Continuous $S$-$(+)$-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass

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Editor’s key points

- Cardiopulmonary bypass is known to be associated with the release of pro-inflammatory cytokines.
- The effect of continuous infusion of $S$-$(+)$-ketamine was studied in attenuating this response.
- Pro-inflammatory cytokines were lower in the Ketamine group and anti-inflammatory cytokines higher.
- The study adds to growing evidence of anti-inflammatory potential of ketamine.

Background. Coronary artery bypass surgery (CABG) with cardiopulmonary bypass (CPB) leads to elevated circulating plasma cytokines. In this prospective randomized study, the effect of an $S$-$(+)$-ketamine-based anaesthetic protocol on perioperative plasma cytokine levels was compared with standard anaesthesia with propofol and sufentanil during CPB.

Methods. Patients undergoing elective on-pump CABG were randomly allocated to anaesthesia with sufentanil–propofol–midazolam (Sufentanil) or $S$-$(+)$-ketamine–propofol–midazolam (Ketamine). Blood samples were obtained before induction of anaesthesia (baseline) and also at 1, 6, and 24 h after aortic unclamping. Plasma levels of the interleukins (IL)-6, IL-8, IL-10, and tumour necrosis factor (TNF)-alpha were determined by enzyme-linked immunosorbent assay.

Results. One hundred and twenty-eight patients were studied (Ketamine: $n=60$; Sufentanil: $n=68$). All measured cytokines increased during and after CPB. However, the increase in the pro-inflammatory cytokines IL-6 and IL-8 6 h after aortic unclamping was significantly lower in the Ketamine group compared with the Sufentanil group [mean (SD): IL-6 56.75 (46.28) pg ml$^{-1}$ (Ketamine) vs 172.64 (149.93) pg ml$^{-1}$ (Sufentanil), $P<0.01$; IL-8 7.74 (14.72) pg ml$^{-1}$ (Ketamine) vs 26.3 (47.12) pg ml$^{-1}$ (Sufentanil), $P<0.01$]. In contrast, the anti-inflammatory cytokine IL-10 showed higher levels 1 h after unclamping in the Ketamine group compared with the Sufentanil group [mean (SD): 69.59 (78.78) vs 24.63 (37.7) pg ml$^{-1}$, $P<0.001$].

Conclusion. Our data demonstrate that $S$-$(+)$-ketamine possesses anti-inflammatory potential. Anaesthesia with $S$-$(+)$-ketamine may have beneficial effects in attenuating the CPB-induced systemic inflammatory response.

Keywords: anaesthetics i.v., ketamine; cardiovascular anaesthesia; immune response; surgery, cardiovascular

During cardiac surgery, cardiopulmonary bypass (CPB) contributes to the secretion of pro-inflammatory and anti-inflammatory cytokines which mediate the inflammatory response observed during and after open-heart surgery. The triggering factors include surgical trauma, endotoxaemia, and the contact of blood with non-biologic tubing surfaces, all of which induce activation of the transcription factor nuclear factor (NF)-κB. Interleukins (IL), released in response to NF-κB activation, such as IL-6, IL-8, IL-10, and tumour necrosis factor-alpha (TNF-α), are established markers of the magnitude of the systemic inflammation after CPB. $^3$

Ketamine possesses several anti-inflammatory properties. It reduces neutrophil integrin expression, $^2$ $^3$ and leucocyte–endothelial interaction, $^2$ $^4$ and also inhibits monocyte $^5$ and macrophage function. $^6$ Ketamine attenuates the in vitro synthesis of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-8 $^7$.
and IL-8 in stimulated macrophages and whole blood. Ketamine also reduces the production of these cytokines during sepsis in rodents and mammals. However, the clinical relevance of these observations has not been fully investigated yet.

Recently, we have demonstrated that in cardiac surgery, the application of ketamine as the sole analgesic neither aggravates the postoperative myocardial damage nor does it alter haemodynamics significantly. Therefore, the use of ketamine as an immunomodulator during cardiac anaesthesia may be of clinical interest, in particular since previous studies suggest beneficial effects on immune cells and cytokine release.

Previous studies investigating the effect of i.v. ketamine on the cytokine response in cardiac surgery have either used ketamine in subanaesthetic doses or as a supplement to conventional anaesthesia with opioids and volatile anaesthetics. It therefore remains unclear whether the effects observed are related exclusively to ketamine or whether interaction with opioids and sedatives might have had an effect. In this study, ketamine was used as the sole analgesic in patients undergoing elective coronary artery bypass grafting (CABG). The aim of the study was to establish if a ketamine-based anaesthetic regimen in comparison with sufentanil indeed reduces markers of inflammation in elective cardiac surgery. We also hypothesized that compared with a single bolus application, an additional continuous infusion of ketamine as maintenance during surgery would have a greater effect in reducing markers of inflammation without increasing the incidence of haemodynamic instability.

**Methods**

After approval by the local Ethics Committee and written informed consent, 142 patients (Fig. 1) undergoing elective CABG with CPB were screened. Exclusion criteria were creatine kinase (CK) levels >170 U litre⁻¹ in the preoperative routine blood results, repeat cardiac surgery and combined operations, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase >150 U litre⁻¹), renal...
impairment (creatinine concentration >132 μmol litre⁻¹), immunosuppressive medication (e.g. glucocorticoids) or immunodeficiency syndromes, and neurologic or psychiatric disorders. Patients with a C-reactive protein (CRP) >16 mg litre⁻¹, an IL-6 level >24 pg ml⁻¹ on the morning of surgery, or both were also excluded from the study.

Patients were scored according to EuroSCORE.16 Preoper-ative cardiac medication was continued until the morning of surgery. All patients received as standard premedication of flunitrazepam 2 mg per os and morphine 30 mg subcutaneously 30 min before anaesthesia.

Using a computer-generated random code, patients were randomly allocated to two anaesthetic protocols, not blinded to the responsible anaesthetists. Anaesthetic regimen differed by using sufentanil in the control group and S-(+)-ketamine in the treatment group as an analgesic agent. In the sufentanil–propofol–midazolam group (Sufentanil), anaesthesia was induced by i.v. bolus of sufentanil 0.25–1.0 μg kg⁻¹, midazolam 0.05 mg kg⁻¹, and pancuronium 0.1 mg kg⁻¹. For maintenance, a continuous infusion of propofol with 3–5 mg kg⁻¹ h⁻¹ and sufentanil with 0.5–2 μg kg⁻¹ h⁻¹ was administered. In the S-(+)-ketamine–propofol–midazolam group (ketamine), anaesthesia was induced by i.v. bolus of S-(+)-ketamine 1–3 mg kg⁻¹, midazolam 0.05 mg kg⁻¹, propofol 0.5–3 mg kg⁻¹, and pancuronium 0.1 mg kg⁻¹. For maintenance, a continuous infusion of propofol with 3–5 mg kg⁻¹ h⁻¹ and S-(+)-ketamine with 2–4 mg kg⁻¹ h⁻¹ was administered. Complete muscle relaxation with pancuronium was maintained until the end of surgery. In all patients, bispectral index monitoring (BIS A2000 system, Aspect Medical Systems, Leiden, The Netherlands) was used to maintain a BIS value of <60 by adaptations of propofol infusion rate and additional midazolam dosing.

During induction of anaesthesia, laryngoscopy, skin incision, sternotomy, and cannulation of the aorta, respectively, special attention was paid to keep systolic arterial pressure and heart rate (HR) within 20% from baseline.

Monitoring before induction of anaesthesia included a five-lead ECG and pulse oximetry. An arterial line, a foley catheter, temperature probes, capnography, and a pulmonary artery catheter were placed before tracheal intubation. Continuous readings of HR, systemic and pulmonary arterial pressures [systolic, diastolic and mean (MAP)], and central venous pressure (CVP) were recorded using a Siemens Sirecust monitoring system (Siemens, Erlangen, Germany). For haemodynamic management, cardiac output was measured by thermodilution, and CVP and the pulmonary capillary wedge pressure were taken as average over the respiratory cycle. Cardiac index, systemic vascular resistance index, and pulmonary vascular resistance index were calculated using standard formulae.

Routine surgical technique and cardioprotective strategies were used in all patients according to the surgeon’s preference. Patients had a median sternotomy with harvesting of saphenous veins and internal thoracic arteries as conduits. CPB was performed in a standardized fashion as described previously by our group.12 Patients were separated from CPB when conditions were appropriate. Weaning from CPB followed a standardized protocol, including optimization of filling pressures and haemodynamics by use of volume and vasoactive drugs according to requirements. Glycerol trinitrate (0.5–1.0 μg kg⁻¹ min⁻¹) was started when deemed clinically necessary by either the cardiac surgeon or the anaesthetist. To maintain blood glucose between 4.4 and 8 mmol litre⁻¹, insulin was administered as needed. After surgery, patients were transferred to the intensive care unit, and weaned from ventilation when haemodynamically stable and re-warmed. None of the physicians caring for the patient during and after the operation was involved in the study.

Blood samples for determination of IL-6, IL-8, TNF-α, TNF receptor 1 (TNF RI), the proapoptotic protein-soluble FAS (sFAS), and IL-10 were obtained from the indwelling arterial line before induction of anaesthesia (baseline), and 1, 6, and 24 h after aortic unclamping. All samples were immediately centrifuged for 10 min at 3000g, and stored at −20°C until further analysis.

Plasma concentrations of IL-6, IL-8, IL-10, and TNF-α were determined using commercially available sandwich enzyme immunoassay sets (Cytosets, Biosource, CA, USA). Plasma levels of TNF RI and sFAS were determined using BD OptEIA sets (BD Biosciences, CA, USA). All assays were performed according to the manufacturer’s instruction.

The sample sizes for the study were calculated with BiAS for Windows based on IL-6 concentration 6 h after aortic unclamping as the primary outcome variable. On the basis of previous studies,15 a difference of ≥100 μg litre⁻¹ between treatment groups was anticipated to reveal statistical significance. For a power of 0.8 and an α of 0.05, a sample size of 50 patients in each group was calculated to be appropriate. We increased the sample size by 16% to compensate for possible loss of power, resulting in a total number of 59 patients per group. The sample size was based on the assumption of normal distribution and homogeneity of variances. Statistical analyses were performed using R for Windows Version 2.8.0. The Shapiro–Wilk test served to assess normal distribution. For all data with normal distribution, repeated-measure analysis of variance was performed with the level of significance being adjusted using the Greenhouse–Geisser–Epsilon method. Data are expressed as mean (SD) or median (range). For those data which were not normally distributed, medians were compared using the non-parametric Mann–Whitney U-test, and the results were displayed as box plots. For categorical data, χ² analysis was used. P<0.05 was considered significant. All P-values were two-tailed.

Results

A total of 128 patients were studied (Fig. 1). 68 in the sufentanil–propofol–midazolam group (Sufentanil) and 60 in the S-(+)-ketamine–propofol–midazolam group (Ketamine). Patients did not differ with regard to biometric data, preoperative medical diagnoses, Euro-SCORE, and preoperative long-term medication (Table 1). There were no significant
differences between the groups with regard to their preoperative cardiac and coronary characteristics (left ventricular end-diastolic pressure, New York Heart Association class, coronary artery disease anatomy and pathology, history of myocardial infarction, and preoperative intra-aortic balloon pump usage), intraoperative treatment (Table 2), and also postoperative troponin T values and 28 day mortality (Table 2).

There were no statistically significant differences in the total dose of anaesthetics used between both groups, although there was a trend towards higher propofol ($P=0.063$) and midazolam ($P=0.078$) use in the Ketamine group (Table 3).

Postoperative IL-6, IL-8, and IL-10 plasma levels were found to be increased from baseline in both groups. However, we observed a significantly diminished postoperative increase in pro-inflammatory cytokines such as IL-6 and IL-8 in the Ketamine group compared with the Sufentanil group (Figs 2 and 3). In addition, patients of the Ketamine group showed significantly higher plasma levels of the anti-inflammatory cytokine IL-10 1 h after opening the aortic cross-clamp (Fig. 4).

There were no statistically significant differences in the parameters between the groups regarding pre- and postoperative plasma levels of TNF-α (Supplementary material), TNF RI (data not shown), and sFAS (data not shown). For TNF-α, only a non-significant trend towards lower levels in the Ketamine group was observed ($P=0.068$).

We also did not find any differences between the groups for preoperative CRP [Sufentanil vs Ketamine, mean (so): 5.47 (2.29) vs 5.07 (2.48) mg litre$^{-1}$, $P=0.042$] and leucocyte count [Sufentanil vs Ketamine, mean (so): 7.39 (1.94) vs 7.43 (2.29) mg litre$^{-1}$, $P=0.547$] and also 24 h postoperative CRP [Sufentanil vs Ketamine, mean (so): 102 (51) vs 102 (65.6) mg litre$^{-1}$, $P=0.299$] and leucocyte count [Sufentanil vs Ketamine, mean (so): 12.2 (3.08) vs 11.3 (2.95) mg litre$^{-1}$, $P=0.735$].

Haemodynamic data, including HR, cardiac output, mean systemic and pulmonary artery pressure, systemic and pulmonary vascular resistance, and CVP, were comparable in both groups at all time points (Supplementary material).

**Discussion**

Our results demonstrate that ketamine used as the sole analgesic during open-heart surgery reduces the inflammatory cytokine response associated with extracorporeal circulation. Furthermore, ketamine may also be able to enhance the production of anti-inflammatory cytokines after major surgery, as was suggested by the significantly higher plasma concentrations of IL-10 at the end of surgery compared with sufentanil-based analgesia.

Ketamine in subanaesthetic doses was shown to have beneficial effects on the immune response during and after

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**Table 1** Patient characteristics. Data are presented as mean (range) for age, mean (so), median (range), and as absolute numbers, respectively. BMI, body mass index; EF, ejection fraction; DM, diabetes mellitus; HTN, arterial hypertension; COPD, chronic obstructive pulmonary disease; HLP, high lipoproteins; ACE, angiotensin-converting enzyme; Ca, calcium channel

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Sufentanil (n=68)</th>
<th>S-(+)-ketamine (n=60)</th>
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<td>66 (62–71)</td>
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<td>84 (13)</td>
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**Table 2** Intraoperative data, postoperative cardiac enzymes, and 28 day mortality. Data are presented as mean (so), median (range), and as absolute numbers, respectively. AoX, aortic cross-clamp; CPB, cardiopulmonary bypass; IMA, internal mammary artery; NPP, number per patient; NOP, number of patients; IABP, intra-aortic balloon pump; GTN, glyceryl trinitrate; PRBC, packed red blood cells; FFP, fresh-frozen plasma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Sufentanil (n=68)</th>
<th>S-(+)-ketamine (n=60)</th>
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<tr>
<td>Intraoperative data</td>
<td></td>
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<tr>
<td>Anaesthesia; duration</td>
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<td>271 (37)</td>
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</tr>
<tr>
<td>Surgery; duration</td>
<td>min</td>
<td>235 (60)</td>
<td>236 (59)</td>
</tr>
<tr>
<td>AoX; duration</td>
<td>min</td>
<td>75 (23)</td>
<td>74 (21)</td>
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<tr>
<td>CPB; duration</td>
<td>min</td>
<td>122 (40)</td>
<td>126 (37)</td>
</tr>
<tr>
<td>IMA; NPP</td>
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<td>Buckberg; NOP</td>
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<td>Bretschneider; NOP</td>
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<td>GTN post-CPB</td>
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<td>25</td>
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<td>13</td>
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<td>1530 (360)</td>
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<tr>
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<td>480 (160)</td>
<td>373 (116)</td>
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<td>1 (0–6)</td>
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<td>FFP; units</td>
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<td>0 (0–6)</td>
<td>0 (0–5)</td>
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<td>Cardiac enzymes 24 h after operation</td>
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<td></td>
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<tr>
<td>Troponin T</td>
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<td>0.55 (0.41)</td>
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<tr>
<td>Creatine kinase-MB</td>
<td>U litre$^{-1}$</td>
<td>60 (55)</td>
<td>40 (31)</td>
</tr>
<tr>
<td>28 day mortality</td>
<td>Number of patients</td>
<td>0</td>
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A recent study has shown that low-dose ketamine (0.5 mg kg\(^{-1}\)) administered at the time of induction of general anaesthesia decreases peak CRP concentrations after cardiac surgery more effectively than the dose of 0.25 mg kg\(^{-1}\). Both doses were effective in decreasing the level of inflammatory cytokine response. However, since in these studies, ketamine was used as an adjunct to fentanyl-based anaesthesia, fentanyl-mediated effects, particularly on natural killer cells as part of the adaptive immune response, cannot be excluded. We therefore studied plasma levels of inflammatory markers with an anaesthetic regimen based on ketamine as the sole analgesic.

The cytokine response in patients undergoing cardiac surgery is well described and is dominated by the pro-inflammatory cytokines TNF-\(\alpha\), IL-6, IL-8, and the anti-inflammatory cytokine IL-10. In contrast to other studies, we could not observe a significant increase in TNF-\(\alpha\) production during cardiac surgery. Ketamine plasma concentrations of 50 \(\mu\)M and more have been described after bolus injection of 2.0–2.2 mg kg\(^{-1}\) body weight,\(^{14-17}\) which is equivalent to the dose applied during induction in our investigation. However, animal studies indicate that higher
ketamine doses may be required to significantly suppress TNF-$\alpha$ production.\textsuperscript{19}

Soluble TNF-$\alpha$ receptor (sTNFRI) is a 55 kDa protein, which is released from membrane-bound TNF-$\alpha$ receptors expressed on monocytes, neutrophils, and endothelial cells. It acts as specific antagonist of TNF-$\alpha$ and limits its deleterious effects.\textsuperscript{20} Anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist are able to activate and promote sTNFRI action.\textsuperscript{21} Only a few studies have demonstrated a relationship between sTNFRI concentration and severity of the systemic inflammatory response after on-pump cardiac surgery.\textsuperscript{22, 23} In acute myocardial ischaemia, TNF-$\alpha$ plays a causative role in subsequent myocardial damage, while sTNFRI is able to attenuate the response to ischaemia and reperfusion (I/R) as shown by a reduction of the infarcted area in rats treated with sTNFRI plasmids.\textsuperscript{24} We could not detect any differences in TNF-$\alpha$ or TNFRI plasma levels in patients treated with ketamine or sufentanil, respectively, indicating that there might be a comparable degree of I/R injury in both groups. This concept is supported by previous work from our group demonstrating that ketamine is safe to give in cardiac surgery and does not increase myocardial damage.\textsuperscript{12}

Interestingly, in our study, we could not only demonstrate lower levels of pro-inflammatory cytokines during and after coronary bypass, we also found higher levels of IL-10 at the end of surgery in patients receiving ketamine-based anaesthesia. IL-10 is a potent anti-inflammatory cytokine produced by monocytes and macrophages which inhibits the production of pro-inflammatory cytokines such as IL-6 and IL-8\textsuperscript{15} and enhances the release of soluble TNF RI and RII. IL-10 also provides protection from I/R injury by reducing endothelial adherence of neutrophils and their subsequent transmigration into the reperfused tissue.\textsuperscript{26} Higher IL-10 concentrations after ketamine treatment may again indicate a favourable effect on I/R injury; however, further studies are required to substantiate this hypothesis. We did not observe a significant difference between troponin T and CK-MB as markers of myocardial damage by I/R injury. It remains to be investigated in further studies, whether higher IL-10 levels observed after ketamine application have a beneficial effect on the incidence of myocardial ischaemia or the extent of I/R injury.

In contrast to our results, on the first postoperative day, Bartoc and colleagues\textsuperscript{15} observed lower plasma levels of IL-10 after a bolus application of ketamine during induction of anaesthesia. The continuous application and the higher total dose administered in our study may help to explain the higher IL-10 concentrations seen in our study. The higher IL-10 concentrations observed at the end of surgery may indicate an enhanced release of anti-inflammatory mediators by ketamine. However, it is worth mentioning that this difference was not sustained during the postoperative period. We therefore suggest that the clinical implications of the cytokine changes observed after ketamine analgesia need to be fully elucidated in larger studies including outcome variables, complication rates, and off-pump procedures.

Induction and maintenance of anaesthesia with ketamine are not without risks. Owing to its sympathomimetic effects, ketamine may lead to hypertension and tachycardia. In order to blunt these side-effects, HRs and arterial pressures exceeding $\pm$20% of the baseline value were treated with antihypertensives or $\beta$-blockers as required. In a previous study, we have demonstrated that stable haemodynamics can be maintained during ketamine/propofol anaesthesia and that extensive myocardial damage as determined by troponin T and CK-MB levels could be avoided.\textsuperscript{12} Further side-effects of ketamine include its psychedelic action. Therefore, all patients in our study received propofol and midazolam in order to prevent ketamine-induced hallucinations.

Several studies have explored the influence of different anaesthetic regimens on the immune response during and after surgery, suggesting that propofol may have beneficial effects on post-traumatic immune changes. In addition, it has been demonstrated that the application of propofol may alleviate the cytokine response observed during septic shock in rodents.\textsuperscript{29} Similarly, midazolam also alters immune function, in particular neutrophil adherence and bacterial killing.\textsuperscript{31} However, in CABG surgery, cytokine response did not differ after volatile anaesthetics, propofol/sufentanil anaesthesia and midazolam/sufentanil anaesthesia.\textsuperscript{32} It remains unclear to which degree immunomodulative effects or propofol and midazolam or their interaction with ketamine may have influenced the results of our study.

Patients in both groups received 30 mg morphine ($=0.4–0.5$ mg kg$^{-1}$) subcutaneously 30 min before induction. Although immune-inhibitory properties of morphine have been well described, it remains unclear whether and to which degree morphine-induced immunoinhibition plays a role in clinical settings.\textsuperscript{8} Since patients in both groups received the same premedication, immunomodulatory effects of ketamine analgesia compared with sufentanil anaesthesia, we cannot attribute the observed differences to morphine effects. Furthermore, we demonstrated a typical increase in pro-inflammatory mediators such as IL8 and IL-6 in both groups. These results suggest that the small morphine dose applied in our study has not blunted the CPB-induced production of cytokines in any of the groups.

At present, it is not fully understood by which mechanisms ketamine exerts its anti-inflammatory properties. Previous studies indicate that ketamine influences cellular immunity, but also interferes with neurohumoral response mechanisms.\textsuperscript{33} It is therefore possible that in addition to direct anti-inflammatory effects, ketamine mediates its anti-inflammatory properties partly by indirect mechanisms. Low-dose ketamine (0.25 mg kg$^{-1}$) during induction of general anaesthesia influences cellular immunity as was shown by an attenuation of neutrophil superoxide production in CABG.\textsuperscript{13} Although it was reported that stereoselective differences between the ketamine enantiomers may not play a major role in ketamine-induced immunomodulation,\textsuperscript{34} in the isolated perfused guinea pig heart, S-(-)-ketamine was able to reduce neutrophil adherence to the coronary vasculature after ischaemia.\textsuperscript{35} This effect could be explained
by an attenuated expression of neutrophil surface molecules after ketamine treatment.  

Moreover, ketamine has been shown to inhibit transcription factors NF-κB and activator protein 1 (AP-1) in human blood neutrophils. These transcription factors regulate the transcription of genes encoding the production of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1, and IL-8. The inhibition of pro-inflammatory cytokines by ketamine has been demonstrated in LPS-treated whole blood and also in endotoxin-treated rats. It is therefore likely that the inhibition of transcription factors such as AP-1 and NF-κB represents a key mechanism by which ketamine attenuates the cytokine response observed in cardiac surgery.

In summary, our results suggest that ketamine used as a sole analgesic during coronary artery bypass grafting reduces the inflammatory cytokine response observed during and after CPB. Ketamine may also have additional beneficial effects on the production of anti-inflammatory mediators. It remains to be investigated whether ketamine displays similar effects in off-pump cardiac surgery. In addition, further studies powered for outcome are necessary to demonstrate the clinical relevance of ketamine-induced immunomodulation in cardiac surgery.

**Supplementary material**

Supplementary material is available at *British Journal of Anaesthesia* online.

**Conflict of interest**

None declared.

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