Endotoxaemia and postoperative hypermetabolism in coronary artery bypass surgery: the role of ketanserin


Summary

In a randomized, double-blind clinical study in 29 patients undergoing elective coronary artery surgery, we assessed the role of ketanserin, an inhibitor of serotonin-induced vasconstriction and weak α₁ sympathetic blocker, in reducing endotoxaemia and postoperative hypermetabolism. Male patients without major organ dysfunction were allocated randomly to receive either ketanserin or placebo. Hypermetabolism was defined as an increase in oxygen consumption in the early postoperative hours (∆VO₂). Circulating endotoxin (P=0.04) and postoperative ∆VO₂ (P=0.03) were lower in the ketanserin patients. Endotoxaemia was associated also with low vascular filling. From these preliminary results we conclude that treatment with ketanserin during cardiac surgery may reduce but not abolish endotoxaemia and postoperative hypermetabolism. (Br. J. Anaesth. 1996;77:473–479)

Key words


The postoperative course after cardiac surgery may be complicated by a systemic inflammatory response. This hypermetabolic response is multifactorial. It may be caused by rewarming after hypothermia, complement activation on contact of blood with material from the extracorporeal circuit or reperfusion after ischaemia. It has also been associated with endotoxaemia and subsequent cytokine release. Circulating endotoxin during cardiac surgery possibly originates from the patient’s own gut flora. Endotoxin permeating from the gut stimulates the host to produce inflammatory mediators that cause the systemic inflammatory response.

One of three factors appear to be necessary for permeation of endogenous bacterial endotoxin from the gut into the systemic circulation: first, bacterial overgrowth in the gut lumen, second, loss of gut barrier function, and third, decreased ability of the reticuloendothelial system to detoxify the permeated endotoxin. The first factor is probably not important during cardiac surgery, but the two other factors may be. Both might be caused by splanchnic hypoperfusion, as may occur during cardiac surgery. In a previous study it was found that during cardiac surgery intestinal permeability between cells increased. The amount of circulating endotoxin was related to this increase. Increased intestinal permeability was associated with pharmacologically induced vasoconstriction and hypovolaemia during operation.

In rats, ketanserin has a beneficial effect on the occurrence of ischaemic lesions in the gastric mucosa. Ketanserin inhibits the action of serotonin on the vasoconstricting 5-HT₂ receptor and on platelet aggregation. It also inhibits the potentiating vasoconstrictive effects of serotonin on noradrenaline and angiotensin, and has a weak α₁ receptor inhibiting effect at higher concentrations. As a result, ketanserin inhibits vasoconstriction and platelet aggregation. This effect is particularly prominent in vessels with decreased endothelial-mediated vasodilatation.

The first aim of this study was to assess if i.v. administration of ketanserin reduces the degree of endotoxaemia during elective coronary artery bypass surgery and ameliorates the postoperative hypermetabolic response. The second aim was to assess if, in addition to ketanserin, other factors, such as haemodynamic state and duration of CPB, are associated with endotoxaemia. Therefore, we have measured the concentration of circulating endotoxin, haemodynamic state and postoperative increase in oxygen consumption in patients receiving i.v. ketanserin or placebo before, during and after coronary bypass surgery.

Patients and methods

Male patients, aged 45–75 yr, undergoing elective coronary artery bypass grafting without valve re-
placement, were eligible for inclusion in the investigation when the following criteria were met: left ventricular ejection fraction more than 40% or an end-diastolic pressure in the left ventricle less than 20 mm Hg, and normal organ function. Patients were excluded if they had unstable angina pectoris, major coagulopathy, history of inflammatory bowel disease or alcohol abuse, had used corticosteroids, antibiotics, ketanserin or aprotinin in the week before operation, had ingested acetylsalicylic acid within 4 days before surgery, or had a QT interval on the electrocardiogram of more than 500 ms (QT prolongation is reported with higher doses of ketanserin). Written informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Free University Hospital, Amsterdam.

As it is not known if ketanserin has any effect on endotoxaemia, we undertook a pilot study. Patients were allocated randomly to receive, in a double-blind design, either ketanserin or a similar volume of placebo. Randomization was performed by Janssen Pharmaceutica BV. In the ketanserin group, patients received ketanserin 0.1 mg kg\(^{-1}\) h\(^{-1}\) i.v. for 4 h, beginning after induction of anaesthesia and insertion of the pulmonary artery catheter preceding sternal incision. To limit the hypotensive effects of ketanserin, the dose was reduced to 0.05 mg kg\(^{-1}\) h\(^{-1}\) after 4 h. The infusion was stopped 18 h after operation.

Endotoxin was measured in blood at baseline (directly after admission to the operating room), during cardiopulmonary bypass (CPB) (10 min after the onset of CPB and on termination of CPB), and in the intensive care unit (ICU) (30 min, 2 h and 18 h after admission). In addition, a sample of the prime fluid of the heart–lung machine was obtained before connection to the patient (ET prime).

Clinical measurements were made at baseline (after induction of anaesthesia and insertion of the pulmonary artery catheter), 30 min after termination of CPB and in the ICU (at fixed times of endotoxin sampling and additionally at 4 and 8 h after admission to the ICU).

The amount of endotoxin appearing in the systemic circulation and the postoperative hypermetabolic response were the end-points of the study. We chose endotoxaemia as the primary end-point as we hypothesized that inhibition of vasoconstriction would improve intestinal and hepatic perfusion and reduce the subsequent permeation of endotoxin from the gut into the systemic circulation. The amount of circulating endotoxin concentration during operation and the concentration of endotoxin at the time of patient admission to the ICU (ET\(_{\text{ICU}}\)) were measurements of special interest. Postoperative hypermetabolism was chosen as the clinical endpoint as it was shown that postoperative hypermetabolism was associated with the endotoxin-related inflammatory response\(^{2}\). Because we studied patients at low risk of postoperative complications, we did not expect to find an effect on duration of ICU stay.

On the morning of surgery, patients received their usual cardiac medication and lorazepam. Anaesthesia was induced with fentanyl 30 μg kg\(^{-1}\) and pancuronium 0.1 mg kg\(^{-1}\), and maintained with a continuous infusion of midazolam and additional doses of fentanyl up to 50 μg kg\(^{-1}\). Volatile anaesthetic, nitrous oxide or corticosteroids were not given. The lungs were ventilated with 40% oxygen and a positive end-expiratory pressure of 5 cm H₂O. A pulmonary artery catheter was inserted after induction of anaesthesia and tracheal intubation.

CPB was performed with moderate systemic hypothermia (28–30 °C), non-pulsatile flow and cold crystalloid cardioplegia for myocardial protection. The CPB circuit consisted of a membrane oxygenator (Avecor, Plymouth, MN, USA), a roller pump (Stockert) with an arterial filter and polyvinyl tubing. The circuit was primed with Ringer’s lactate 2000 ml, 20% human albumin 200 ml, 20% mannitol 100 ml, 8.4% sodium bicarbonate 50 ml and bovine heparin 5000 u. A standard cannulation technique was used with a two-stage venous cannula, an arterial cannula in the ascending aorta and subtotal bypass. During CPB, pH was regulated according to the α-stat concept. Rewarming was started just before the last distal anastomosis was made by slowly increasing temperature, at first to 32 °C and then to 39.5 °C. Rewarming was continued until nasopharyngeal temperature was > 36.5 °C.

After releasing the aortic cross-clamp, nitroglycerine 2 mg h\(^{-1}\) and dopamine 2 μg kg\(^{-1}\) h\(^{-1}\) were started. Fluid therapy was titrated according to cardiac filling pressures and cardiac index. Target values were as follows: central venous pressure (CVP) 8–10 mm Hg, pulmonary artery occlusion pressure (PAOP) 12 mm Hg and cardiac index (CI) > 2.5 litre min\(^{-1}\) m\(^{-2}\). In the ICU all patients were warmed externally with a heating mattress until rectal temperature exceeded 36.5 °C and the difference between rectal and toe temperature was less than 5 °C. All patients received controlled mechanical ventilation for at least 8 h after operation. Doses of dopamine and nitroglycerin were increased when cardiac index remained low after adequate filling. Packed cells were transfused to maintain haemoglobin > 8.8 g dl\(^{-1}\). In order to relieve pain and stress, prevent shivering and obtain a reliable value of oxygen consumption and cardiac output, patients were sedated with morphine 5–10 mg i.v. and diazepam 5–10 mg i.v. for 8 h after operation. After that, when temperature and circulation were stable, patients were allowed to wake up, pressure support ventilation was started and the trachea was extubated generally in the morning after operation.

Blood for measurement of endotoxin was obtained from a newly inserted radial artery catheter or from the arterial cannula of the extracorporeal circuit. Blood samples were collected in tubes (Monovette, Sarstedt, Nümbrecht, Germany) containing pyrogen-free heparin (Thromboliquine, Organon, Oss, The Netherlands) at a final concentration of 30 u. ml\(^{-1}\), under endotoxin-free conditions, and were immersed immediately in ice. Platelet-rich plasma was prepared directly by centrifugation (4 °C) at 190 g for 10 min and stored immediately at −70 °C. Endotoxin was measured with an optimized chromogenic assay (Coatest Endotoxin, Kabi-Chromogenix, Malmö, Sweden) based on the lipopolysaccharide-dependent activation of Limulus amoebocyte lysate (LAL) and subsequent measurement of the activated LAL enzyme(s) with a chromogenic substrate. This assay has been described previously\(^{16}\). The LAL material contained in
this batch of Coatest endotoxin kits is insensitive to LAL-reactive material such as β-glucan. The assay has a detection limit of 0.036 EU ml⁻¹ (endotoxin units per millilitre of platelet rich plasma). This corresponds to 3 pg ml⁻¹ of the endotoxin standard used in this study.

Haemodynamic measurements included heart rate, arterial pressure, CVP, pulmonary artery pressure, PAOP and cardiac output using an arterial and pulmonary artery catheter. Cardiac output was measured by the thermodilution method using room temperature injectate. The mean of four measurements was calculated. Cardiac index (CI) was calculated from cardiac output: CI = cardiac output/total body area.

Oxygen consumption ($V_{O2}$) was measured continuously by respiratory gas analysis with an open circuit indirect calorimeter (Deltatrac, Datex Instrumentarium, Helsinki, Finland) as long as the patient was undergoing artificial ventilation. This metabolic monitor has been validated previously and described in detail. $F_{O2}$ was always less than 50%. Minute volume and $F_{O2}$ remained constant for 60 min before measurements were obtained. Calibrations were made before starting, after transport of the patient and instrument to the ICU and at 8-h intervals thereafter. A meticulous check on gas leakage was made; minute volume, as measured by the ventilator and the calorimeter, was checked routinely. Care was taken that the patient was sedated adequately and shivering was prevented. The Deltatrac calorimeter averages $V_{O2}$ measurements over a period of 1 min, and the mean of at least five measurements was taken. These values were also compared with the continuously printed values to exclude short-term variability. Values of $V_{O2}$ were adjusted for total body area (ml min⁻¹ m⁻²).

Hypermetabolic response was assessed by the postoperative increase in oxygen consumption from baseline ($ΔV_{O2}$). Oxygen supply was calculated according to the following equation: oxygen supply = CI × (1.39 × haemoglobin (g dl⁻¹) × arterial oxygen saturation + 0.0031 × $Pa_{O2}$).

### DATA ANALYSIS

Statistical analysis was performed using Statview SE+ Graphics computer software (Abacus concepts, Berkeley, CA, USA). Data are presented as mean (SEM). Individual measurements were compared between groups using a two-tailed Student’s t test for unpaired observations and serial measurements between groups with a two-way analysis of variance (ANOVA) with a design for repeated measures. For single measurements of special interest in a series, Bonferroni’s correction for repeated measures was made. To quantify the amount of endotoxin in the systemic circulation during operation between groups, the area under the curve (AUC) was calculated for the concentration–time curve. To correct for differences in the duration of CPB, AUC was divided by total time.

In the analysis of $ΔV_{O2}$, measurement of $ΔV_{O2}$ 2 h after admission to the ICU was of special interest, as this value was related to the inflammatory response to endotoxaemia. The time pattern of $ΔV_{O2}$ in the ketanserin group was different from that in the placebo group, making a two-way ANOVA for repeated measures inappropriate. We therefore compared mean postoperative $ΔV_{O2}$ (AUC from 30 min to 8 h after ICU admission) between groups.

Regression analysis was performed in the entire group of patients (ketanserin and placebo) to investigate if variables, other than ketanserin, could explain the remaining variability of $ET_{ICU}$ and $ΔV_{O2}$. A two-sided $P$ value of less than 0.05 was considered statistically significant.

### Results

We studied a total of 31 consecutive male patients undergoing CPB for elective coronary artery bypass grafting. Study medication was stopped prematurely in two patients (one in each group) because of severe bleeding and myocardial ischaemia before the onset of CPB. These patients were excluded from the study before unblinding and analysis. In total, 14 patients were treated with ketanserin and 15 patients received placebo. In one placebo patient, the endotoxin results could not be measured for technical reasons. All other data were evaluated.

There were no significant differences in patient characteristics, preoperative myocardial function, surgical characteristics (table 1) or baseline haemodynamics (table 2). All patients were discharged from the ICU on the first day after operation and all survived. Re-operation for postoperative bleeding was necessary once in each treatment group. In the ketanserin group, two patients had peroperative myocardial infarction as a result of incomplete revascularization.

### COMPARISON OF ENDOTOXIN CONCENTRATIONS

Circulating endotoxin, analysed using two-way analysis of variance for repeated measures with all measurements included, was lower in patients treated with ketanserin than in placebo patients ($P=0.04$). There was no significant group–time interaction ($P>0.5$) (fig. 1). In nine of 14 patients in the placebo group, and in two of 14 patients in the ketanserin group, endotoxin concentration was positive 10 min after the start of CPB compared with baseline ($P<0.05$). At the end of CPB, endotoxin concentration was positive in 12 of 14 patients in the placebo group and in eight of 14 in the ketanserin group (ns). The mean concentration of circulating endotoxin during operation ($AUC/time$) was 0.130

### Table 1 Patient data (mean (SEM or range) or number)

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Ketanserin group</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>61.1 (49–74)</td>
<td>69.6 (47–73)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>9.9 (0.89)</td>
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</tr>
<tr>
<td>Long-acting vasodilators (n)</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>70 (5.5)</td>
<td>80 (6.6)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>110 (7)</td>
<td>119 (10)</td>
</tr>
<tr>
<td>No of distal anastomoses (median range)</td>
<td>4 (2–6)</td>
<td>4 (1–7)</td>
</tr>
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</table>
EU ml⁻¹ in the ketanserin group and 0.193 EU ml⁻¹ in the placebo group, indicating a 33% reduction in endotoxaemia during operation in patients treated with ketanserin (P = 0.03). The concentration of circulating endotoxin on admission to the ICU was 0.199 EU ml⁻¹ in the ketanserin group and 0.314 EU ml⁻¹ in the placebo group (P = 0.05).

The mean concentration of endotoxin in the prime fluid was 0.123 (0.039) EU ml⁻¹ in the ketanserin group and 0.078 (0.032) EU ml⁻¹ in the placebo group (ns).

### COMPARISON OF OXYGEN CONSUMPTION AND OTHER CLINICAL VARIABLES

Δ\(\dot{V}_O_2\) 2 h after admission to the ICU was significantly lower in patients treated with ketanserin than in placebo patients (P < 0.001). Postoperative Δ\(\dot{V}_O_2\) (AUC) was 44% lower in the ketanserin group than in the placebo group (P = 0.03) (fig. 2).

Mean arterial pressure was lower in the ketanserin than in the placebo group (P = 0.04 with two-way ANOVA for repeated measures); the group–time interaction was not significant (P = 0.5) (table 2).

There was no significant difference in the other haemodynamic variables; oxygen supply (table 2), use of dopamine and postoperative concentrations of lactate. Blood loss and the use of blood products were not significantly different between groups. Fluid balance during surgery was not different between groups, but there was a trend towards a more positive fluid balance in the ICU in the ketanserin group. This difference started 4 h after admission to the ICU and coincided with increased administration of fluids to patients treated with ketanserin in the period from 4 to 18 h after ICU admission (P = 0.03).

Times for tracheal extubation and discharge from the ICU were not significantly different between groups (table 3).

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**Table 2** Mean (SEM) haemodynamic measurements and oxygen delivery in the placebo (P) and ketanserin (K) groups. HR = heart rate, MAP = mean arterial pressure (mm Hg), CVP = central venous pressure (mm Hg), POAP = pulmonary artery occlusion pressure (mm Hg), CI = cardiac index (1 litre⁻¹ min⁻¹ m⁻²), Do2I = oxygen delivery (ml min⁻¹ m⁻²), SVRI = systemic vascular resistance (dyn s cm⁻⁵ m²).

*Significant difference between groups (two-factor ANOVA for repeated measures)

<table>
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<tr>
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<th>Baseline</th>
<th>30 min after CPB</th>
<th>30 min ICU</th>
<th>2 h ICU</th>
<th>4 h ICU</th>
<th>8 h ICU</th>
<th>18 h ICU</th>
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<td>HR P</td>
<td>58 (2.9)</td>
<td>88 (5.2)</td>
<td>84 (5.5)</td>
<td>85 (5)</td>
<td>82 (3.6)</td>
<td>89 (3.6)</td>
<td>87 (3)</td>
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<td></td>
<td>K 63 (3)</td>
<td>92 (4.5)</td>
<td>92 (6.5)</td>
<td>86 (4)</td>
<td>85 (3.3)</td>
<td>85 (3.3)</td>
<td>82 (3)</td>
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<td>MAP*</td>
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<td>P 74 (3.0)</td>
<td>81 (3.8)</td>
<td>80 (3.3)</td>
<td>79 (4.1)</td>
<td>73 (2.5)</td>
<td>72 (1.6)</td>
<td>79 (2.4)</td>
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<tr>
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<td>75 (2.6)</td>
<td>74 (3.3)</td>
<td>72 (2.1)</td>
<td>70 (2.0)</td>
<td>68 (2.1)</td>
<td>74 (1.7)</td>
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<tr>
<td>CVP</td>
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<tr>
<td>K 9.8 (0.5)</td>
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<td>Do2I</td>
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<td>202 (9.3)</td>
<td>225 (12)</td>
<td>208 (10)</td>
<td>228 (11)</td>
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<td>K 184 (9.1)</td>
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<td>219 (16)</td>
<td>200 (13)</td>
<td>228 (6)</td>
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<td>SVRI</td>
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<td>1625 (117)</td>
<td>1592 (123)</td>
<td>1594 (94)</td>
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<td>1369 (131)</td>
<td>1304 (94)</td>
<td>1218 (89)</td>
<td>1384 (47)</td>
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**Figure 1** Plasma concentrations of endotoxin (mean, SEM) vs time for patients who received ketanserin (●) or placebo (▲) at the following times: baseline (after induction of anaesthesia and insertion of the pulmonary artery catheter) (1); 10 min after the start of CPB (2) and after termination of CPB (3); and in the ICU (30 min (4), 2 h (5) and 18 h (6) after admission). Circulating endotoxin (ANOVA) was significantly lower in ketanserin patients (P = 0.04).

**Figure 2** Increase in oxygen consumption (Δ\(\dot{V}_O_2\)) from baseline (B) (mean, SEM) for the ketanserin (●) and placebo (▲) groups 30 min and 2, 4, 8 and 18 h after admission to the ICU. Postoperative Δ\(\dot{V}_O_2\) (AUC) was significantly lower in ketanserin patients (P = 0.03).
Endotoxins and postoperative hypermetabolism in CPB

RELATION OF CIRCULATING ENDOTOXIN WITH OTHER VARIABLES

To investigate if haemodynamic variables could explain the variability of ETICU, these variables were used in a simple regression analysis, and then the significant factors were entered in a forward stepwise regression analysis. Baseline CVP, baseline PAOP and fluid balance during operation were significantly associated with ETICU ($P < 0.05$). Of these, the relation between baseline CVP and ETICU was the most significant (fig. 3).

In the forward stepwise regression analysis, baseline CVP was entered first, fluid balance during operation and ketanserin treatment were entered next, and baseline PAOP was entered in the fourth step. After entering PAOP, CVP was removed from the model yielding a better fit after the other variables were entered. CVP and PAOP were interrelated. The final model is presented in table 4. ETICU was higher in patients with low baseline filling pressures, with a less positive fluid balance during operation in the placebo group. ETICU was not related to baseline CI or to duration of CPB. Endotoxin concentration 10 min after the start of CPB was not related to ET prime.

RELATION OF $\Delta V_{O_2}$ WITH OTHER VARIABLES

Apart from ketanserin, $\Delta V_{O_2}$ was related to ETICU. $\Delta V_{O_2}$ was not related to systemic oxygen supply, systemic vascular resistance, use of dopamine or concurrent temperature.

**Discussion**

We have found that i.v. administration of ketanserin may reduce the degree of endotoxemia during low-risk coronary bypass surgery, but does not prevent it. Ketanserin appeared to be more protective early after the onset of CPB than at the end. After the onset of CPB, tissue perfusion may decrease as a result of acute changes in vascular volume caused by haemodilution with a decrease in oncotic pressure, induction of hypothermia, extracorporeal circulation with non-pulsatile flow, and release of vasoactive substances such as angiotensin and noradrenaline.

Splanchnic vasoconstriction is one of the physiological compensation mechanisms maintaining blood flow to the heart and brain during such acute changes. However, subsequent splanchnic hyperperfusion may result in a loss of gut barrier function for intraluminal endotoxin and a decreased ability of the reticuloendothelial system to detoxify the permeated endotoxin.

The most plausible mechanism by which ketanserin reduces endotoxemia is thought to be related to inhibition of vasoconstriction. This may lead to improvement in the microcirculation and cardiac performance. However, this conclusion cannot be deduced directly from this study, as the splanchnic microcirculation was not measured. Nevertheless, our data give some indication. Patients with low baseline filling pressures and a less positive fluid balance during surgery had higher circulating endotoxin concentrations. The splanchnic vasoconstrictive response is thought to be more pronounced in patients with low vascular filling. While baseline filling pressures and fluid balance during operation were not significantly different between groups, ketanserin may have mitigated this response. That baseline filling pressures are important for ETICU and not baseline CI might be explained as follows. The major increase in circulating endotoxin occurred during CPB when the patient’s heart is excluded from the circulation and the heart–lung machine provides circulation, with pump flow standardized according to body surface area. Therefore, vascular filling and pump flow are the important determinants of circulation during CPB, and CI is irrelevant. After CPB, there was a trend towards a higher CI in the

**Table 4** Determinants of the concentration of circulating endotoxin on the patient’s admission to the ICU. The concentration of circulating endotoxin on ICU admission (ETICU (EU ml$^{-1}$)) can be expressed as a function of ketanserin treatment ($1$ = yes, $2$ = no), fluid balance during operation (ml) and pulmonary artery occlusion pressure at baseline (mm Hg) in the following equation: $\text{ETICU} = 0.8 - 0.01$ (ketanserin treatment) $-(\text{PAWP}_{\text{baseline}})-0.067$ (fluid balance$_{\text{operation}}$). The $F$ value describes the strength of the relation. $F \geq 4$ is considered statistically significant.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient</th>
<th>SEM</th>
<th>$F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>0.8</td>
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<td></td>
</tr>
<tr>
<td>Ketanserin treatment</td>
<td>-0.1</td>
<td>0.031</td>
<td>5.7</td>
</tr>
<tr>
<td>PAOP$_{\text{baseline}}$</td>
<td>-0.027</td>
<td>0.0061</td>
<td>19.6</td>
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<tr>
<td>Fluid balance$_{\text{operation}}$</td>
<td>-0.067</td>
<td>0.016</td>
<td>16.4</td>
</tr>
</tbody>
</table>

$F=0.78, r^2$ (adj) 0.57, $F$ test of the model 12.7, $P < 0.01$
ketanserin group. This higher CI might also have contributed to a lower ETICU in patients treated with ketanserin, but may also have been an effect. Although our study design was not appropriate to explain the mechanism by which ketanserin reduced endotoxaemia, a combined strategy to reduce endotoxaemia may be advised. This strategy should aim at inhibition of vasoconstriction by the use of ketanserin and expansion of intravascular volume before, during and after CPB in the period that the patient is at risk for splanchnic vasoconstriction.

At the end of CPB, ketanserin appeared to be less effective. This might be attributed to the fact that maintenance of normovolaemia was not a goal of treatment during cardiopulmonary bypass. In addition, the use of the large prime fluid causing hypo-oncotic haemodilution may also have contributed to endotoxaemia. At the end of CPB, other factors may also affect permeation of endotoxin into the systemic circulation, such as reperfusion of the ischaemic myocardium inducing distant tissue damage by circulating toxic mediators. These might impair gut barrier function or detoxification of the permeated endotoxin by the RES, or both.

From the results of this study it also appears that treatment with i.v. ketanserin during low-risk coronary bypass surgery reduces ΔV0₂. In our study there was no evidence for a supply-limited V0₂ in patients treated with ketanserin, as oxygen supply and lactate concentrations were not significantly different between groups. However, both ketanserin treatment and ETICU were associated with ΔV0₂. The effect of ketanserin on ΔV0₂ was probably related to its effect on endotoxaemia, but might also be the result of better tissue perfusion during operation with less depletion of cellular energy stores. The reduction in ΔV0₂ during treatment with ketanserin might be especially beneficial in patients with poor myocardial function, as the lower oxygen demand without impairment of myocardial performance improves oxygen balance.

All patients were discharged from the ICU on the first day after operation. However, there was a trend towards a longer duration of ventilatory support in the ketanserin patients. This effect coincided with administration of more fluids later in the ICU. In this study, ketanserin was administered in a standard dose until 18 h after operation, far beyond the period that the patient is at risk of compensatory vasoconstriction. After a longer infusion time, the α₁-adrenergic block effect of ketanserin increases and this may explain the lower arterial pressure and administration of more fluids later in the ICU. It has been shown that ketanserin decreases the lower limit of autoregulation in the kidneys, sufficient organ perfusion is likely to be guaranteed at a lower arterial pressure while ketanserin is administered. Titration of ketanserin dose should preferably be based on circulation, and administration of ketanserin can generally be discontinued when the circulation has become stable.

From the preliminary results of this clinical study, we conclude that treatment with i.v. ketanserin, an inhibitor of vasoconstriction, may reduce the degree of endotoxaemia and postoperative hypermetabolism, but does not prevent their occurrence. Low vascular filling was also associated with endotoxaemia. Prevention of endotoxaemia is likely to require a combined strategy aiming at inhibition of vasoconstriction before and during operation using ketanserin and expansion of intravascular volume.

Acknowledgements

This study was performed in the University Hospital “Vrije Universiteit”, Amsterdam, and supported financially by Janssen Cilag BV ( Tilburg, The Netherlands).

References


British Journal of Anaesthesis
Endotoxaemia and postoperative hypermetabolism in CPB