Xenon Myocardial Protection in Cardiac Surgery: Effective around the Clock?

To the Editor:

We read with great interest the article by Hofland *et al.*,[1] which reported that xenon anesthesia was noninferior to sevoflurane anesthesia and superior to total intravenous anesthesia with propofol regarding cardiac troponin I release after on-pump coronary artery bypass surgery. In a milestone translational work, Montaigne *et al.*[2] have recently reported that time of day of on-pump cardiac surgery (morning *vs.* afternoon) affected outcome, attributed to a differential gene expression profile. Specifically, surgery in the morning was predictive of major postoperative adverse cardiac events in the retrospective analysis and was associated with higher cardiac troponin T release in the prospective randomized part of this work. We write to inquire whether Hofland *et al.* have data which may inform on the circadian nature of xenon noninferiority to sevoflurane and superiority to propofol. More broadly, the timing of the surgery should be, in our opinion, a must-have parameter for future cardiac surgery clinical trials.

Competing Interests

The authors declare no competing interests.

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In Reply:

We appreciate the interest of Lagier *et al.* in our article.[1] The authors highlighted in their letter the work of Montaigne *et al.*,[2] who have recently published on the circadian rhythm in relation to ischemia reperfusion injury in a single-center retrospective propensity-matched cohort study addressing this subject on 596 (matched-pairs) patients undergoing aortic valve replacement with or without coronary artery bypass grafting, together with a single-center randomized study in 88 patients undergoing isolated aortic valve replacement, in which the perioperative myocardial injury has been assessed with the geometric mean of perioperative cardiac troponin T release. Together with these reported studies these authors also reported in the same article on an *ex vivo* analysis of the human myocardium that showed an intrinsic morning afternoon variation concomitant with a circadian variation of Rev-Erbα. An accompanying comment noticed that gene-expression analysis, mainly performed in rodents, had shown in the early 2000s a rhythmic expression of clock genes in the heart[3]; whether or not clock genes modulate cell death directly and whether they affect ischemia reperfusion injury remained to be established, even after the publication of Montaigne.[4]

For answering the question of Lagier *et al.* we had to reexamine our dataset, as this question had not been addressed in our study protocol. To begin, it was expected that the chosen randomization strategy should have done its work and that distribution of morning *versus* afternoon operation timing over the 3 treatment groups should be about equal. Indeed, analyzing the time of randomization in the intention-to-treat population, randomization being done just after induction of anesthesia as we have described, we found that the distribution of the "morning" patients was as follows: xenon group, n = 106 (66%); sevoflurane group, n = 109 (66%); total intravenous anesthesia group, n = 107 (65%). For the "afternoon" patients this was as follows: xenon group, n = 55 (34%); sevoflurane group, n = 56 (34%); total intravenous anesthesia group, n = 59 (35%). Thus, the found noninferiority for xenon to sevoflurane and the found superiority of xenon over total intravenous anesthesia on cardiac troponin I release in low-risk, on-pump coronary artery bypass graft surgery patients are not confounded by an imbalance in randomization allocation in the daytime.

Furthermore, to investigate whether for on-pump, low-risk isolated coronary artery bypass graft (CABG) surgery, a circadian rhythm in the patients undergoing this operation might exist, we again reexamined our intention-to-treat

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dataset. It must be noted first of all, that our study was not designed for answering this question, which makes statistical analysis improper. Thus, only descriptive data are provided. The mean overall 24-h cardiac troponin I release, ng/ml (95% CI), was for morning (n = 322) *versus* afternoon (n = 169) patients: 3.05 (2.26 to 3.85) *versus* 2.33 (1.85 to 2.80), medians being 1.38 *versus* 1.15 ng/ml, suggesting that some circadian variation indeed might exist in patients undergoing isolated CABG surgery as well.

The mean xenon group 24-h cardiac troponin I release, ng/ml (95% CI), for morning (n = 106) *versus* afternoon (n = 55) patients was 2.36 (1.68 to 3.05) *versus* 2.32 (1.34 to 3.31), medians being 1.23 *versus* 1.11 ng/ml. The mean sevoflurane group 24-h cardiac troponin I release for morning (n = 109) *versus* afternoon (n = 55) patients was 2.91 (1.96 to 3.86) *versus* 2.15 (1.47 *vs.* 2.82), medians being 1.42 *versus* 1.11 ng/ml. The mean total intravenous anesthesia group 24-h cardiac troponin I release for morning (n = 107) *versus* afternoon (n = 59) patients was 3.89 (1.78 to 6.00) *versus* 2.49 (1.66 to 3.33), medians being 1.49 *versus* 1.42 ng/ml. Thus, in all groups we also found a higher 24-h post-CABG-surgery cardiac troponin I release value (both mean and median) in the morning patients.

We agree with Lagier *et al.* that for reporting on outcome of future cardiac surgery clinical trials, adding information about the time of day the surgery is performed seems to be of value.

Competing Interests

The following authors received grants, personal fees, or nonfinancial support from Air Liquide Santé International (Jouy-en-Josas, Paris, France) to conduct the Xenon-CABG study: Drs. Hofland, Ouattara, and Bein. The following authors received grants, personal fees (*e.g.*, lecture fees), or nonfinancial support from Air Liquide Santé International for activities other than the work for the Xenon-CABG study: Drs. Hofland and Outtara. Dr. Bein reports personal fees from Abbvie (Wiesbaden, Germany), CSL Behring (Marburg, Germany), GE Healthcare (München, Germany), Pulsion Medical Systems (Feldkirchen, Germany), MSD (Graz, Austria), CNSystems (Graz, Austria), Edwards Life Sciences (Untersleißheim, Germany), 3M (Neuss, Germany), Orion Pharma (Hamburg, Germany), The Medicines Company (München, Germany), TEVA Ratiopharm (Ulm, Germany), and MASIMO (Puchheim, Germany) for activities outside the work for the Xenon-CABG study. Ms. Schaller was an employee of Air Liquide Santé International during the study.

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Editorial Views and Policies

To the Editor:

We thank Drs. Kharasch and Houle[1] for commenting on an article[2] and an editorial[3] published in *Anaesthesia* in their Editorial Views. It would be more usual for questions to be posed to the authors of a journal article by means of correspondence to the primary journal, and we are sure that Drs. Carlisle, Loadsman, and McCulloch would be delighted to respond to any such letters. We would therefore refer the readers of Anesthesiology to such correspondence in *Anaesthesia* for further discussion of these articles and the issues arising.

In response to the specific suggestions made about the editorial policy of *Anaesthesia*, the Journal stands by its decision (and is supported in doing so by the Editorial Board) to screen all submitted randomized controlled trials for data distribution.[4] However, we would like to point out that no article has ever been, or will ever be, rejected based on this screening alone[5]; a finding that a submission appears to have an unusual distribution of data is always followed by a request to the authors for original trial data,[6] and it is the analysis of these data, along with the authors' responses to further questioning, that leads to any decision to accept or reject. Many submissions initially flagged using this screening method are found to have done so through authors' errors rather than intentional deception or worse.

Anaesthesia and its Editorial Board also stand by the suggestion that extreme distributions of baseline data merit further investigation, the expectation being that many, if not most, will turn out to be due to errors. The scientific record must be reliable, and *Anaesthesia* is happy to take the lead in checking past, as well as current/future, publications.

Competing Interests

Dr. Klein is current Editor-in-Chief of *Anaesthesia*. Dr. Yentis is the Immediate Past Editor-in-Chief of *Anaesthesia*. Dr. Clyburn is Chair of the Editorial Board of *Anaesthesia* and President of the Association of Anaesthetists of Great Britain and Ireland (London, United Kingdom).

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