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ORIGINAL ARTICLE

Intraoperative hypotension and its association with acute kidney injury in patients undergoing elective cardiac surgery: a large retrospective cohort study

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BACKGROUND Intraoperative hypotension (IOH) is known to affect renal outcomes in noncardiac surgery. However, it is unclear whether intraoperative hypotension (IOH) causes postoperative acute kidney injury following cardiac surgery.

OBJECTIVE This study aimed to determine whether the duration of IOH during cardiac surgery is associated with the incidence of postoperative acute kidney injury (AKI) and identify its impact on long-term outcomes.

DESIGN Retrospective cohort study.

SETTING Academic university hospital (Heart and Diabetes Center, Bad Oeynhausen, Germany).

PATIENTS A cohort of 28 909 patients who underwent elective cardiac surgery between 1 January 2009 and 31 December 2018.

INTERVENTIONS IOH was defined as intraoperative mean arterial blood pressure (MAP) of less than 60 mmHg for more than 2 min. The cumulative duration of these IOH events was recorded each patient.

MAIN OUTCOME MEASURES The primary outcome was the incidence of AKI according to the KDIGO criteria (Kidney Disease: Improving Global Outcomes). Logistic regression analysis was used to analyse the associations between IOH and the incidence of AKI. Secondary outcomes were the independent predictors for the incidence of AKI.

RESULTS Postoperative AKI was observed in 42.9% of patients. The cumulative duration of IOH (minutes) had a significant influence on the incidence of AKI [odds ratio (OR) 1.004; 95% confidence interval (CI) 1.003 to 1.005; P < 0.001] (P > 0.001 versus P < 0.001). The survival time was significantly shorter in patients with a higher cumulative duration of IOH, patients aged more than 70 years, and those who developed AKI (P < 0.001). Logistic regression analysis identified eight predictors of AKI: age, cumulative duration of IOH, duration of surgery, chronic obstructive pulmonary disease, body mass index, type of surgery, American Society of Anesthesiologists stage, and Euroscore 2.

CONCLUSIONS The cumulative duration of IOH is an independent risk factor for the occurrence of postoperative AKI after cardiac surgery.

TRIAL REGISTRATION Ethics Committee of the Ruhr University Bochum (Register number 2019-491).

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KEY POINTS

- Intraoperative hypotension, defined as a MAP of less than 60 mmHg for at least two minutes occurs commonly during cardiac surgery (96.1%).
- Acute renal failure was observed in 42.9% of the total cohort, with a large proportion of patients developing KDIGO stages 1 and 2 (approximately 80%).
- The cumulative duration of intraoperative hypotension and increasing age are independent risk factors for the incidence of acute kidney injury.
- Prolonged duration of intraoperative hypotension has a direct impact on mortality.

Introduction

The incidence of acute kidney injury (AKI) has been frequently reported following cardiac surgery and is associated with high morbidity and mortality. Cardiac surgery-associated AKI has been estimated to occur in approximately 40% of patients, and it has a significant impact on global healthcare costs. AKI, in its most severe form, increases the odds ratio of postoperative mortality, length of stay in the intensive care unit and hospital, and the total costs of care.^{1–3}

Over the last decade, clinical studies have analysed the incidence rates and significance of intraoperative hypotension (IOH) and its impact on end-organ dysfunction, especially acute kidney injury (AKI).

According to normal physiological conditions, renal blood flow is constant with a mean arterial pressure (MAP) greater than 65 mmHg. When MAP decreases, renal blood flow becomes pressure-dependent with subsequent risk of ischaemia–perfusion injury and AKI. Large retrospective studies have revealed an association between IOH in noncardiac settings and AKI, suggesting an increased risk for AKI with MAP levels below 55 to 60 mmHg.^{4,5}

Additionally, an increasing number of clinical studies have reported that IOH may contribute to multiorgan injury caused by compromised perfusion and a subsequent increase the 30-day to 1-year mortality rates.^{6–11} IOH may be associated with end-organ dysfunction after cardiac surgery, especially in cases where the frequency, duration and severity of IOH is increased.^{6,12,13} However, a concrete definition has not been established for low intraoperative MAP. Bijker *et al.*¹⁴ revealed that 140 definitions of IOH were used in 130 publications, thus demonstrating the complexity and divergence between researchers and medical practitioners worldwide.

To the best of our knowledge, a universally accepted definition for IOH in the cardiac setting has not been

established, and its association with postoperative AKI remains unclear. Therefore, the primary aim of this study was to determine the cumulative duration of a MAP of <60 mmHg for at least 2 minutes. The secondary aim was to analyse the association between this cumulative duration of IOH and different stages of AKI according to the KDIGO guidelines and identify the independent risk factors for the incidence of AKI.

Methods

Ethics

The Ethical Committee of Ruhr-University Bochum, Bad Oeynhausen, Germany approved this study on 13 May 2019 (Register number: 2019-419).

Data collection

The perioperative data were collected from the electronic patient data management system (PDMS) Copra (CO-PRA System GmbH, Berlin) and the hospital information system ORBIS (DH Healthcare GmbH, Bonn). Patients who underwent elective cardiac surgery between 2009 and 2018 were eligible for inclusion in this study.

All patients underwent intra-arterial catheterisation to facilitate continuous blood pressure monitoring and blood-gas analyses. Mean arterial pressure recorded every 15 s. Postoperative survival was determined based on the annual queries by the Institute for Data Management of the Heart and Diabetes Center (NRW).

The inclusion criteria were as follows: patients age at least 18 years; patients undergoing coronary bypass surgery with or without cardiopulmonary bypass (CPB), valve surgery with or without CPB, combination surgery, or aortic surgery.

The exclusion criteria were: the requirement for preoperative kidney transplantation, emergency interventions, heart and lung transplantation or assist device implantation (left and right ventricular assist device) patients who underwent one of included surgical procedures but who lacked preoperative and postoperative (7 days) levels of serum creatinine, and similarly patients with undocumented urine volumes for the first seven postoperative days. American Society of Anesthesiologists Physical status score (ASA) was not an exclusion criterion.

Outcomes

- 1. Postoperative AKI was defined as an increase in postoperative serum creatinine levels and a low urine volume. According to the KDIGO guidelines, a postoperative increase of more than 50% or more than 0.3 mg dl^{-1} in the serum creatinine level from baseline or a urine output of less than $0.5 \text{ ml kg}^{-1} \text{ h}^{-1}$ for more than 6 h indicated an AKI.
- 2. All-cause 30-day and 1-year mortality rates were the secondary outcomes.

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Statistical methods

IOH was defined as an intraoperative MAP of less than 60 mmHg for more than 2 min. The cumulative duration of IOH was determined for each patient and divided into the following quartiles. Quartile 1: no IOH and cumulative IOH for 2 to 17 min; quartile 2: cumulative IOH for 18 to 44 min; quartile 3: cumulative IOH for 45 to 83 min, and quartile 4: cumulative IOH for more than 83 min. Subgroups were formed according to the duration of IOH and the incidence of AKI, which were subsequently examined to assess various outcome parameters. All statistical analyses were performed using IBM SPSS software version 26 (IBM Corp, Armonk, New York, USA).

The normality of the data was assessed visually using boxplots, histograms, and qq-plots. The χ^2 test or Mann– Whitney U test was used to compare the differences in patient characteristics and potential confounders among the groups. The effect size was calculated using Pearson's r and Cramer V statistics. Survival time analysis was performed using the Kaplan–Meier method. The logrank test was used to determine the significance of the differences between various subgroups.

Data were analysed using univariate and multiple analyses. A logistic regression model was created with adjustments for the factors. Univariate analysis was performed for each variable that could influence the incidence of AKI. Variables that had a significant influence, that is, P less than 0.05, were included in the multivariate analysis. The significance level was set at P less than 0.05. All P values were considered nonconfirmatory owing to the explorative nature of this study.

Results

Figure 1 presents the patient flow chart. Among the 31 817 patients who underwent cardiac surgery between the years 2009 to 2018, 2908 patients were excluded. Thus, 28 909 patients were included in the final analyses after applying the inclusion and exclusion criteria. The overall incidence of AKI was 42.9%. In total, 3905 patients (31.5%), 5915 patients (47.7%) and 2568 patients (20.7%) met the KDIGO stage 1, 2 and 3 criteria, respectively. The mean \pm SD total duration of surgery was 195.0 \pm 73.5 min.

IOH, defined as MAP of less than 60 mmHg for 2 min or more, was observed at least once in 96.1% of patients. The median cumulative duration of IOH was 44 min. These 44 min of IOH represented a median of 25% of the total duration of surgery. To analyse and compare the duration of IOH, the patient cohort was categorised into quartiles based on the duration of hypotension (min).

Survival

The mean survival duration of the entire cohort was 2692 ± 10 days, and 6378 patients (22.1%) died during the observation period. The survival duration of patients in the four different groups differed significantly (log-rank test, P < 0.01) when the cohort was divided into quartiles





AKI, acute kidney injury; BP, blood pressure; HDZ, Heart and Diabetes Centre, Bad Oeynhausen.

based on the duration of hypotension. The 30-day, 1-year, and 3-year survival rates are presented in Table 1 and Fig. 2.

A group comparison was performed by comparing the recorded parameters between quartiles 1 to 3 and quartile 4 owing to the increased mortality in quartile 4, which was graphically visible. All parameters examined showed significant differences, with P values of less than 0.05. The calculated r and Cramer V statistics showed effect sizes with a level of r/Cramer V of greater than 0.1 for the ASA status, type of surgery, requirement for postoperative Kidney transplantation and the number of deaths. In addition to the good significance level, a weak effect was also demonstrated for these parameters. For the type of surgery, the effect size with a Cramer V value of 0.316 indicated a medium effect. Table 2 presents the differences in the patient characteristics according to the IOH quartile.

Subgroup analysis: acute kidney injury according to Kidney Disease: Improving Global Outcomes criteria

Nearly all demographic characteristics, medical history, surgery characteristics and intraoperative and postoperative factors showed significant differences between the AKI and no AKI groups. However, only body mass index



Table 1 Cumulative probability of survival

Survival time	First quartile IOH	Second quartile IOH	Third quartile IOH	Fourth quartile IOH
30 days survival	0.987	0.983	0.975	0.941
1-year survival	0.943	0.943	0.927	0.856
3-year survival	0.896	0.897	0.876	0.793
Survival days (mean \pm SD)	2733 ± 18	2783 ± 19 days	2699 ± 16	2456 ± 18

IOH, intraoperative hypotension; SD, standard deviation.

(BMI), ASA status, requirement for postoperative Kidney transplantation, and the number of deaths had an effect size of more than 0.1 (Table 3).

The mean duration of MAP of less than 60 mmHg was 41 and 50 min in the non-AKI and AKI groups, respectively. The proportion of patients with AKI increased as the IOH quartile progressed, similar to the proportion of patients with KDIGO stage 3 (Fig. 3). Figure 4 presents the survival duration according to the KDIGO stage. Patients who met the criteria for KDIGO stage 3 had significantly lower survival.

Logistic regression model

Binary logistic regression was used to analyse the effect of several factors on the incidence of AKI and estimate the probability of the incidence of AKI depending on the duration of hypotension or a change in age. Sex was excluded owing to its low significance in the univariate analysis (P = 0.23).

The full multivariate model revealed a statistical significance level of P < 0.001, high goodness of fit (Hosmer– Lemeshow test, $\chi(8) = 11121$, P > 0.05), and small effect size ($f^2 = 0.11$) for AKI. Eight factors that had a significant effect on the predictive performance of the model were identified.

Fig. 2 Survival according to the intraoperative hypotension quartiles.

An increase in the duration of IOH and age resulted in a significant increase in the risk of AKI, with an odds ratio of 1.004, 95% confidence interval (CI) 1.003 to 1.005, and 1.010, 95% CI 1.008 to 1.013, respectively. Table 4 presents the coefficients and odds ratios of all models.

Discussion

This large retrospective cohort study investigated the effects of IOH on nephrological outcomes and mortality in adult patients undergoing cardiac surgery. The primary findings are as follows.

The Incidence of IOH with MAP less than 60 mmHg for at least 2 min was a common occurrence (96.1%).

Acute renal failure occurred in 42.9% of patients, with a large proportion of patients developing KDIGO stages 1 and 2 (approximately 80%). The cumulative duration of IOH and increasing age were independent risk factors for AKI. Other risk factors were also identified. An increase in the duration of IOH affects mortality.

At least one hypotensive episode (> $2 \min$) was observed in approximately 96% of patients. The median duration of hypotension was 44 min, indicating that the proposed definition of IOH revealed a high incidence despite close operative haemodynamic monitoring, thereby confirming



IOH, intraoperative hypotension.

Table 2 Patient characteristics according to the intraoperative hypotension quartile

		1011 0 4	Direct	Effect star
	IOH-Q 1 to 3	IOH-Q 4	Plevel	Effect size
Age (median)	71	71	P<0.01	r = 0.036
Sex				
Male	74.8%	25.2%	P=0.037	Cramer <i>V</i> = 0.012
Female	75.9%	24.1%		
BMI	27.1	26.8	P<0.01	r=0.034
Coronary artery disease	66.1%	55.3%	P<0.01	Cramer <i>V</i> = 0.097
Diabetes mellitus	26.9%	24.9%	P<0.01	Cramer V = 0.019
Hypertension	81.7%	77.1%	P<0.01	Cramer <i>V</i> = 0.050
COPD	11.8%	12.6%	P=0.048	Cramer V = 0.012
Preop. history of stroke	4.0%	5.0%	P<0.01	Cramer <i>V</i> = 0.023
Preop. history of myocardial infarction	18.4%	16.3%	P<0.01	Cramer V=0.024
ASA status				
1	0.0%	0.1%	P<0.01	Cramer-V=0.114
2	2.7%	1.7%		
3	75.5%	65.5%		
4	21.5%	31.9%		
5	0.3%	0.9%		
Surgery type				
Off-pump	40.5%	6.6%	P<0.01	Cramer V = 0.316
On-pump	10.2%	12.7%		
Open heart	49.3%	80.7%		
Kidney transplantation postop.	4.6%	15.0%	P<0.01	Cramer <i>V</i> = 0.173
Died during observation period	18.9%	31.6%	P<0.01	Cramer V = 0.132

BMI, body mass index; IOH-Q, intraoperative hypotension quartile; Postop, postoperative; Preop, preoperative; ASA, American Society of Anesthesiologists physical status score.

Table 3 Patient characteristics according to the incidence of acute kidney injury

		AKI according to KDIGO criteria				
	No AKI	AKI	P level	Effect size		
Number (n)	16521	12388				
Age (median)	70	72	P<0.01	r=0.076		
Age						
<70 years	7916	5044	P<0.001	Cramer <i>V</i> = 0.072		
\geq 70 years	8605	7344				
Sex Male	11024	8183	P<0.232	Cramer <i>V</i> = 0.007		
Female	5497	4205				
BMI (median)	26.7	27.6	P<0.001	r=0.116		
CAD	10138	8194	P<0.001	Cramer V = 0.049		
Diabetes mellitus	3979	3657	P<0.001	Cramer <i>V</i> = 0.061		
Hypertension	13082	10210	P<0.001	Cramer <i>V</i> = 0.040		
COPD	1780	1683	P<0.001	Cramer <i>V</i> = 0.043		
Preop. history of stroke	556	662	P<0.001	Cramer <i>V</i> = 0.049		
Preop. myocardial infarction	2466	2707	P<0.001	Cramer <i>V</i> = 0.089		
ASA status						
1	8	5	P<0.001	r = 0.115		
2	436	273				
3	12750	8362				
4	3307	3642				
5	20	106				
Type of surgery						
Off-Pump	5510	3760	P<0.001	Cramer <i>V</i> = 0.036		
On-Pump	1687	1448				
Open heart	9324	7180				
IOH time MAD <60 mmHg (median)	41 min	50 min	P<0.001	r=0.091		
Average RR <60 mmHg	24%	27%	P<0.001	r = 0.069		
Kidney transplantation postop.	154	1929	P<0.001	Cramer V = 0.280		
Died during observation period	2725	3653	P<0.001	Cramer $V = 0.15$		

AKI, acute kidney injury; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IOH, intraoperative hypotension; postop, postoperative; preop, preoperative; ASA, American Society of Anesthesiologists physical status score.





AKI, acute kidney injury.

the clinical data published worldwide. Bijker *et al.*¹⁴ reported that 93% of patients had at least one episode of IOH (depending on the definition given), which is consistent with the findings of the present study findings.

Intraoperative hypotension and acute kidney injury

The proportion of patients who developed AKI postoperatively was remarkably high, at 42.9% of the total cohort, which demonstrates the significance of this, especially in patients undergoing cardiac surgery. Of these,

Fig. 4 Survival according to the acute kidney injury stages.



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	R	SE	Wald	df	D	OP	
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Age in years	0.010	0.001	73.638	1	0.000	1.010	1.008 to 1.013
BMI	0.056	0.003	414.440	1	0.000	1.058	1.052 to1.064
CAD	0.045	0.032	1.910	1	0.167	1.046	0.982 to 1.114
Euroscore 2	0.019	0.002	117.830	1	0.000	1.019	1.015 to 1.022
Number Presurgeries	0.051	0.041	1.574	1	0.210	1.052	0.972 to 1.139
IOH time in min	0.004	0.001	42.270	1	0.000	1.004	1.003 to 1.005
Clamping time in min	-0.001	0.000	7.291	1	0.007	0.999	0.998 to 1.000
Surgery duration in min	0.003	0.000	148.058	1	0.000	1.003	1.002 to 1.003
Off-pump			4.151	2	0.126		
On-pump	0.099	0.049	4.150	1	0.042	1.104	1.004 to 1.214
Open-heart	0.048	0.046	1.056	1	0.304	1.049	0.958 to 1.149
PAOD	0.044	0.045	0.941	1	0.332	1.045	0.956 to 1.142
Diabetes mellitus	0.048	0.029	2.675	1	0.102	1.049	0.991 to 1.111
Hypertension	0.003	0.033	0.010	1	0.920	1.003	0.940 to 1.071
COPD	0.104	0.038	7.313	1	0.007	1.109	1.029 to 1.196
ASA stage	0.204	0.027	56.589	1	0.000	1.227	1.163 to 1.294
Constant	-4.151	0.155	718.919	1	0.000	0.016	

Table 4 Results of the logistic regression

AKI, acute kidney injury; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; IOH, intraoperative hypotension; PAOD, peripheral arterial occlusive disease; ASA, American Society of Anesthesiologists physical status score.

KDIGO stage 2 was observed most frequently (47.7% of patients), followed by KDIGO stage 1 (31.5% of patients) and KDIGO stage 3 (<20.7% of patients).

In summary, group comparisons (AKI vs. no AKI) revealed statistically significant differences in BMI, ASA status, postoperative requirement for Kidney transplantation, and the number of deaths, which also had an effect size of greater than 0.1. The survival duration was significantly shorter in patients with AKI. The average survival duration in patients with AKI was 2377 \pm 13 days; this average survival duration was 516 days less than the survival for patients without AKI. Significantly, higher mortality was observed in patients who met the criteria for KDIGO stage 3. This finding is consistent with the findings of the study by Abelha *et al.*,¹ John *et al.*¹⁵ and Uchino *et al.*, who reported that the incidence of AKI results in increased morbidity and mortality.²

The proportion of patients who developed AKI postoperatively increased with the progression of the IOH quartiles. This proportion was 11.4% higher in quartile 4 (>83 min IOH time) than that in quartile 1 (0 to 17 min). Furthermore, the proportion of patients with KDIGO stage 3 AKI increased with the progression of the IOH quartiles. This could also be attributed to more severely ill patients, with possibly longer surgery, being more susceptible to developing AKI, and major surgery and increased cardiovascular comorbidity being risk factors for the incidence of IOH.^{16,17} The survival analysis performed using the Kaplan-Meier method revealed significantly lower survival in quartile 4, which was particularly striking. The group comparison revealed a difference in the type of surgery performed; the patients in quartile 4 mainly underwent open-heart procedures. The group difference was statistically significant (P value of <0.01), with an effect size of Cramer V = 0.316.

Ali *et al.* reported that AKI occurs in 30.3% of patients following open-heart surgery. Al-Githmi *et al.* reported an incidence rate of 34%, whereas Xu *et al.* reported an incidence rate of 53%.^{18–20} However, these studies did not consider the duration of IOH as a possible risk factor. Thus, further prospective studies with subgroup analyses (CPB vs. non CPB) must be conducted in the future.

Age and risk factors

The patients included in our study were older than those included in previous studies. The median age of patients was 71 years in this study, which is quite high but consistent with that of the cardiosurgical cohort, as increasing age is a risk factor for cardiovascular diseases and possible surgical interventions.^{21,22} This also explains the high incidence of concomitant diseases; arterial hypertension was the most common comorbidity, affecting 80.6% of patients. Several preexisting conditions and cardiosurgical surgery are risk factors for AKI, which also explains the high incidence. Thus, the recorded frequencies fit the overall picture in the literature.^{1,23,24}

At 73%, ASA class 3 (comprising patients with severe systemic disease) was the most frequently recorded ASA class. In addition, more than two-thirds of the patients underwent surgery using a heart-lung machine. Thus, a large proportion of patients were high-risk, which is likely to increase the rate of postoperative complications compared with a nonselected noncardiac surgery cohort.^{25,26}

Logistic regression model

The logistic regression model revealed the influence of various factors on the postoperative incidence of AKI. The correlations observed between the remaining predictors were not strong (r < 0.90), indicating that multicollinearity did not confound the analysis.

The model was statistically significant (P < 0.001). The Hosmer–Lemeshow test revealed a high goodness of fit, indicating that the most important predictors were included in the model and that there was no overdispersion.

The effect of some of the predictors, which were investigated in various studies (such as a higher BMI or ASA status), was confirmed in this study. In addition, this study also revealed that older age and the duration of surgery were risk factors for AKI, consistent with the current findings.^{1,27}

The present study investigated the influence of the cumulative duration of IOH on AKI and reported that the duration of IOH in minutes had a significant influence on the incidence of AKI. However, to date, this has not been demonstrated in a comparable population of patients undergoing cardiac surgery. The odds ratio for the duration of IOH was 1.004 (95% CI, 1.003 to 1.005; P > 0.001), indicating that the risk of AKI increased by 0.4% with each additional minute of IOH. This finding is consistent with the findings of the study by Ngu et al., who investigated the requirement for postoperative kidney transplantation in patients undergoing cardiac surgery. Persistence of MAP of less than less than 65 mmHg for at least 10 min was associated with an increased risk of a requirement for kidney transplantation.¹³ Badin et al.²⁸ reported that patients with AKI and septic shock had a lower MAP than those with septic shock without AKI. Thus, IOH appears to be a risk factor for the incidence of postoperative acute renal failure that needs to be addressed clinically.

Limitations

Compared with previous international studies, the cohort of the present study was very large. Thus, a larger spectrum of cardiosurgical patients was represented, resulting in high power. However, the subgroup analysis revealed a fundamental problem in the statistical evaluation: with the large number of cases even small differences or weak correlations were statistically significant. An assessment of the effect size is of particular importance when examining the relevance of the results.^{29,30} Nevertheless, it can be assumed that other factors were confounded in the present study as the median duration of IOH of the non-AKI and AKI groups did not diverge substantially (41 vs. 50 min). Also, the OR for the duration of IOH was nearly 1 in the logistic regression analysis.

There is no consensus regarding the definition of IOH. In the current study, IOH was defined as the cumulative duration of periods when a MAP of less than 60 mmHg occurred for more than 2 min; however, there are at least 140 other definitions.¹⁴ In our study, no distinction was made between continuous IOH phases and the cumulative duration of interrupted phases of IOH. It is likely that different haemodynamic consequences could occur in these different circumstances, which we did not investigate. Nevertheless, cumulative 2-minute periods with a MAP of less than 60 mmHg significantly increased the risk of developing AKI postoperatively. The results of this study can serve as the basis for further prospective randomised studies to make a definitive statement on the critical blood pressure limit while considering further risk factors.

Conclusion

In summary, we were able to show that the cumulative duration of IOH and increasing age are independent risk factors for the occurrence of AKI. Furthermore, IOH and AKI are common complications during and after cardiac surgery. However, the question remains what defines IOH. The data we collected is of clinical importance with regards to intraoperative blood pressure management to prevent AKI in patients undergoing cardiac surgery. Our findings support the need for further clinical prospective studies to establish risk stratification and patient-specific thresholds for blood pressure control in cardiac surgery.

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