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

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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) μg 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.²³

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 peri-operative 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 \(\mu\)mol 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 \(\pm20\%\) 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.](image-url)
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 infusion 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, capnography, and a pulmonary artery catheter. Continuous measurement of HR, systemic and pulmonary arterial pressures [systolic, diastolic, and mean (MAP)], and central venous pressure (CVP) was done using a Siemens Sirecust monitoring system (Siemens, Erlangen, Germany). Thermodilution cardiac output was measured in triplicates by cold bolus injection and the mean was recorded. CVP and the pulmonary capillary wedge pressure were taken as an average over the respiratory cycle. Cardiac index (CI), systemic vascular resistance index (SVR1), 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 ino-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 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.² Weaning from CPB followed a standardized protocol, including optimization of filling pressures and haemodynamics by use of volume and vasoactive drugs according to requirements. Glyceryl 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 3000 g, 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 considered 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 compensate 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–Wilk test served to assess normal distribution. Since some variables were not normally distributed, 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-episolon 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
incomplete data (in six patients 6 and 24 h values of cTnT, in four patients 24 h values of cTnT and postoperative ECG were lacking).

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 status, and the intraoperative treatment (surgical time and technique, CPB time, aortic cross-clamp time, myocardial protection strategy employed, anti-fibrinolytic therapy, insulin usage, and transfusion requirement). However, in the KMP group, fewer had to be defibrillated to convert ventricular fibrillation to sinus rhythm after aortic unclamping (SMP 54% vs KMP 29%; P<0.01).

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) \(\mu\)g 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) \(\mu\)g 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, but this difference failed to reach statistical significance. There was no significant difference in the number of patients needing cardiovascularly active drugs during induction, during the pre- and post-bypass periods, or within the first 24 h after operation. After induction and before skin incision, patients in the KMP group had statistically significant higher HR [SMP: 60 (12)] vs KMP: 66 (13) beats min\(^{-1}\); P<0.01]. However, all other steady-state haemodynamic variables before skin incision and at skin closure did not differ significantly between the groups. Apart from higher CI [SMP: 2.6 (0.7)] vs KMP: 2.7 (0.6) mm Hg; P=0.029] and MAP [SMP: 81 (10)] vs KMP: 89 (9) mm Hg; P=0.005] as well as lower PVRI [SMP: 283 (102)] vs KMP: 216 (63) mm Hg; P=0.001] in the KMP group, haemodynamic variables were also comparable 6 h after operation.

Postoperative cTnT levels increased in all groups over time. Six hours after aortic unclamping, there was a significant difference in cTnT levels between the KMP and the SMP groups, with lower levels in patients in the KMP group. At all other time points, however, cTnT levels did not differ significantly (Table 2). Twenty-four hours after aortic unclamping, cTnT levels had a similar distribution in both groups. There was no difference in the pre- and postoperative CK and CK-MB levels.

No significant differences were observed in the incidence of new ECG signs of ischaemia, arrhythmias, CPR, PMI, and the use of IABP (Table 3). Time to tracheal extubation did not differ between the groups [SMP: 6 (4–20) vs KMP: 7 (3–24) h; P=0.222]. A total of three patients died within 28 days after surgery: one patient died from myocardial infarction at Day 20, one from ischaemic stroke, and one from sepsis with multiple organ failure.

**Discussion**

After on-pump CABG surgery, troponins are elevated in the vast majority of patients. Interpretation of individual troponin levels can therefore be challenging.\(^{13}\) Multiple surgical and non-surgical factors contribute to the ‘background noise’ of myocardial markers after CABG.\(^{4}\) In addition, the choice of the anaesthetic regimen may also have some influence.\(^{14,15}\) A recent meta-analysis concluded that compared with opioid-based i.v. anaesthesia, the use of volatile agents for on- and off-pump CABG surgery produces beneficial effects such as higher cardiac indices, lower troponin serum concentrations, and less inotropic support.\(^{15}\) The average cTnT level in patients anaesthetized with volatile agents (n=490) was 0.61 (0.35) \(\mu\)g litre\(^{-1}\) (cTn levels converted to cTnT). Clinical and experimental data suggest that volatile agents can produce myocardial protective effects by pre- and postconditioning.\(^{16}\) However, as the effect on outcome variables is unconfirmed, the clinical relevance of these findings still is debatable.

It is generally recommended that ketamine should be used with caution in patients with CAD, since its sympathomimetic effects may produce myocardial injury. We chose 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 and may contribute to coronary perfusion by direct vasorelaxation. 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. S- (+)-ketamine reduces post-ischaemic adherence of polymorphonuclear neutrophils in the coronary circulation as a crucial step in reperfusion injury. 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. With on-pump CABG, cTnT concentrations do not exceed 1.0 µg litre\(^{-1}\) in uncomplicated cases. However, the incidence of cTnT levels >1.0 µg 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, which failed to detect clinical advantages for a particular anaesthetic agent in coronary bypass patients.

Sympathomimetic effects of S- (+)-ketamine have been reported and include increases in arterial pressure and heart rate. 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. 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. However, in our study, we used propofol in combination with S- (+)-ketamine, which may have influenced haemodynamic responses. Secondly, we maintained

<table>
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<th>Variables</th>
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<th>S- (+)-ketamine–midazolam–propofol (n=101)</th>
<th>P-value</th>
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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

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<tr>
<th>Variables</th>
<th>Unit</th>
<th>Median</th>
<th>IQR; range</th>
<th>CI</th>
<th>Median</th>
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Table 2 Biochemical data. Data are presented as median, inter-quartile range (IQR), range, and confidence interval (CI), respectively. P<0.05 denotes significant difference between study groups.
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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