmHg)</th>
<th>PCWP (mmHg)</th>
<th>CI (l/m²/min)</th>
<th>LVSWI (g/m²)</th>
<th>RVSWI (g/m²)</th>
<th>TPR (dyn/s/cm²)</th>
<th>PVR (dyn/s/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min after 4 mg etilerfine</td>
<td>29,9</td>
<td>25</td>
<td>1</td>
<td>848</td>
<td>42</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>5 min after 6 mg etilerfine</td>
<td>30,9</td>
<td>39</td>
<td>6</td>
<td>881</td>
<td>42</td>
<td>136</td>
<td></td>
</tr>
</tbody>
</table>

For key see Table II.
Although etilefrine caused a significant rise in pulse rate, the highest mean rate reached was 86/min, a rate not likely to impair myocardial oxygen supply significantly or increase demand. The pulse rate of 1 patient increased from 113 to 126/min.) Diastolic hypotension was largely abolished by this drug and it must be noted that TPR did not change significantly. On the debit side, the PCWP was significantly increased and the β₂-stimulant activity of etilefrine caused an increase in dp/dt, both of which increased oxygen consumption. However, it must be borne in mind that so-called 'pressure work' requires much more oxygen than the same amount of work done against a low pressure ('flow work'). The increase in cardiac output raised blood pressure without significantly increasing TPR, thereby limiting the increase in oxygen demand. It could be argued that the lack of effect on TPR is due to the vasodilating action of metabolites after release of the cross-clamp, but it has been shown that in situations where such metabolites do not play a role TPR is not increased by etilefrine.

Further advantages of this drug are the enhancement of ventricular filling by β₂-stimulation and the fact that it decreases renal blood flow only slightly.

In conclusion, etilefrine is a satisfactory agent for the treatment of hypotension not due to blood loss. It seems to be particularly advantageous in patients with myocardial ischaemia.

**REFERENCES**


**Effect of intramuscular atropine and glycopyrrolate on the cardiovascular response to tracheal intubation**

**E. A. SHIPTON, J. A. ROELOFSE, H. G. LUUS**

**Summary**

The effect of premedication with intramuscular atropine and glycopyrrolate on the cardiovascular changes resulting from the performance of laryngoscopy and tracheal intubation has been evaluated in two groups of 25 patients undergoing surgery. Neither atropine nor glycopyrrolate attenuated the hypertensive and tachycardic response to laryngoscopy and intubation; both significantly enhanced it (P < 0.05).

The present study was undertaken to investigate the effect of the premedicants atropine and glycopyrrolate on the cardiovascular response to instrumentation and intubation.

**Patients and methods**

Two treatment groups (1 and 2) and a control group were used. All patients were carefully selected according to the American Society of Anesthesiologists' classification and were in the status 1 category. Treatment group 1 consisted of 25 patients (10 men and 15 women) who received 1,0 mg/kg pethidine, 0,3 mg/kg promethazine and 0,02 mg/kg atropine (to a maximum of 0,6 mg) 60 minutes before induction; they ranged in age from 14 to 53 years (mean age 26,6 years) and had a mean weight of 65,4 kg. Treatment group 2 consisted of 25 patients (12 men and 13 women) who received 1,0 mg/kg pethidine, 0,3 mg/kg promethazine and 0,008 mg/kg glycopyrrolate (to a maximum of 0,3 mg) 60 minutes before induction; they ranged in age from 16 to 37 years (mean age 24,4 years) and had a mean weight of 63,4 kg. The control group consisted of 25 patients (7 men and 18 women) who received 1,0 mg/kg pethidine and 0,3 mg/kg promethazine as premedication 60 minutes before induction; they ranged in age from 11 to 39 years (mean age 21,7 years) and had a mean weight of 60,3 kg. All patients underwent oral surgical procedures. In all cases anaesthesia was induced with etomidate 0,3 mg/kg and relaxation obtained with suxamethonium 1 mg/kg. Maintenance was with a mixture of 60% N₂O and 40% O₂. Enflurane 1 - 2,5% was added.

Pulse rates were measured with a Diacope DS 521 electrocardiographic and pulse rate monitor. Systolic and diastolic blood pressures were measured with a Critikon Dinamap.