Ketamine for induction and maintenance during elective on-pump coronary artery bypass grafts

Editor—We read with interest the article on the alterations to the inflammatory response during cardiopulmonary bypass, after induction and maintenance with ketamine.\(^1\) However, we have a couple of questions for the authors.

Anaesthetic depth was monitored using the bispectral index. This is known to be an unreliable marker of anaesthetic depth in the presence of ketamine.\(^2\) This could therefore have resulted in more anaesthetic drugs being administered in the ketamine-treated group. Indeed, both midazolam and propofol doses were higher in this group. Since the definitive changes in ‘immune function’ caused by propofol and midazolam are still unclear,\(^3\) might not the altered cytokine response result solely from the extra use of these drugs? We also notice that attempts were made to blunt the sympathomimetic response to ketamine. The authors state that both \(\beta\)-blockers and antihypertensives were used as necessary. We would be interested to have more information, as some of these drugs are now being recognized to have additional properties, including alterations in the inflammatory cytokine response.\(^4\)

While the study demonstrates significantly different levels of interleukin 6, 8, and 10 in the early hours after cardiopulmonary bypass in the ketamine-treated group, the troponin and creatine kinase-MB levels were similar. There were few incidences where it is thought that manipulating the cytokine response to a major insult may be beneficial.\(^5\) However, there are also many incidences where no benefit or harm has been demonstrated.\(^6\) The overall clinical implications from the observed cytokine responses might be difficult to predict. We therefore believe that using ketamine as induction and maintenance on the basis of this study may be difficult to justify.

Conflict of interest

None declared.

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Reply from the authors

Editor—We would like to thank Drs Bigham and Jaggar for their comments on our study.\(^1\) They raise the question whether the use of higher doses of propofol and midazolam in the ketamine group, even though statistically not significant, could be responsible for the observed differences in cytokine responses. The fundamental difference between our study groups was the presence or absence of \(S\)-(+)\)-ketamine.\(^1\) Our results clearly show that the propofol and midazolam doses did not differ significantly between the groups. It is hence unlikely that differences in sedative drugs can explain the inhibition of proinflammatory cytokine release in the ketamine group. It is worth noting that the described differences in cytokine response were detectable despite high standard variation and non-normal distribution of data, while the data on propofol doses showed more homogeneity. Therefore, significant differences in propofol and midazolam dosing would have been detected with acceptable reliability. Furthermore, from the clinical and immunological perspective, it also appears questionable that 220 mg of propofol (i.e. approximately 0.5 mg kg\(^{-1}\) h\(^{-1}\)) or 1.2 mg of midazolam applied during a 6 h anaesthetic can be made responsible for differences in the immune response. The study cited by Bigham and Jaggar\(^2\) was performed in rats and used a bolus injection of 10 mg kg\(^{-1}\) propofol followed by an infusion of 10 mg kg\(^{-1}\) h\(^{-1}\). This suggests that at least 10-fold higher additional doses of sedatives are required to elicit a measurable effect on cytokine response. Monitoring of anaesthetic depth using bispectral index during ketamine administration is not an established procedure. However, recent experience suggests that ketamine may neither influence BIS values\(^3\) nor increase the incidence of postoperative delirium, if given in combination with other anaesthetics.\(^5\) \(\beta\)-Blockers have been thoroughly investigated for immune effects. However, we would like to emphasize that \(~80\%\) of the patients in both study groups were on \(\beta\)-blockers as their usual treatment. \(\beta\)-Blockade was continued on the day of surgery. Hence,
this patient population was not suitable to assess any effects of intraoperative β-blockers on immune function. In both groups, intraoperative doses of metoprolol were administered to blunt tachycardia unresponsive to top-up doses of anaesthetics, but the use of β-blockers did not differ between the groups. Hence the concept that intraoperative β-blockade may have contributed to the inhibition of the proinflammatory response is not supported by our results. A more detailed description of the cardiovascular effects of S(-)+)-ketamine in comparison with sufentanil as the main analgesic in a similar patient group has been published before.5 Our study was not designed to show differences in outcome. The clinical significance of the anti-inflammatory effects of S(-)+)-ketamine during and after adult cardiopulmonary bypass remains to be elucidated. Therefore, further research is needed to fully evaluate the specific influence of ketamine on immune response and outcome after cardiac surgery. We conclude that based on our results, the use of ketamine in cardiac anaesthesia is safe and is potentially associated with a beneficial immunologic profile.

Conflict of interest
None declared.

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doi:10.1093/bja/aer321

Pressure recording analytical method to measure cardiac output after cardiac surgery: some practical considerations

Editor—We read with interest the paper ‘Lack of agreement between pulmonary arterial thermodilution cardiac output and the pressure recording analytical method in postoperative cardiac surgery patients’.1 The study aimed to determine the reliability of pressure recording analytical method (PRAM)-derived cardiac output (PRAM-CO) in comparison with thermodilution-derived CO (ThD-CO) in a heterogeneous group of patients after cardiac surgery. Large differences between PRAM-CO and ThD-CO were found and the authors concluded that PRAM-CO could not replace ThD-CO in such patients.

The authors sought explanations for the discrepancies between their work and previous studies showing the accuracy of PRAM to measure CO when compared with ThD-CO.2–4 We wish to share some considerations that may help to clarify this issue.

First, pressure artifacts are a common phenomenon that must be addressed whenever using pulse contour methods (PCMs) to estimate CO. In fact, different catheter–transducer systems for arterial waveform transmission could give different results in terms of measured pressures.5 PRAM analyses the arterial signal using a sampling frequency of 1000 Hz. The high-frequency sampling permits a better precision, which is of primary importance for the calculation of the arterial impedance and the correct measurement of pressures. Indeed, in case of an eventual resonance effect of the catheter–transducer system, the device allows to adapt its setting to maximize the signal-to-noise ratio. A pressure waveform altered by under-damping might affect both the amplitude and morphology of the signal evaluated by PRAMS. If resonance occurs, dP/dt_max provided by PRAM is abnormally high, reflecting the poor quality of the arterial trace. In this situation, PRAM could likely overestimate systolic arterial pressure and stroke volume. Conversely, there could be under-estimation in the case of over-damped signals. Indeed, PRAM is more sensitive to artifacts than other PCMs as its algorithm is exclusively based on the analysis of the pressure wave morphology and not on external (e.g. bolus dilution) or internal pre-estimated parameters.4 In their article,1 the authors have not provided sufficient information concerning pressure signal quality, stroke volume, and systolic arterial pressure values, which could help to evaluate whether these confounding factors may have influenced CO measurement.

Secondly, when comparing a PCM with bolus thermodilution, for each determination of ThD-CO, a corresponding value for PCM must be obtained by averaging the CO obtained by individual beats over the time needed for the reference method estimation.5 In their study,1 the average of three 1 min continuous registrations with 1 min intervals was taken (5 min total period) for PRAM, but the authors did not explain how the average of individual beats within 1 min intervals was calculated (i.e. Visually? Downloading the data by the transfer-card?). Also, ThD-CO was calculated as the mean of at least three separate measurements obtained over a total period of 3 min. It appears that the time interval used for PRAM-CO measurement did not match the interval for ThD-CO calculation. Although this may be acceptable for extremely stable patients, it is a methodological limitation of the study.