Of Railroads and Roller Coasters

Considerations for Perioperative Blood Pressure Management?

Yannick Le Manach, M.D., Ph.D.,* Christian S. Meyhoff, M.D., Ph.D., Gary S. Collins, Ph.D., Eske K. Aasvang, M.D., D.M.Sc., Martin J. London, M.D.

Management of intra- and early postoperative hemodynamics is the "bread and butter" of the operative anesthesiologist's toolkit, a skill that gives many of us great pride. Who hasn't rejoiced at the end of a long case to think to themselves, or better yet to brag to the surgeon, the recovery room nurse, or even a colleague, that the hemodynamics were "railroad tracks" all the way through? On the flip side, how many of us have gone home exhausted after a long case "battling" the "roller coaster" of blood pressure and/or heart rate? Although heart rate has been the subject of great controversy during the 1980s through early 2000s during the peak period of the beta blocker controversy, blood pressure has now assumed the forefront of this scrutiny. The pioneering work of many groups, applying rigorous techniques to the capture and analysis of large amounts of data downloaded from monitoring equipment, has provided numerous observational cohort analyses relating intra-, and more recently, early postoperative data to a variety of clinically important outcomes.

"…[T]he long-standing focus on blood pressure as the only surrogate for perfusion should be tempered…"

In this issue of Anesthesiology, investigators at Erasmus University (Rotterdam, The Netherlands) present data regarding associations between intra- and early postoperative mean arterial pressure and myocardial injury.[1] A unique feature of this study is the availability of postoperative high-sensitivity troponin T measurements as part of an ongoing registry whereby such measurements are "routine." Patients 60 yr of age or older undergoing intermediate to high-risk noncardiac surgery with expected duration of hospitalization of at least 24 h who were admitted to a "high dependency" unit (a unit intermediate in acuity between an intensive care unit and a post-anesthesia recovery unit) were monitored intra- and for 24 h postoperatively frequently (1 to 5 min intra- and 1- to 15-min intervals postoperatively). The association between a variety of calculated metrics of mean blood pressure (absolute thresholds and time-weighted parameters) and myocardial injury (high sensitivity troponin T 50 ng/l or greater) occurring within the first 3 postoperative days were assessed. Myocardial injury was associated with higher prolonged durations of all mean arterial pressure thresholds used, and after adjustment for clinical confounders adjusted odds ratios from 2.18 to 3.26 were observed. Of note, intraoperative hypotension had no independent effect on myocardial injury.

The results and conclusions presented in the article by Liem *et al.*[1] can be viewed and interpreted through different lenses. We present alternate and complementary perspectives on these data. Drs. Le Manach and Collins provide insight into implications of observational study designs and statistics, while Drs. Meyhoff and Aasvang focus on some of the more specific clinical considerations as well as implications for more advanced or remote postoperative clinical monitoring.

Image: J. P. Rathmell.

This editorial accompanies the article on p. 510. Y.L.M. and C.S.M. contributed equally to this work.

Accepted for publication June 5, 2020. Published online first on July 24, 2020. From the Population Health Research Institute, Perioperative Medicine and Surgical Research Unit, Departments of Anesthesia and Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada (Y.L.M.); Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark (C.S.M.); Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom (G.S.C.); Department of Anaesthesia, Center for Cancer and Organ Diseases, Rigshospitalet, University of Copenhagen, Denmark (E.K.A.); and Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, CA (M.J.L.); San Francisco Veterans Affairs Medical Center, San Francisco, CA (M.J.L.).

*Deceased (https://healthsci.mcmaster.ca/hei/news-article/2020/07/16/dr.-yannick-lemanach-october-16-1974---july-13-2020).

 Anesthesiology 2020; 133:489–92. DOI: 10.1097/ALN.0000000000003446

<zdoi;. DOI: 10.1097/ALN.0000000000003446>

Implications of Study Design and Statistics

Interest in the incidence, predictors, and implications of perioperative hypotension have been a major focus of perioperative research over the past decade. Numerous observational studies have demonstrated that intraoperative hypotensive events are associated with postoperative complications (including cardiac, renal, and death), and many investigators have attempted to define blood pressure thresholds associated with such outcomes.[2] Other studies have defined blood pressure metrics (*e.g.*, cumulative minutes, duration, area and time-weighted-averages) to better describe this relationship.[3] Liem *et al.* provide data demonstrating that postoperative hypotension is associated with myocardial injury, but intraoperative hypotension was not.[1] Although intraoperative hypotension occurred in this cohort, the reported profiles were similar in patients whether they experienced postoperative myocardial injury or not. Therefore, knowing the intraoperative blood pressure did not provide information regarding which patients will develop postoperative myocardial injury. Hypotension occurring after surgery was more prevalent in those with myocardial injury.

As with most of the existing studies, establishing a causal relationship between hypotension and the primary outcome was not possible. Observational data are not a substitute to randomized data. One can likely conclude that in most instances, any hypotension is an undesirable condition, but no existing studies (including this current observational study) demonstrate that controlling blood pressure can prevent the undesirable outcomes reported. To accomplish this, an interventional design is required.

While acknowledging the paucity of randomized data, Liem *et al.* used a frequent reporting pattern (as many other authors of similar studies) and claim that postoperative hypotension (*i.e.*, the exposure) was *independently associated* with myocardial injury (*i.e.*, the outcome).[1] Independence from the other variables included in a predictive model is an *assumption* of regression methods. Yet, to verify this assumption is nontrivial in clinical datasets, where multidimensional interactions are frequent. At best, researchers can exclude important collinearity between two variables. It is paramount for the readers to understand that an *independent association* (from any other variables, known or not) between an exposure and an outcome defines a causal relationship (*i.e.*, removing the exposure would prevent the outcome). Even though the nomenclature of regression refers to variables as *independent*, it is a fallacy to declare a variable *independent* and thus suggest causality. A variable's *independence* is an assumption of regression methods, *not a result*. The strongest approach to create an independent exposure is to randomize it. Randomization reduces bias by creating an exposure allocation *independent* from any other variables and allows an efficient mechanism to explore cause–effect relationships and to determine causality. Therefore, claiming *independence* between exposure and outcome suggests to the reader that limiting the exposure would prevent the outcome, with no supporting evidence for the causal nature of the observed association.

One could be tempted to argue that looking at the magnitude of the association, the causal link between hypotension and postoperative outcome doesn't need to be demonstrated and that the level of evidence is enough to justify aggressive perioperative management to prevent hypotension, thus perhaps improving outcome.[4] One could even define a variety of anesthesia care quality metrics based on blood pressure parameters (*e.g.*, blood pressure nadir during surgery, time spent below pre-established thresholds of blood pressure, *etc.*).[3] Further, there is growing enthusiasm for implementing some form of standardized metrics for perioperative blood pressure management based primarily on the large amount of accumulated observational research over the past decade.[5] Although assumptions of the potential benefits are frequent, the interventions required to achieve perioperative blood pressure control are rarely discussed. This concept is not new, and it has been previously implemented in a tentative manner to improve perioperative care based on heart rate control.[6]

In the study by Liem *et al.*, intraoperative hypotension was not statistically associated with postoperative myocardial injury.[1] This suggests that interventions targeting the control of intraoperative blood pressure are not likely to prevent postoperative myocardial injury in this specific population. However, Liem *et al.* do report an association between postoperative hypotension and myocardial injury. Although the causal relationship between this exposure and the outcome cannot be affirmed with this study design, this observation emphasizes the possibility for enhanced monitoring of postoperative blood pressure to identify patients more likely to develop myocardial injury.[1] However, none of the results presented provides direct evidence that simply restoring blood pressure to an arbitrary value would prevent myocardial injury.

Implications for Postoperative Clinical Monitoring

Despite advances in surgical technique and perioperative medicine, surgery still entails risk of life-threatening adverse cardiac outcomes, emphasizing the need for a better understanding of the pathophysiologic mechanisms involved to institute prophylactic or immediate interventions.

The study of high-risk patients by Liem *et al.*, in which blood pressures and high sensitivity troponin T concentrations were prospectively captured, adds to our knowledge by supporting previous findings of the importance of postoperative hypotension on the risk for myocardial injury after major surgical procedures.[4] It combines both the duration and severity of hypotension to risk-stratify patients. One of the key methodologic strengths is the use of invasive blood pressure monitoring with a sampling frequency between 1 and 15 min.

Liem *et al*. focus on events detected in the high dependency unit to explain the observed troponin alterations, which is understandable because frequent or even continuous measurements to detect and correct vital sign deviations are currently only feasible in the intensive care unit, operating room, post anesthesia recovery unit, and other high-dependency units with a high staffing-to-patient ratio and access to monitoring equipment.[1] However, from a physiologic standpoint, there is no reason to assume that deviations only occur in these units.[7] The literature suggests a paucity in our understanding of complications occurring in general wards and especially after discharge.[8] Future studies should also aim outside these highly specialized settings when caring for patients at high risk of cardiovascular and other surgical complications.[9,10] Thus, the few studies on continuous monitoring in the general wards have shown that a large proportion of cases go undetected by the usual manual intermittent measurements with up to 8 or 12 h in-between, or at home, where standards for out-of-hospital monitoring have yet to be established.[4,9–11]

An intriguing aspect of the current study is why severe hypotension lasting for hours was allowed to occur. Were the long durations of low blood pressure refractory or unrecognized? As such, the study does not elucidate the practical approach to treat persistent hypotension. Given the fact that the study took place in a high-dependency unit, low-staffing or inadequate access to treatment modalities (fluid therapy, vasopressors) would not be expected to explain the prolonged duration. This raises the important question of *how* we alert clinical staff about adverse physiologic deviations to ensure timely interventions in a way where alarms do not cause alarm fatigue and other causes for unresponsiveness to alerts.[7] This should be an important research objective, if results such as the ones found by Liem *et al*. are to alter clinical practice.

As such, this study also tells us that the long-standing focus on blood pressure as the only surrogate for perfusion should be tempered, and a more integrated assessment of tissue and myocardial perfusion and oxygenation is needed.[12] The time has come to move beyond single-modality assessments and using a multimodal sensor and patient characteristics approach to form the basis for real-time risk models to identify patients developing severe postoperative complications. This would allow timely and effective interventions, not only in high-dependency units but also extending into the general wards in high-risk procedures and patients, and ultimately at home, allowing for safe and early discharge. Achieving this goal would be the next big step in improving perioperative care, and the study by Liem *et al*. has identified essential information for the blood pressure component of such potential systems.

Hopefully, the perspectives presented above will facilitate the necessary journey toward more enlightened and, most importantly, evidence-based management of perioperative blood pressure, hopefully by a smooth railroad, but more likely we will continue to live with the dreaded roller coaster, to the appropriate destination in one of the "last great frontiers" of anesthetic and perioperative medical practice.

Acknowledgments

The coauthors wish to acknowledge the many contributions Dr. Le Manach has made to the field of perioperative medicine over his exciting career and his passion and enthusiasm for clinical research. We will miss him greatly.

Competing Interests

Drs. Meyhoff and Aasvang are members of the WARD Project management committee, a research project investigating wireless monitoring. The WARD Project is funded by Innovation Fund Denmark (Copenhagen, Denmark), Novo Nordic Foundation (Copenhagen, Denmark), Danish Cancer Society (Copenhagen, Denmark), Radiometer Medical (Copenhagen, Denmark), Copenhagen Center for Health Technology (Copenhagen, Denmark), Isansys Ltd (Oxfordshire, United Kingdom), and AP Møller Foundation (Copenhagen, Denmark). Dr. Meyhoff also reports direct and indirect research funding from Ferring Pharmaceuticals (Copenhagen, Denmark), Merck, Sharp & Dohme Corp. (New Jersey), and Boehringer Ingelheim (Ingelheim am Rhein, Germany) outside the submitted work as well as lecture fees from Radiometer. Dr. Aasvang also reports institutional research funding from Norpharma A/S (Copenhagen, Denmark) outside the submitted work as well as lecture fees from Radiometer. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. London: Martin.london@ucsf.edu

References

1. Liem VGB, Hoeks SE, Mol KHJM, Potters JW, Grüne F, Stolker RJ, van Lier F: Postoperative hypotension after noncardiac surgery and the association with myocardial injury. Anesthesiology 2020; 133:510–22
2. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology 2013; 119:507–15
3. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, Miller TE, Miller TE, Mythen MG, Grocott MP, Edwards MR; Perioperative Quality Initiative-3 workgroup; POQI chairs; Physiology group; Preoperative blood pressure group; Intraoperative blood

pressure group; Postoperative blood pressure group: Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019; 122:563–74
4. Sessler DI, Khanna AK: Perioperative myocardial injury and the contribution of hypotension. Intensive Care Med 2018; 44:811–22
5. Meng L, Yu W, Wang T, Zhang L, Heerdt PM, Gelb AW: Blood pressure targets in perioperative care. Hypertension 2018; 72:806–17
6. Abbott TEF, Minto G, Lee AM, Pearse RM, Ackland GL; POM-HR, POMO-O and OPTIMISE study groups: Elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment in high-risk surgical patients. Br J Anaesth 2017; 119:87–94
7. Haahr-Raunkjær C, Meyhoff CS, Sørensen HBD, Olsen RM, Aasvang EK: Technological aided assessment of the acutely ill patient: The case of postoperative complications. Eur J Intern Med 2017; 45:41–5
8. Aasvang EK, Luna IE, Kehlet H: Challenges in postdischarge function and recovery: The case of fast-track hip and knee arthroplasty. Br J Anaesth 2015; 115:861–6
9. Bojesen RD, Fitzgerald P, Munk-Madsen P, Eriksen JR, Kehlet H, Gögenur I: Hypoxaemia during recovery after surgery for colorectal cancer: A prospective observational study. Anaesthesia 2019; 74:1009–17
10. Duus CL, Aasvang EK, Olsen RM, Sørensen HBD, Jørgensen LN, Achiam MP, Meyhoff CS: Continuous vital sign monitoring after major abdominal surgery: Quantification of micro events. Acta Anaesthesiol Scand 2018; 62:1200–8
11. Khanna AK, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, Lee S, Ti LK, Urman RD, McIntyre R, Jr., Tornero C, Dahan A, Saager L, Weingarten TN, Wittmann M, Auckley D, Brazzi L, Le Guen M, Soto R, Schramm F, Ayad S, Kaw R, Di Stefano P, Sessler DI, Uribe A, Moll V, Dempsey SJ, Buhre W, Overdyk FJ: Prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: An international prospective, observational trial. Anesth Analg 2020 Apr 16 [Epub ahead of print]
12. Foss NB, Kehlet H: Perioperative haemodynamics and vasoconstriction: Time for reconsideration? Br J Anaesth 2019; 123:100–3