Artak Petrosyan, Julie Bellet (Clinical Research Department, Lille University Hospital, France); and Sandrine Brisset (Clinical Research Department, Amiens Picardie University Hospital, France).

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Postoperative Hypotension and Myocardial Injury: Comment

To the Editor:

We have read with great interest the observational cohort study "Postoperative Hypotension after Noncardiac Surgery and the Association with Myocardial Injury," by Liem *et al.*[1] In this study the authors examined postoperative hypotension after noncardiac surgery as a risk factor for myocardial injury by defining multiple mean arterial pressure (MAP) thresholds and different characterizations of blood pressure exposures. We commend the authors for further emphasizing the association between postoperative hypotension and myocardial injury and stressing the potential benefit of postoperative continuous blood pressure monitoring. May we ask the authors to provide some additional details that will help address some concerns and will better put their findings into clinical perspective? First, the secondary outcome of 30-day all-cause mortality was not compared between patients with *versus* patients without myocardial injury. May we kindly ask the authors to provide baseline characteristics including 30-day all-cause mortality stratified for myocardial injury and no myocardial injury? Second, the authors concluded that postoperative duration under a MAP threshold of 75 mmHg was associated with increased risk of myocardial injury. We are concerned that the corresponding figure 3 may lead some readers to falsely interpret the results, because the association between duration under a MAP threshold of 75 mmHg and myocardial injury was only significant for a duration of more than 635 min. Additionally, for a duration of more than 635 min under a MAP threshold of 75 mmHg, CIs are gradually increasing. Moreover, when comparing duration under MAP for five different thresholds, duration under a threshold of 75 mmHg did not remain significant. Please consider highlighting alternative thresholds that might be better supported by your data. Third, previous studies have additionally adjusted for use of cardiovascular medications before surgery (*i.e.*, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, calcium channel blocker, β-blocker, statin, diuretics, aspirin, oral anticoagulants).[2–4] We are concerned that not adjusting for preoperative cardiovascular medication may have led to an overestimation of the association between hypotension and injury or death. Please provide a sensitivity analysis adjusting for those important confounders. This will help clinicians to further understand the impact of postoperative hypotension on myocardial injury.

Competing Interests

Dr. Mueller reports grants and nonfinancial support from the Swiss National Science Foundation (Bern, Switzerland), the Swiss Heart Foundation (Bern, Switzerland), the University Hospital Basel (Basel, Switzerland), Basel University (Basel, Switzerland), the Foundation for Cardiovascular Research Basel (Basel, Switzerland), Abbott (Baar, Switzerland), Beckman Coulter (Nyon, Switzerland), Idorsia (Basel, Switzerland), Novartis (Basel, Switzerland), Ortho Diagnostics (Zug, Switzerland), Quidel (San Diego, California), Roche (Basel, Switzerland), Siemens (Zuerich, Switzerland), Singulex (Basel, Switzerland), and BRAHMS (Hennigsdorf, Germany) outside the submitted work. The other authors declare no competing interests.

David Schulthess, M.D., Melissa Amrein, Ph.Dc., Noemi Glarner, M.D., Ph.Dc., Pedro Lopez-Ayala, M.D., Christian Mueller, M.D. Cardiovascular Research Institute Basel (CRIB) and University Hospital of Basel, University of Basel, Basel, Switzerland (D.S.). david.schulthess@usb.ch

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Postoperative Hypotension and Myocardial Injury: Reply

In Reply:

We are more than happy to answer the questions Schulthess *et al.*[1] have, based on our previous publication.[2] The first question was to provide baseline characteristics of patients with and without myocardial injury. Their second question was related to the exposure and the associated risk for myocardial injury. Schulthess *et al.* are correct that duration under a mean arterial pressure (MAP) threshold of 75 mmHg is only associated with myocardial injury for prolonged periods of time. To graphically represent the relation between length of hypotension and myocardial injury, we could have chosen a MAP target of 60 mmHg where all durations, above 1 h, show an increased risk for myocardial injury. However, we

Table 1. Baseline and Perioperative Characteristics of High-dependency Ward Patients, Stratified for Myocardial Injury

	No Myocardial Injury (n = 1,472)	Myocardial Injury (n = 238)
Patient characteristics		
Age, yr	70 [65, 75]	74 [68, 79]
Male sex, n (%)	823 (56)	161 (68)
Procedural, n (%)		
Emergency	42 (3)	33 (14)
High-risk	384 (26)	55 (23)
General anesthesia	1,442 (98)	229 (96)
Type of surgery, n (%)		
General	270 (18)	38 (16)
Orthopedic	167 (11)	40 (17)
Urologic or gynecologic	153 (10)	22 (9)
Neurologic	505 (34)	27 (11)
Vascular	225 (15)	82 (34)
Other	152 (10)	29 (12)
Medical history, n (%)		
Hypertension	813 (55)	175 (74)
Insulin-dependent diabetes mellitus	144 (10)	50 (21)
Chronic obstructive pulmonary disease	236 (16)	54 (23)
Myocardial infarction	206 (14)	83 (35)
Coronary artery disease	265 (18)	104 (44)
Congestive heart failure	100 (7)	48 (20)
Cerebrovascular disease	234 (16)	71 (30)
Renal failure	53 (4)	69 (29)
Peripheral artery disease	115 (8)	38 (16)
Preoperative medication, n (%)		
β-blockers	585 (40)	137 (58)
Statins	642 (44)	147 (62)
Angiotensin converting enzyme-inhibitors	345 (23)	73 (31)
Angiotensin II antagonists	273 (19)	55 (23)
Calcium channel blockers	281 (19)	67 (28)
Diuretics	448 (30)	116 (49)
Aspirin	397 (27)	111 (47)
Oral anticoagulants	202 (14)	57 (24)
Preoperative		
Hemoglobin, g/dl	14 ± 2	13 ± 2
Glomerular filtration rate, ml · min · 1.73 m^{-2}	75 [61, 87]	50 [28, 77]
Heart rate, beats per min	74 [66, 82]	74 [66, 84]
MAP, mmHg	97 [90, 105]	94 [87, 101]
Intraoperative		
Length of surgery, min	242 [178, 326]	210 [153, 296]
Estimated blood loss, ml	300 [100, 650]	250 [50, 700]
Postoperative		
Peak high-sensitive troponin T, ng/l	14 [9, 21]	86 [62, 152]
Myocardial injury, n (%)	0	238 (100)
30-day mortality, n (%)	30 (2)	20 (8)

MAP, mean arterial pressure.

Table 2. Univariate and Multivariate Associations of Postoperative Hypotension, Defined as Different Exposures, and Myocardial Injury

Minutes below MAP, mmHg	Total (n = 1,710)	Myocardial Injury (n = 238)	Univariate Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)	Adjusted Odds Ratio* (95% CI) [Full Model]†	*P* Values
Intraoperative MAP < 65						
Reference (0)	254	39 (15.35)				
Q1: 1–8	377	52 (13.79)	0.88 (0.56–1.39)	0.92 (0.54–1.57)	0.87 (0.51–1.49)	0.599
Q2: 9–22	370	49 (13.24)	0.84 (0.53–1.33)	1.18 (0.70–2.03)	1.15 (0.67–1.98)	0.624
Q3: 23–53	351	44 (12.54)	0.79 (0.50–1.26)	1.28 (0.73–2.25)	1.11 (0.63–1.98)	0.713
Q4: > 53	358	54 (15.08)	0.98 (0.63–1.54)	1.66 (0.93–3.00)	1.36 (0.75–2.50)	0.313
Postoperative MAP < 75						
Reference (0)	268	24 (8.96)				
Q1: 1–86	361	40 (11.08)	1.27 (0.75–2.18)	1.19 (0.66–2.21)	1.17 (0.64–2.17)	0.621
Q2: 87–312	360	59 (16.39)	1.99 (1.22–3.35)	1.75 (0.99–3.21)	1.74 (0.97–3.19)	0.069
Q3: 313–635	360	45 (12.50)	1.45 (0.87–2.48)	1.42 (0.77–2.67)	1.34 (0.72–2.55)	0.363
Q4: > 635	361	70 (19.39)	2.45 (1.51–4.08)	2.91 (1.60–5.46)	2.69 (1.45–5.12)	0.002
Area under threshold mmHg · min						
Intraoperative MAP < 65						
Reference (0)	254	39 (15.35)				
Q1: 1–32	366	48 (13.11)	0.83 (0.53–1.32)	0.93 (0.54–1.59)	0.87 (0.51–1.50)	0.619
Q2: 33–108	362	49 (13.54)	0.86 (0.55–1.37)	1.18 (0.69–2.02)	1.08 (0.63–1.86)	0.789
Q3: 109–279	364	42 (11.54)	0.72 (0.45–1.15)	1.13 (0.65–1.98)	0.97 (0.55–1.72)	0.915
Q4: > 279	364	60 (16.48)	1.09 (0.70–1.70)	1.76 (1.01–3.12)	1.44 (0.81–2.59)	0.219
Postoperative MAP < 75						
Reference (0)	268	24 (8.96)				
Q1: 1–337	361	42 (11.63)	1.34 (0.80–2.30)	1.22 (0.67–2.25)	1.20 (0.66–2.22)	0.563
Q2: 338–1513	360	50 (13.89)	1.64 (0.99–2.78)	1.52 (0.85–2.79)	1.49 (0.82–2.76)	0.196
Q3: 1514–4419	360	58 (16.11)	1.95 (1.19–3.29)	1.88 (1.04–3.48)	1.83 (1.00–3.42)	0.053
Q4: > 4419	361	64 (17.73)	2.19 (1.35–3.67)	2.59 (1.41–4.88)	2.36 (1.26–4.51)	0.008
Time-weighted average, mmHg						
Intraoperative MAP < 65						
Reference (0)	254	39 (15.35)				
Q1: 0–0.14	364	44 (12.09)	0.76 (0.48–1.21)	0.93 (0.54–1.61)	0.88 (0.51–1.54)	0.661
Q2: 1.14–0.46	364	49 (13.46)	0.86 (0.54–1.36)	1.14 (0.67–1.96)	1.03 (0.60–1.79)	0.921
Q3: 0.46–1.12	364	44 (12.09)	0.76 (0.48–1.21)	1.16 (0.67–2.02)	1.02 (0.58–1.79)	0.943
Q4: > 1.12	364	62 (17.03)	1.13 (0.73–1.76)	1.54 (0.90–2.67)	1.25 (0.71–2.21)	0.438
Postoperative MAP < 75						
Reference (0)	268	24 (8.96)				
Q1: 0–0.29	361	37 (10.25)	1.16 (0.68–2.01)	1.07 (0.59–2.00)	1.06 (0.58–1.97)	0.858
Q2: 1.29–1.33	360	56 (15.56)	1.87 (1.14–3.16)	1.74 (0.97–3.18)	1.71 (0.95–3.14)	0.078
Q3: 2.33–3.67	360	55 (15.28)	1.83 (1.12–3.10)	1.82 (1.00–3.38)	1.74 (0.95–3.28)	0.077
Q4: > 3.67	361	66 (18.28)	2.27 (1.40–3.80)	2.70 (1.48–5.09)	2.51 (1.35–4.80)	0.004

There were no significant interactions between postoperative and intraoperative hypotension within the models. Bonferroni correction was used to adjust for the three defined exposures for postoperative hypotension. $P < 0.05/3 = 0.017$ was considered statistically significant. MAP, mean arterial pressure.

*Multivariate logistic model adjusted for age, sex, high-risk surgery, emergency procedures, intraoperative hypotension, intra- and postoperative heart rate, previous history of hypertension, insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, renal disease, estimated blood loss, length of surgery, and preoperative use of β-blockers, statins, angiotensin converting enzyme inhibitors, angiotensin II antagonists, calcium channel blockers, diuretics, aspirin, and oral anticoagulants; one observation deleted because of missingness. †Full model: Model with both intraoperative and postoperative exposures in the model (in quartiles).

have specifically chosen to report the highest threshold because this threshold was selected based on the figure in the supplemental digital content of the original article. Furthermore, we believe this threshold is relevant because the amount of time that was associated with myocardial injury (greater than 10 h) can be easily reached during the first postoperative night. The final question was with regard to certain preoperative medication and the risk of confounding. In our analysis we used the widely accepted rule of 10 events per variable to prevent imprecise and biased estimates in the logistic regression analysis. We therefore chose to adjust for the variables mostly associated with myocardial injury or hypotension. Sensitivity analysis including adjustment for the preoperative cardiovascular medication showed marginal differences in our results. Please find all the requested analysis in the tables 1–3.

Competing Interests

The authors declare no competing interests.

Table 3. Association of Postoperative Hypotension, as Duration under Multiple MAP Thresholds, and Myocardial Injury

Postoperative MAP Thresholds	Duration under MAP Threshold (h)	Total (n = 1,710)	Myocardial Injury (n = 238)	Adjusted Odds Ratio* (95% CI)† [Full Model]	*P* Values†
MAP < 60 mmHg					
	0	1,010	114 (11.29)	Ref	
	0–1	466	70 (15.02)	1.53 (1.04–2.26)	0.030
	1–2	91	23 (25.27)	2.73 (1.45–4.99)	0.001
	2–4	76	16 (21.05)	3.30 (1.57–6.64)	0.001
	> 4	67	15 (22.39)	2.04 (0.93–4.28)	0.065
MAP < 65 mmHg					
	0	693	74 (10.68)	Ref	
	0–1	474	64 (13.50)	1.47 (0.97–2.23)	0.067
	1–2	153	26 (16.99)	1.78 (0.97–3.16)	0.055
	2–4	160	23 (14.37)	1.81 (0.98–3.26)	0.054
	> 4	230	51 (22.17)	3.01 (1.79–5.06)	< 0.001
MAP < 70 mmHg					
	0	466	49 (10.52)	Ref	
	0–1	371	50 (13.48)	1.25 (0.77–2.03)	0.359
	1–2	174	16 (9.20)	0.80 (0.39–1.56)	0.527
	2–4	195	28 (14.36)	1.28 (0.71–2.29)	0.407
	> 4	504	95 (18.85)	2.19 (1.37–3.57)	0.001
MAP < 75 mmHg					
	0	268	24 (8.96)	Ref	
	0–1	285	32 (11.23)	1.15 (0.61–2.19)	0.662
	1–2	157	21 (13.38)	1.53 (0.74–3.13)	0.245
	2–4	178	21 (11.80)	1.29 (0.63–2.61)	0.482
	> 4	822	140 (17.03)	2.04 (1.19–3.64)	0.012
MAP < 80 mmHg					
	0	153	17 (11.11)	Ref	
	0–1	191	13 (6.81)	0.52 (0.22–1.22)	0.132
	1–2	122	18 (14.75)	1.48 (0.66–3.36)	0.344
	2–4	164	23 (14.02)	1.20 (0.55–2.66)	0.646
	> 4	1080	167 (15.46)	1.39 (0.75–2.73)	0.319

There were no significant interactions between postoperative and intraoperative hypotension within the models. MAP, mean arterial pressure.

*Multivariate logistic model adjusted for age, sex, high-risk surgery, emergency procedures, intraoperative hypotension, intra- and postoperative heart rate, previous history of hypertension, insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, renal disease, estimated blood loss, length of surgery, and preoperative use of β-blockers, statins, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, calcium channel blockers, diuretics, aspirin, and oral anticoagulants; one observation deleted because of missingness. †Bonferroni correction was used to adjust for the five defined MAP thresholds for postoperative hypotension. $P < 0.05/5 = 0.01$ was considered statistically significant.

Victor G. B. Liem, M.D., M.Sc., Sanne E. Hoeks, Ph.D., Felix van Lier, M.D., Ph.D. Erasmus University Medical Center, Rotterdam, The Netherlands (F.v.L.). F.vanlier@erasmusmc.nl

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Anesthesia and Circulating Tumor Cells: Comment

To the Editor:

With great interest we have read the article by Hovaguimian *et al.*[1] regarding the effect of different anesthesia drugs (sevoflurane or propofol) on the number of circulating tumor cells in patients undergoing breast cancer surgery. We appreciate and congratulate the authors for setting up a meaningful randomized, controlled trial and sharing such useful findings. There are, however, two important points of concern.

First of all, the study used a mixed Poisson model. However, we noted that the first quartile of circulating tumor cell count results at all time points was zero, and the median was also zero