Comparison of S-(+)-ketamine- with sufentanil-based anaesthesia for elective coronary artery bypass graft surgery: effect on troponin T levels

C. Neuhausër, V. Preiss, M.-K. Feurer, M. Müller, S. Scholz, M. Kwapisz, M. Mogk and I. D. Welters*

Department of Anaesthesiology, Intensive Care Medicine and Pain Treatment, University Hospital Giessen and Marburg GmbH, Campus Giessen, Germany
*Corresponding author: School of Clinical Science, UCD, Duncan Building, Daubly Street, L69 3GA Liverpool, UK. E-mail: i.welters@liverpool.ac.uk

Background. S-(+)-ketamine anaesthesia carries potential benefits for the cardiovascularly compromised patient. However, the use of S-(+)-ketamine in ischaemic coronary artery disease is controversial. In a prospective, randomized, clinical trial, we have investigated whether an S-(+)-ketamine-based anaesthetic protocol leads to increased cardiac troponin T levels (cTnT) after coronary artery bypass grafting (CABG).

Methods. Two hundred and nine patients undergoing elective CABG were randomized to receive either i.v. anaesthesia with sufentanil–midazolam–propofol (SMP; n=108) or S-(+)-ketamine–midazolam–propofol (KMP; n=101). Haemodynamic variables were maintained within the normal range. Invasive haemodynamic monitoring was performed using a pulmonary artery catheter. Plasma cTnT levels were sampled before induction and 1, 6, and 24 h after aortic unclamping. Cardiovascular adverse events, such as electrocardiographic signs of ischaemia, perioperative myocardial infarction, and death, were recorded.

Results. Patient characteristics, cardiac profile, intraoperative management, and the incidence of cardiovascular adverse events were comparable between the groups. Plasma cTnT levels increased after operation in both groups. cTnT levels were significantly lower in the KMP group 6 h after aortic unclamping compared with the SMP group (\(P=0.004\)), but did not differ 24 h after aortic unclamping [median (range): SMP 0.4 (0.01–3.9) vs KMP 0.4 (0.07–6.6) \(\mu\text{g}\text{ litre}^{-1}\), \(P=0.338\)].

Conclusions. S-(+)-ketamine does not accentuate postoperative cTnT rises in haemodynamically stable elective CABG patients.

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The isomer S-(+)-ketamine offers certain advantages over racemic ketamine for anaesthetic use. Its analgesic effect is three to four times more potent than R-(−)-ketamine due to a higher affinity at the N-methyl-D-aspartate glutamate receptor.\(^1\) There is a quicker recovery due to a 35% higher clearance with a similar distribution volume, and it shows similar actions on cholinergic receptors, which may explain the lower incidence of psychomimetic side-effects.\(^1\) The cardiovascular actions seem to be comparable, as both, racemic ketamine and S-(+)-ketamine, stimulate rather than depress the circulatory system.\(^2\)\(^3\)

The use of ketamine has been advocated for anaesthesia in hypovolaemic or cardiovascularly compromised patients because of its sympathomimetic actions,\(^1\) but there are concerns that these effects may be harmful in patients with coronary artery disease (CAD). In patients with stenosed coronary arteries with limited blood flow, increases in myocardial oxygen demand caused by ketamine may not be met by appropriate increases in oxygen supply, which can result in myocardial injury. Owing to their sensitivity and specificity, troponins T and I have become the gold standard for diagnosis of myocardial cell necrosis after...
coronary ischaemia, and are widely used to detect perioperative cardiac damage.\textsuperscript{4–7} Data on troponin levels after ketamine anaesthesia are lacking. The clinical data on S(-)-ketamine include only four studies of patients with CAD.\textsuperscript{3 8–10}

The main objective of this study was to investigate whether an S(-)-ketamine-based anaesthetic puts coronary patients at additional risk of myocardial damage, as measured by higher postoperative cardiac troponin T (cTnT).

**Methods**

After approval by the local ethics committee and written informed consent, 219 patients undergoing elective coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) were enrolled in the study. Exclusion criteria included patients presenting with a preoperative creatine kinase (CK) level $>170$ U litre$^{-1}$, repeat surgery and combined operations, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase $>150$ U litre$^{-1}$), renal impairment (creatinine concentration $>132$ µmol litre$^{-1}$), and neurological and/or psychiatric disturbances. Patients were scored using EuroSCORE.\textsuperscript{11}

Preoperative cardiac medication was continued until the morning of surgery.

Using a computer-generated code, patients were randomly allocated to one of two anaesthetic protocols (Fig. 1), which was not blinded to the responsible anaesthetist. We chose a sufentanil–midazolam–propofol-based anaesthetic for the control group (SMP) and an S(-)-ketamine–midazolam–propofol-based anaesthetic for the treatment group (KMP). Complete muscle relaxation with pancuronium was maintained until the end of surgery.

Induction of anaesthesia was with the respective induction agents (see Fig. 1). During induction of anaesthesia, laryngoscopy, skin incision, sternotomy, and cannulation of the aorta, respectively, systolic arterial pressure (SAP) and heart rate (HR) were maintained within $\pm 20\%$ of baseline.

**Fig 1** Flow sheet: anaesthetic agents used for induction and maintenance of anaesthesia are given for each group. S(-)-ketamine, sufentanil, and propofol during surgery were given as continuous infusion. A total of 10 patients were excluded from analysis (see text). p.o., oral medication, s.c., subcutaneous; i.v., intravenous.
Haemodynamic changes during anaesthesia, such as tachycardia with a HR >100 beats min⁻¹, hypertension (SAP >160 mm Hg), and hypotension (SAP <100 mm Hg) were recorded and corrected as deemed clinically necessary by the anaesthetist. For this purpose, appropriate doses of anaesthetics (e.g. propofol, midazolam, sufentanil, and S-(+)-ketamine), cardiovascular drugs (e.g. metoprolol, nor-epinephrine, urapidil (an α-adrenoceptor blocker)), and infu-
sion of fluids (e.g. Ringer’s solution, hydroxyethylstarch 10%) were administered. Bradycardia was not corrected, unless associated with hypotension.

Monitoring included a five-lead ECG, pulse oximetry, arterial line, urinary catheter, temperature probe, capnogra-
phy, and a pulmonary artery catheter. Continuous measure-
ment of HR, systemic and pulmonary arterial pressures [systolic, diastolic, and mean (MAP)], and central venous pressure (CVP) was done using a Siemens Sirecust monitor-
ing system (Siemens, Erlangen, Germany). Thermodilution cardiac output was measured in triplicates by cold bolus injection and the mean was recorded. CVP and the pulmon-
ary capillary wedge pressure were taken as an average over the respiratory cycle. Cardiac index (CI), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI) were calculated according to standard formulae. In all patients, bispectral index monitoring (BIS A2000 system, Aspect Medical Systems, Leiden, The Netherlands) was used to maintain a BIS value <60 using propofol dosing. ST segment and T-wave in the ECG were continuously analysed during the whole study period. Minimum criteria for the diagnosis of new myocardial ischaemia included either 1 mm J point depression with horizontal down-sloping ST segment, 2 mm ST depression 80 ms after the J point with up-sloping ST segment, or 1 mm ST segment elevation. Intraoperative and postoperative events such as arrhythmias, the use of intra-aortic balloon pump (IABP), defibrillations, cardiopulmonary resuscitation (CPR), and death within the first 28 days after surgery were recorded. Serial 12-lead ECGs were obtained for each patient the day before surgery, on arrival at the ICU, and on the first postoperative day. The diagnosis of perioperative myocardial infarction (PMI) was confirmed by two blinded reviewers based on the presence of ECG changes such as new Q-waves of 40 ms duration or more, and/or a reduction in R waves of >25% in at least two consecutive leads, and a greater than eight-fold increase from normal in CK-MB and cTnT at 24 h after aortic unclamping.

Routine surgical technique and cardioprotective strategies were used in all patients according to the surgeon’s prefer-
ence. 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. 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. Insulin was administered as needed to maintain blood glucose between 4.4 and 8 mmol litre⁻¹. 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.

Haemodynamic measurements were taken before skin incision, during skin closure, and 6 h after surgery. Blood samples for cTnT determination 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 analysis. Serum enzyme activities were measured at 37°C.

Serum CK and CK-MB were determined as routine blood testing before surgery and on the morning of the first postoperative day. Plasma concentrations of cTnT were measured by an electrochemiluminescence immunoassay with an automated analyser (Roche Diagnostics, Mannheim, Germany). The lower limit of detection of the assay is 0.01 μg litre⁻¹, and the reference range is 0.01– 0.1 μg litre⁻¹. CK and CK-MB activity was determined photometrically (Bayer, Leverkusen, Germany). Reference levels were <170 U litre⁻¹ for CK, and <12 U litre⁻¹ for CK-MB, respectively.

Sample size of the study was calculated with BiAS for Windows based on cTnT concentration 24 h after aortic unclamping as the primary outcome variable; a difference of ≥0.2 μg litre⁻¹ between treatment groups was con-
sidered clinically significant. A sample size of 85 patients in each group was calculated to give a power of 0.8 and α of 0.05. We increased the sample size by 16% to compen-
sate for possible loss of power, requiring a total number of 99 patients per group. The sample size was based on the assumption of normal distribution and homogeneity of variances.

Statistical analyses were performed using SPSS 14.0 for Windows. The Shapiro–Wilks test served to assess normal distribution. Since some variables were not normally dis-
tributed, medians were compared using the Kruskal–Wallis test. For multiple comparisons, Dunn’s post hoc procedure was performed. For categorical data, χ² analysis was used. Haemodynamic data were tested using repeated measure analysis of variance, and the level of significance was adjusted using the Greenhouse–Geisser-epsilon method. Data are expressed as mean (SD), median (range), or absolute numbers. P<0.05 was considered significant. All P-values were two-tailed.

Results

A total of 209 patients were studied (Fig. 1), 108 patients in the SMP group and 101 patients in the KMP group. Ten patients were excluded from analysis because of
Variables | Unit | Sufentanil–midazolam–propofol (n=108) | S(+)-ketamine–midazolam–propofol (n=101) |
--- | --- | --- | --- |
Age | yr | 68 (62–73) | 67 (62–71) |
Height | cm | 171 (8) | 171 (7) |
Weight | kg | 83 (14) | 83 (13) |
BSA | m² | 2 (0.2) | 2 (0.2) |
BMI | kg m⁻² | 29 (4) | 29 (4) |
Gender | M:F | 85:15 | 64 (15) |
EF | % | 4.5 (0–10) | 4 (0–10) |
Euro-SCORE | | | |
DM | n | 26 | 21 |
HTN | n | 77 | 74 |
COPD | n | 10 | 12 |
HLP | n | 82 | 88 |
Beta-blockers | n | 79 | 81 |
ACE-inhibitors | n | 71 | 67 |
Ca-blockers | n | 29 | 30 |
Nitrates | n | 57 | 53 |
Diuretics | n | 46 | 51 |
Statins | n | 70 | 62 |

For induction of anaesthesia, a total dose of 0.08 (0.03–0.15) mg kg⁻¹ [median (range)] of midazolam and 0.45 (0.26–1.0) μg kg⁻¹ of sufentanil was used in the SMP group; 0.08 (0.02–0.18) mg kg⁻¹ of midazolam, 2.17 (0.5–4.57) mg kg⁻¹ of S(+)-ketamine, and 1.26 (0.45–3.13) mg kg⁻¹ of propofol were used in the KMP group. For maintenance, a total of 4.5 (1.5–13.8) μg kg⁻¹ sufentanil and 14.1 (6.7–27.1) mg kg⁻¹ propofol (but no midazolam) was used in the SMP group; 14.2 (3.6–24.9) mg kg⁻¹ S(+)-ketamine, 18.7 (5.7–41.6) mg kg⁻¹ propofol, and 0.2 (0.09–0.37) mg kg⁻¹ midazolam were used in the KMP group.

During induction and maintenance of anaesthesia, more patients in the KMP group had increases in HR and SAP, because S(+)ketamine instead of racemic ketamine, because S(+)-ketamine offers potential cardiovascular
advantages: S- (+)-ketamine has been shown to have less direct negative inotropy than racemic ketamine\(^\text{17}\) and may contribute to coronary perfusion by direct vasorelaxation.\(^\text{18}\) Some studies have found stereo-selective effects for ketamine, indicating that racemic ketamine, but not S- (+)-ketamine, reduces ischaemic preconditioning by its effects on adenosine-triphosphate-sensitive potassium channels.\(^\text{19–22}\) S- (+)-ketamine reduces post-ischaemic adherence of polymorphonuclear neutrophils in the coronary circulation as a crucial step in reperfusion injury.\(^\text{23}\) In our investigation, i.v. anaesthesia with S- (+)-ketamine did not lead to increased cTnT levels \(24\) h after aortic unclamping compared with sufentanil-based anaesthesia. Elevated cTnT values \(24\) h after aortic unclamping have been shown to be associated with an adverse clinical outcome.\(^\text{7}\) With on-pump CABG, cTnT concentrations do not exceed 1.0 \(\mu g\) litre\(^{-1}\) in uncomplicated cases.\(^\text{4}\) However, the incidence of cTnT levels \(>1.0\) \(\mu g\) litre\(^{-1}\) at \(24\) h after aortic unclamping was similar after S- (+)-ketamine- or sufentanil-based anaesthesia. Although our study was not powered to evaluate outcome variables, there were no significant differences in PMI, CPR, or \(28\) day mortality. Our investigation therefore supports previous studies,\(^\text{24–26}\) which failed to detect clinical advantages for a particular anaesthetic agent in coronary bypass patients.

Sympathomimetic effects of S- (+)-ketamine have been reported\(^\text{27}\) and include increases in arterial pressure and heart rate.\(^\text{2,3,9}\) A study comparing racemic ketamine (4 mg kg\(^{-1}\)) and S- (+)-ketamine (2 mg kg\(^{-1}\)) combined with midazolam (0.1 mg kg\(^{-1}\)) for induction of anaesthesia in patients with coronary disease was terminated because of a high incidence of sinus and ventricular tachycardia during intubation.\(^\text{7}\) Significant increases in heart rate after laryngoscopy were reported in 90 patients undergoing CABG, although tachycardia with a heart rate \(>100\) beats min\(^{-1}\) was rarely seen during induction with S- (+)-ketamine.\(^\text{3}\) However, in our study, we used propofol in combination with S- (+)-ketamine, which may have influenced haemodynamic responses. Secondly, we maintained

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**Table 2** Biochemical data. Data are presented as median, interquartile range (IQR), range, and confidence interval (CI), respectively. \(P<0.05\) denotes significant differences between study groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unit</th>
<th>Sufentanil–midazolam–propofol ((n=108))</th>
<th>S- (+)-ketamine–midazolam–propofol ((n=101))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(cTnT)</td>
<td>(\mu g) litre(^{-1})</td>
<td>(0.01)</td>
<td>(0.01)</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>(0.01)</td>
<td>(0.01)</td>
<td>0.49</td>
</tr>
<tr>
<td>1 h</td>
<td></td>
<td>(0.3)</td>
<td>(0.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>6 h</td>
<td></td>
<td>(0.3)</td>
<td>(0.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>24 h</td>
<td></td>
<td>(0.3)</td>
<td>(0.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>(CK)</td>
<td>(U) litre(^{-1})</td>
<td>(60)</td>
<td>(60)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pre-OP</td>
<td></td>
<td>(45–100)</td>
<td>(45–100)</td>
<td>0.05</td>
</tr>
<tr>
<td>24 h</td>
<td></td>
<td>(533–1100)</td>
<td>(533–1100)</td>
<td>0.05</td>
</tr>
<tr>
<td>(CK-MB)</td>
<td>(U) litre(^{-1})</td>
<td>(3)</td>
<td>(3)</td>
<td>0.89</td>
</tr>
<tr>
<td>Pre-OP</td>
<td></td>
<td>(2–5)</td>
<td>(2–5)</td>
<td>0.89</td>
</tr>
<tr>
<td>24 h</td>
<td></td>
<td>(67–478)</td>
<td>(67–478)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

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**Table 3** Cardiovascular events during the study period and \(28\) day mortality. Data are presented as median with range and absolute numbers. \(P<0.05\) denotes significant differences between study groups. IABP, intra-aortic balloon pump; ST-deviation, new ST segment changes during and after surgery (as defined in the text); PMI, perioperative myocardial infarction; CPR, cardiopulmonary resuscitation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unit</th>
<th>Sufentanil–midazolam–propofol ((n=108))</th>
<th>S- (+)-ketamine–midazolam–propofol ((n=101))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IABP</td>
<td>(n)</td>
<td>(2)</td>
<td>(2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>(n)</td>
<td>(23)</td>
<td>(22)</td>
<td>0.99</td>
</tr>
<tr>
<td>ST-deviation</td>
<td>(n)</td>
<td>(22)</td>
<td>(18)</td>
<td>0.59</td>
</tr>
<tr>
<td>PMI</td>
<td>(n)</td>
<td>(1)</td>
<td>(2)</td>
<td>0.785</td>
</tr>
<tr>
<td>CPR</td>
<td>(n)</td>
<td>(0)</td>
<td>(0)</td>
<td>0.361</td>
</tr>
<tr>
<td>(28) day mortality</td>
<td>(n)</td>
<td>(1)</td>
<td>(2)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
haemodynamic variables within the normal range, with vasoactive drugs if required. As a consequence, intraoperative haemodynamic variables were similar between the groups. Tachycardia rather than hypertension or hypotension precipitates myocardial ischaemia during CABG even without obvious haemodynamic changes. In our study, most of the patients were on long-term beta-blockade. Beta-blockade was also given intraoperatively to blunt tachycardia as a key mechanism by which S-(-)-ketamine may cause myocardial damage. Even though this may be a limitation of our study design, no statistical difference in beta-blockade usage was found between the two groups. The use of beta-blockers for treatment and prophylaxis of perioperative tachycardia as a therapeutic concept to decrease morbidity and mortality in CAD patients undergoing non-cardiac surgery is now well appreciated.

We therefore conclude that maintenance of stable haemodynamics can be safely achieved with S-(-)-ketamine-propofol-based anaesthesia during CABG surgery. However, the clinically relevant question whether S-(-)-ketamine is beneficial in the cardiovascularly compromised patient remains elusive. In our study, decreases and increases in arterial pressure occurred with the same incidence during induction with S-(-)-ketamine, and S-(-)-ketamine failed to lower the need for catecholamines in the post-bypass period. Experimental and clinical data indicate that in conditions of decreased contractility, the sympathomimetic actions of racemic ketamine may not prevent further haemodynamic deterioration. Although we observed fewer decreases in arterial pressure during induction with S-(-)-ketamine than with sufentanil, S-(-)-ketamine may not be suitable for patients with cardiovascular compromise. Interestingly, we observed significantly lower defibrillation rates after aortic unclamping in patients receiving S-(-)-ketamine, which agrees with a previous clinical study. Possible explanations may include a lidocaine-like effect on myocardial sodium channels.

Some unresolved questions remain, such as the incidence of postoperative agitation and confusion, which may limit the use of S-(-)-ketamine for CABG surgery. Transient hallucinations have been noted in about 9% of the patients, when S-(-)-ketamine was used as an analgesic adjunct for 48 h after CABG surgery, but opioid consumption was reduced and the patient satisfaction was significantly higher with S-(-)-ketamine compared with opioids alone. A comparison of S-(-)-ketamine- and remifentanil-based anaesthesia found no difference in neurocognitive tests 10 weeks after CABG.

In conclusion, our study confirms that the use of S-(-)-ketamine is not related to the extent of myocardial damage reflected by troponin rises in the postoperative period of CABG surgery. Although i.v. anaesthesia with S-(-)-ketamine may not be generally recommended for CABG surgery, it can be safely used in haemodynamically stable patients with CAD.

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References
25 Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 1989; 70: 179–88