

4. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Vender JS, Benson J, Newmark RL: Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: A randomized, double-blinded, controlled trial. *ANESTHESIOLOGY* 2017; 126:822–33

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Blood Pressure Components and Organ Injury: Comment

To the Editor:

We read with great interest the article by Ahuja *et al.*¹ on the association between various intraoperative blood pressure components and postoperative morbidity. They identified an association among the arterial systolic, mean, and pulse pressure hypotension with myocardial and renal injury. Although the main finding—a lower blood pressure can be associated with postoperative myocardial injury after noncardiac surgery and acute kidney injury—offers clinically valuable information, we believe that some inherent bias in the study design should be discussed and clarified.

First, compared with previously published studies, this study had an important difference in the definition of myocardial injury after noncardiac surgery.² The outcome definition of myocardial injury in this study (*i.e.*, elevation of troponin or creatinine kinase-myocardial bound during the first 7 postoperative days)¹ was different from that approved by the consensus diagnostic criteria in 2014, which defined myocardial injury after noncardiac surgery as “elevated post-operative troponin measurement judged as resulting from myocardial ischemia during or within 30 days after non-cardiac surgery.”^{3,4} In addition, this study did not exclude nonischemic etiologies (sepsis, arrhythmias, pulmonary embolism, *etc.*). A previous study showed that elevation of troponin levels in 11 to 14% cases after noncardiac surgery was due to nonischemic etiologies.³ Therefore, without an adequate outcome assessor, the results of Ahuja *et al.*¹ tend to overestimate the actual incidence of myocardial injury by including nonischemic etiologies. Although this exclusion was not possible because of the retrospective study design using electronic medical records, the authors should discuss this aspect in the study limitations.

Second, residual confounding might have been present because compared with routine postoperative biomarker screening, the postoperative measurements of cardiac biomarkers were likely to be influenced by clinical indication (“confounding by indication”).⁵ As stated by the authors, the postoperative troponin concentration was measured in only 25% of the samples, and the authors assumed that myocardial injury was absent in patients without troponin surveillance.¹ This assumption can induce serious outcome detection bias. In clinical practice, postoperative cardiac biomarkers (troponin or creatinine kinase-myocardial bound) are not measured routinely. Results of previous studies indicate that majority of the patients with myocardial injury after noncardiac surgery (approximately 90%) do not have clinical cardiac symptoms and are not surveilled for troponin measurement.^{6,7} Therefore, measurement of postoperative cardiac biomarkers was mostly restricted to only high-risk patients or those with clinical signs of myocardial ischemia.⁸ In addition, differential surveillance for outcome assessment in patients who experienced or did not experience intraoperative hypotension can induce surveillance bias.^{9,10} If possible, Ahuja *et al.* should perform sensitivity analyses in patients who undergo troponin surveillance (5,699 patients) to test the robustness of their results. This information will be valuable to the readers of *ANESTHESIOLOGY*.

Competing Interests

The author declares no competing interests.

Hiroshi Yonekura, M.D., M.P.H., Mie University Hospital, Mie, Japan. komekurahiroshi@gmail.com

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References

- Ahuja S, Mascha EJ, Yang D, Maheshwari K, Cohen B, Khanna AK, Ruetzler K, Turan A, Sessler DI: Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: A retrospective cohort analysis. *ANESTHESIOLOGY* 2020; 132:291–306
- Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307:2295–304
- Devereaux PJ, Szczeklik W: Myocardial injury after non-cardiac surgery: Diagnosis and management. *Eur Heart J* 2019 May 16 [Epub ahead of print]
- Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, Guyatt G, Cruz P, Graham M,

Wang CY, Berwanger O, Pearse RM, Biccarrd BM, Abraham V, Malaga G, Hillis GS, Rodseth RN, Cook D, Polanczyk CA, Szczeklik W, Sessler DI, Sheth T, Ackland GL, Leuwer M, Garg AX, Lemanach Y, Pettit S, Heels-Ansdell D, Luratibuse G, Walsh M, Sapsford R, Schünemann HJ, Kurz A, Thomas S, Mrkobrada M, Thabane L, Gerstein H, Paniagua P, Nagele P, Raina P, Yusuf S, Devereaux PJ, Devereaux PJ, Sessler DI, Walsh M, Guyatt G, McQueen MJ, Bhandari M, Cook D, Bosch J, Buckley N, Yusuf S, Chow CK, Hillis GS, Halliwell R, Li S, Lee VW, Mooney J, Polanczyk CA, Furtado MV, Berwanger O, Suzumura E, Santucci E, Leite K, Santo JA, Jardim CA, Cavalcanti AB, Guimaraes HP, Jacka MJ, Graham M, McAlister F, McMurtry S, Townsend D, Pannu N, Bagshaw S, Bessissow A, Bhandari M, Duceppe E, Eikelboom J, Ganame J, Hankinson J, Hill S, Jolly S, Lamy A, Ling E, Magloire P, Pare G, Reddy D, Szalay D, Tittley J, Weitz J, Whitlock R, Darvish-Kazim S, Debeer J, Kavsak P, Kearon C, Mizera R, O'Donnell M, McQueen M, Pinthus J, Ribas S, Simunovic M, Tandon V, Vanhelder T, Winemaker M, Gerstein H, McDonald S, O'Bryne P, Patel A, Paul J, Punthakee Z, Raymer K, Salehian O, Spencer F, Walter S, Worster A, Adili A, Clase C, Cook D, Crowther M, Douketis J, Gangji A, Jackson P, Lim W, Lovrics P, Mazzadi S, Orovan W, Rudkowski J, Soth M, Tiboni M, Acedillo R, Garg A, Hildebrand A, Lam N, Macneil D, Mrkobrada M, Roshanov PS, Srinathan SK, Ramsey C, John PS, Thorlacius L, Siddiqui FS, Grocott HP, McKay A, Lee TW, Amadeo R, Funk D, McDonald H, Zacharias J, Villar JC, Cortés OL, Chaparro MS, Vásquez S, Castañeda A, Ferreira S, Coriat P, Monneret D, Goarin JP, Esteve CI, Royer C, Daas G, Chan MT, Choi GY, Gin T, Lit LC, Xavier D, Sigamani A, Faruqui A, Dhanpal R, Almeida S, Cherian J, Furuq S, Abraham V, Afzal L, George P, Mala S, Schünemann H, Muti P, Vizza E, Wang CY, Ong GS, Mansor M, Tan AS, Shariffuddin II, Vasanthan V, Hashim NH, Undok AW, Ki U, Lai HY, Ahmad WA, Razack AH, Malaga G, Valderrama-Victoria V, Loza-Herrera JD, De Los Angeles Lazo M, Rotta-Rotta A, Szczeklik W, Sokolowska B, Musial J, Gorka J, Iwaszczuk P, Kozka M, Chwala M, Raczek M, Mrowiecki T, Kaczmarek B, Biccarrd B, Cassimjee H, Gopalan D, Kisten T, Mugabi A, Naidoo P, Naidoo R, Rodseth R, Skinner D, Torborg A, Paniagua P, Urrutia G, Maestre ML, Santaló M, Gonzalez R, Font A, Martínez C, Pelaez X, De Antonio M, Villamor JM, García JA, Ferré MJ, Popova E, Alonso-Coello P, Garutti I, Cruz P, Fernández C, Palencia M, Díaz S, Del Castillo T, Varela A, de Miguel A, Muñoz M, Piñeiro P, Cusati G, Del Barrio M, Membrillo MJ, Orozco D, Reyes F, Sapsford RJ, Barth J, Scott J, Hall A, Howell S, Loblely M, Woods J, Howard S, Fletcher J,

Dewhurst N, Williams C, Rushton A, Welters I, Leuwer M, Pearse R, Ackland G, Khan A, Niebrzegowska E, Benton S, Wragg A, Archbold A, Smith A, McAlees E, Ramballi C, Macdonald N, Januszewska M, Stephens R, Reyes A, Paredes LG, Sultan P, Cain D, Whittle J, Del Arroyo AG, Sessler DI, Kurz A, Sun Z, Finnegan PS, Egan C, Honar H, Shahinyan A, Panjasawatwong K, Fu AY, Wang S, Reineks E, Nagele P, Blood J, Kalin M, Gibson D, Wildes T; Vascular events In noncardiac Surgery patients cOhort evaluation (VISION) Writing Group, on behalf of The Vascular events In noncardiac Surgery patients cOhort evaluation (VISION) Investigators; Appendix 1. The Vascular events In noncardiac Surgery patients cOhort evaluation (VISION) Study Investigators Writing Group; Appendix 2. The Vascular events In noncardiac Surgery patients cOhort evaluation Operations Committee; Vascular events In noncardiac Surgery patients cOhort evaluation VISION Study Investigators: Myocardial injury after noncardiac surgery: A large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *ANESTHESIOLOGY* 2014; 120:564–78

5. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA: Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. *Br J Anaesth* 2018; 121:706–21
6. Writing Committee for the VISION Study Investigators, Devereaux PJ, Biccarrd BM, Sigamani SK, Walsh M, Abraham V, Pearse R, Wang CY, Sessler DI: Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017; 317:1642–51
7. Ruetzler K, Khanna AK, Sessler DI: Myocardial injury after noncardiac surgery: Preoperative, intraoperative, and postoperative aspects, implications, and directions. *Anesth Analg* 2019; 131:173–86
8. Brady K, Hogue CW: Intraoperative hypotension and patient outcome: Does “one size fit all?” *ANESTHESIOLOGY* 2013; 119:495–7
9. Haut ER, Pronovost PJ: Surveillance bias in outcomes reporting. *JAMA* 2011; 305:2462–3
10. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ: GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011; 64:407–15

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Blood Pressure Components and Organ Injury: Reply

In Reply:

Dr. Yonekura notes that we failed to exclude patients with potential nonischemic causes of troponin elevation, thus possibly including some patients who did not actually have myocardial injury after noncardiac surgery.¹ It is likely that most patients who have troponin elevations and conditions that might falsely elevate troponin concentrations actually do have myocardial injury. Nonetheless, nonischemic causes should have been excluded from our analyses.²

Had the purpose of our study been to determine the incidence of myocardial injury, it would be critical to include only patients with scheduled (not-for-cause) troponin screening. But that was not our purpose at all. Detection and ascertainment bias are therefore irrelevant to our analysis. Instead, we asked which blood pressure components best predicted myocardial injury. Because all four components were evaluated *in each patient*, there was no bias.

Per request, we present a sensitivity analysis that excludes patients with medical conditions that might explain nonischemic troponin elevations (Supplemental Digital Content, table 1, <http://links.lww.com/ALN/C427>) and is restricted to patients who had scheduled (not for cause) troponin measurements. The analysis included 4,886 patients. The overall observed incidence of myocardial injury after noncardiac surgery was 17%.

The statistically determined thresholds and visual cutoff points did not change by clinically important amounts, although the systolic threshold decreased from 87 to 79 mmHg and pulse pressure threshold decreased from 35 to 30 mmHg (table 1, fig. 1, and Supplemental Digital Content, table 2, <http://links.lww.com/ALN/C428>). Univariable and multivariable

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

relationships between blood pressure components and myocardial injury were essentially unchanged except for pulse pressure (fig. 1). Interestingly, pulse pressure demonstrated a relatively flat curve between 25 and 45 mmHg—implying a weak relationship between pulse pressure and myocardial injury. The odds of patients experiencing a composite of serious complications were significantly higher for the fourth quartile of area under curve under the threshold for systolic, mean, and pulse pressure compared to patients who never went below the threshold, but not for diastolic pressure (fig. 2).

Power was limited when analysis was restricted to patients with scheduled troponin surveillance. But among the four blood pressure components, systolic and mean pressures continue to be most predictive and were comparable in their strength of association with myocardial injury. The relationship with diastolic pressure remained poor, but pulse pressure was as well, which differs from our original analysis. We therefore conclude that systolic pressure at a threshold of 80 to 90 mmHg and mean pressure at a threshold near 65 mmHg are the blood pressure components most associated with myocardial injury in patients who have major noncardiac surgery. Similar thresholds for renal injury were identified in our original analysis.¹

Competing Interests

Drs. Sessler and Maheshwari are consultants to Edwards Lifesciences (Irvine, California). The other authors declare no competing interests.

Sanchit Ahuja, M.D., Edward J. Mascha, Ph.D., Barak Cohen, M.D., Dongsheng Yang, M.A., Chao Ma, M.S., Kamal Maheshwari, M.D., M.P.H., Daniel I. Sessler, M.D. Cleveland Clinic, Cleveland, Ohio (D.I.S.). DS@OR.org

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References

1. Yonekura H: Blood pressure components and organ injury: Comment. *ANESTHESIOLOGY* 2020; 133:673–4

Table 1. Myocardial Injury Change-point Tests in All Patients *versus* Those with Scheduled Troponin Measurements and Troponin Elevations Excluding Potential Nonischemic Causes

Blood Pressure Components	All Patients (N = 23,140)	Patients with Scheduled Troponin and Excluding Potential Nonischemic Causes (N = 4,886)	P Value
	Change point (95% CI)		
	Estimate (95% CI)	Estimate (95% CI)	
Systolic (mmHg)	87 (85–90)	79 (73–86)	< 0.001
Mean (mmHg)	65 (63–69)	65 (57–74)	< 0.001
Diastolic (mmHg)	51 (48–56)	49 (44–58)	< 0.001
Pulse pressure (mmHg)	35 (34–37)	30 (25–39)	< 0.001

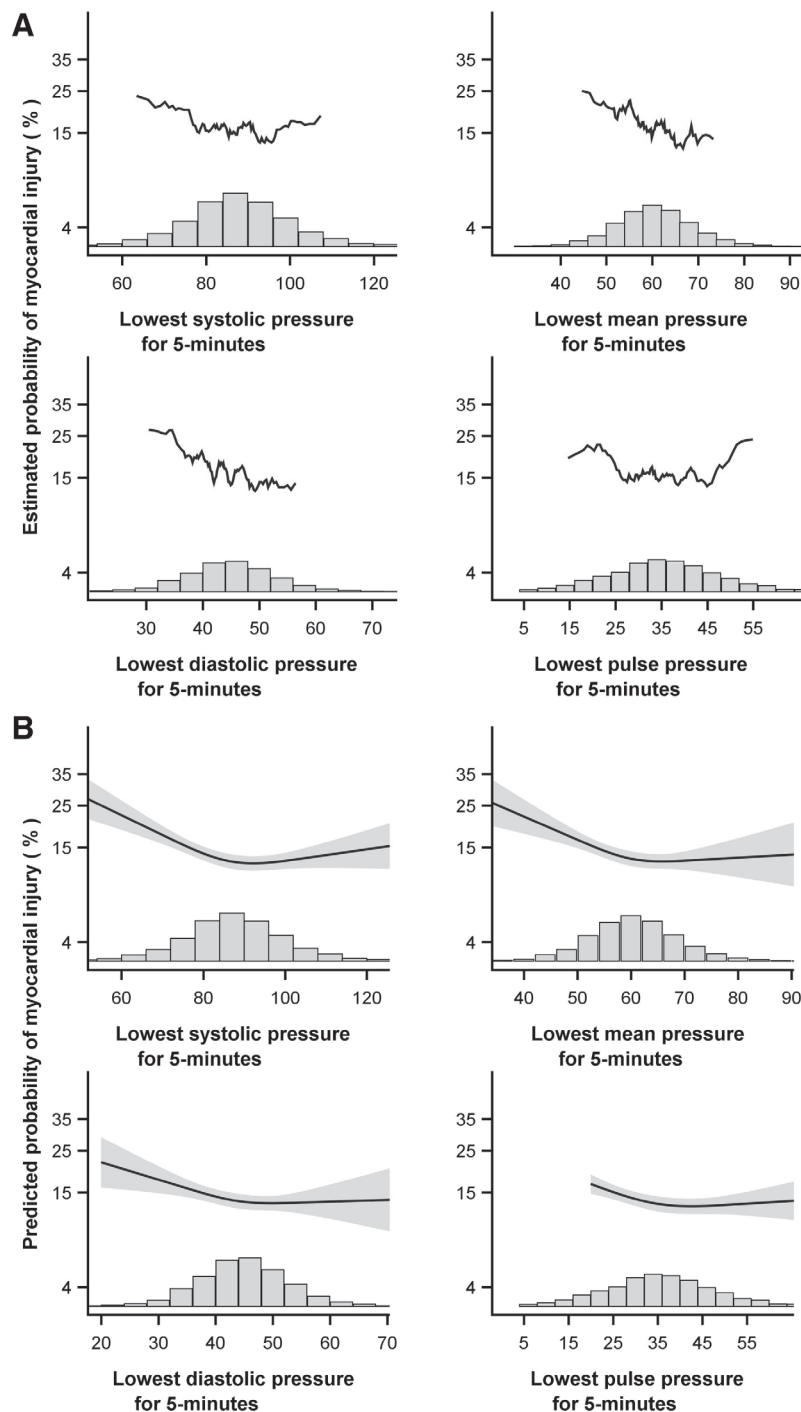


Fig. 1. Relationship between lowest blood pressure values and myocardial injury, restricted to patients with scheduled troponin testing and excluding potential nonischemic etiologies of troponin elevation. Univariable and multivariable relationship between myocardial injury and lowest blood pressure for 5 cumulative minutes for each of four blood pressure components. (A) Estimated probability of myocardial injury from a univariable moving window with a bin width of 10% of the data. (B) Multivariable logistic regression smoothed by restricted cubic spline with 3 degrees and knots at 10th, 50th, and 90th percentiles of given blood pressure component. Based mainly on the multivariable plots, blood pressure components thresholds of 80 mmHg for systolic blood pressure, 65 mmHg for mean arterial pressure, 50 mmHg for diastolic blood pressure, and 35 mmHg for pulse pressure were visual change-points associated with increasing odds of myocardial injury. The *histogram* at the bottom of each graph shows the fraction of patients at each lowest blood pressure value. The *blue lines* in A and *smoothed lines* with 95% confidence bands in B indicate estimated probability of myocardial injury as a function of the lowest 5 min of each component.

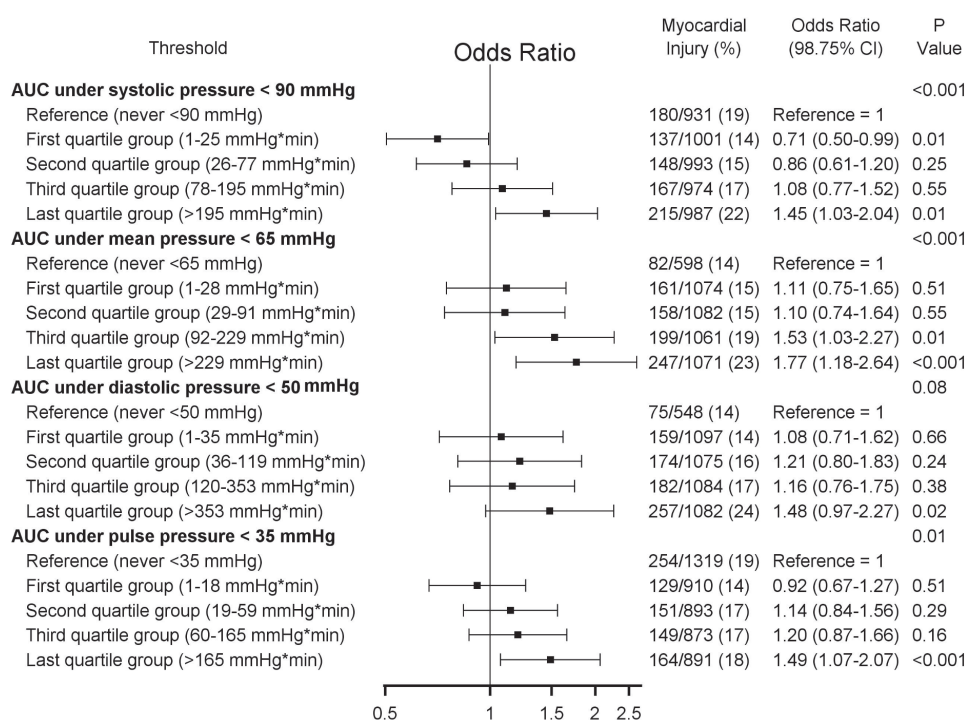


Fig. 2. Multivariable associations between myocardial injury and area under curve (AUC) under each blood pressure component threshold restricted to patients with scheduled troponin testing and excluding potential nonischemic etiologies of troponin elevation. Bonferroni correction was used to adjust for four comparisons to the reference group within each exposure of interest so that $P < 0.0125$ ($0.05/4$) was considered statistically significant.

- Ahuja S, Mascha EJ, Yang D, Maheshwari K, Cohen B, Khanna AK, Ruetzler K, Turan A, Sessler DI: Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: A retrospective cohort analysis. *ANESTHESIOLOGY* 2020; 132:291–306

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COVID-19 Infection: Perioperative Implications: Comment

To the Editor:

We read with great interest the manuscript by Greenland *et al.*, discussing the perioperative and

critical care implications of coronavirus disease 2019 (COVID-19) infection with a focus on management of associated respiratory failure.¹ We congratulate the authors for the comprehensive article which is imperative in these times for the critical care physicians.

The authors have discussed the typical presentation enumerating the primary presenting symptoms, major complications, and variations in presentation. However, we would like to add to this list an important aspect of involvement of the central nervous system. In a recent case series of 214 patients, about 36.4% (78 of 214) of the patients had neurologic manifestations pertaining to the central and peripheral nervous systems and skeletal muscle injury.² The patients who had severe infection were prone to develop neurologic manifestations. The symptoms observed were dizziness, headache, seizures, impaired consciousness, acute cerebrovascular disease, and ataxia. The loss of smell and taste seen in these patients indicates the possible involvement of the peripheral nervous system by the virus. The transsynaptic transfer from peripheral to central nervous system is quite a possibility. The neurotropism of this novel coronavirus is believed to be similar to other coronaviruses.³ The report of acute necrotizing encephalopathy affecting the thalamus, brain stem, white matter, and cerebellum strongly indicates the involvement of the nervous system by this novel virus.⁴