



Commentary

Cardiac surgery in the morning or not in the morning: “When?” is the question

Martin E. Young

Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, 703 19th St. S., ZRB 308, Birmingham 35294, Alabama, United States

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Virtually all aspects of life on Earth revolve around the 24 hour day-night cycle. In mammals, daily rhythms can be seen at molecular (e.g., mRNA, protein), cellular (e.g., signaling, metabolism), organ (e.g., hormone secretion, contractility), and whole-body (e.g., sleep and eating behavior) levels [1]. This is readily apparent for the cardiovascular system; parameters such as heart rate and blood pressure change dramatically over the course of day, rising steeply in the morning [2]. Unfortunately, a rise in adverse cardiovascular event incidence (e.g., arrhythmias, myocardial infarction [MI]) is also observed in the morning (due in part to an increased presence of triggers at this time, such as catecholamines and platelet aggregability) [3]. In the case of MI, it appears that the time of day at which an ischemic event occurs has a significant bearing on tissue damage severity; higher circulating levels of myocardial damage markers (e.g., troponin I, creatine kinase) are observed in patients experiencing MI in the morning (versus the afternoon) [4]. Animal-based studies often report similar findings, with poorer outcomes when ischemic events occur at the sleep-to-wake transition (relative to other times of the day) [5]. Given that specific cardiac surgeries (including aortic valve replacement [AVR] and coronary artery bypass grafting [CABG]) inherently involve ischemic events, the aforementioned observations suggest that the morning might not be the optimal time for these characteristically non-emergency interventions (in terms of patient outcomes).

A milestone study by Montaigne *et al* in 2018 interrogated the question whether clinically-relevant outcomes were dependent on the time-of-day at which AVR was performed [6]. Propensity score was used to match patients who underwent AVR either in the

morning or the afternoon; outcomes were followed for 500 day, revealing that patients undergoing surgery in the morning had an increased incidence of major adverse cardiac events and acute heart failure development (relative to those patients undergoing surgery in the afternoon at the same hospital) [6]. Moreover, a randomized control trial reported greater perioperative cardiac troponin I release following surgery in the morning (versus the afternoon) [6]. Collectively, these findings were consistent with reduced tolerance of the heart to an ischemic episode in the morning. However, subsequent to this initial study, multiple retrospective studies have failed to observe differences in cardiac surgery patient outcomes, with respect to the time of day at which cardiac surgeries were performed [7-9]. These reports therefore called into question whether surgical time-of-day is of major clinical significance.

In this issue of The Lancet Regional Health – Europe, Fuduluet *al* [10] applied multiple strategies to address this question. First, a meta-analysis was performed on eligible studies investigating whether AVR and/or CABG outcomes were different for surgeries performed in the morning versus the afternoon (totaling 18,377 patients). The UK national adult cardiac surgery audit (NACSA) database was next mined, from which available data on 91,248 patients undergoing AVR or CABG was analyzed. Lastly, data from the remote ischemic preconditioning (RIPC; 124 patients) trial for markers of cardiac injury (plasma troponin I and cardiac nucleotide levels) were stratified based on whether cardiac surgeries were performed in the morning or the afternoon. Both the meta-analysis and the NACSA database retrospective analysis failed to identify significantly higher risk of MI or mortality during the 30-day period following cardiac surgeries that were performed in the morning (relative to those performed in the afternoon). Similarly, markers of cardiac injury in the RIPC trial were not different between patients undergoing cardiac

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E-mail address: meyoung@uab.edu

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surgery in the morning versus the afternoon. Collectively, these observations suggest that acute (i.e., 1 month) outcomes following AVR and/or CABG are not dependent on the time-of-day at which surgery is performed.

Based on the multi-pronged approach of Fudulu and colleagues, coupled with the magnitude of patient data analyzed, is closure possible on the question whether cardiac surgery outcomes are impacted by time-of-day? Several limitations should be highlighted prior to drawing such a conclusion. Regarding the meta-analysis, only 5 studies were selected, for which appreciable heterogeneity exists. This is particularly apparent when comparisons are made with the Montaigne study, for which a single surgery (AVR) was interrogated at a single hospital in propensity matched patients. Differences in outcome measures are also evident; the Montaigne study focused primarily on 500-day major adverse cardiac events (which included cardiovascular death) and heart failure, whereas the Fudulu study reported 30-day MI and mortality. Interestingly, differences in heart failure incidence between morning and afternoon surgeries were not observed by Montaigne *et al* at the 30-day point; differences first emerge after 150 days post cardiac surgery (i.e., a long-term outcome). Consistent with the study by Montaigne *et al*, a trend (OR 0.82, 95% CI: 0.65-1.03, $p=0.094$) for reduced risk of 30-day mortality is observed by Fudulu *et al* when AVR is performed in the afternoon (versus the morning). The manner with which patients were grouped is also noteworthy; patients undergoing surgeries between 8:00am and 12:00noon were grouped together (i.e., “morning”), while surgeries between 12:01pm and 5:00pm were grouped (i.e., “afternoon”); this questions whether an increased time resolution analysis might reveal that outcomes from early morning surgeries (e.g., 8:00am) differ from those late in the day (e.g., 5:00pm). Further studies are therefore recommended before discarding chronotherapeutic considerations from the cardiac surgery arena.

Declaration of Competing Interest

Dr. Young has no competing interests.

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