Master thesis / Original study

Intraoperative hypotension and postoperative complications in non-cardiac surgery: a narrative review

R. Vossen[1], J. Lauweryns[1]

[1]*Department of Anesthesiology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.*

Corresponding author: Vossen, R. MD, Department of Anesthesiology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail: robbert.vossen@uzleuven.be

Abstract

Background: **The incidence of IOH varies between 5% and 99%, depending on which definition is used. There have been numerous reports on the association between IOH and different postoperative outcomes.**
Objective: **The goal of this study was to evaluate the association between intraoperative hypotension (IOH) and common postoperative outcomes, namely acute kidney injury, myocardial injury, cerebral ischemia, and postoperative delirium.**
Methods: **For this review, we developed a search strategy and searched all relevant medical databases. We searched for cohorts focusing on IOH and the different postoperative outcomes conducted in the past ten years. Eventually we were able to include 16 articles.**
Results: **Regarding acute kidney injury (AKI), there is sufficient high-quality evident that IOH is an independent risk factor for developing AKI. We identified three studies evaluating the association between IOH and myocardial injury. They found a high incidence of myocardial injury, up to 30%. Furthermore, we found an independent association between IOH and myocardial injury. Regarding cerebral ischemia, we identified four cohorts. For now, there has not been a consensus regarding the association between IOH and cerebral ischemia. A few, but not all,studies find an association between IOH and cerebral ischemia. Conflicting evidence regarding a possible association between IOH and postoperative delirium was found.**
Discussion and conclusion: **There seems to be enough evidence that episodes of IOH might be associated with both AKI and myocardial ischemia. The data regarding IOH and cerebral ischemia and POD however are inconsistent. There is a lot of variety between studies regarding the definition of IOH as the study population, so no hard conclusion can be drawn from this review.**

Keywords: **Hypotension, Acute kidney Injury, Myocardial Ishemia, Stroke, Delirium.**

Introduction

Intraoperative hypotension (IOH) is a well-known entity for anesthesiologists. It has a high occurrence in general anesthesia for non-cardiac surgery. There are observational studies regarding an association between IOH and postoperative complications[1]. Therefor it could be modifiable risk factor for postoperative complications. In this narrative review we evaluate the association between IOH and four common postoperative outcomes: acute kidney injury (AKI), myocardial injury, cerebral ischemia, and postoperative delirium.

Methodology

We conducted a structured systematic search on 23-03-2021 in all relevant medical databases: PudMed, Embase and the Web of Science Core Collection. We searched for all relevant cohorts looking at an association between intraoperative hypotension and any of the four postoperative outcomes previously mentioned in patients undergoing general anesthesia for non-cardiac surgery. AKI was defined using the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) classification, which requires an at least 50% increase in serum creatinine. We defined myocardial injury as the occurrence of myocardial injury during surgery or within 30 days after surgery. This can be identified with the use of high-sensitivity troponin T (hsTnT). For cerebral ischemia we used the definition by the Society of Neuroscience in Anesthesiology and Critical Care (SNACC) as a brain infarction or hemorrhagic etiology during surgery or within 30 days after surgery[2]. Postoperative delirium (POD) is defined by a disturbance of consciousness with reduced ability to focus, sustain and shift attention and awareness. The search strategy can be found in Table I.

After this extensive search, we excluded all duplicates, papers only focused on cardiac surgery and papers not in English. Initial selection was done by the first author (RV) based on title and abstract. The final selection was also done by the first author (RV). Final selection was after assessment for full text. We included randomized control trails and cohort studies evaluating a possible association between IOH and the several postoperative outcomes.

Results

Our search strategy yielded a total of 1 219 articles. After removal of duplicates, non-related articles (for example: studies regarding cerebral hypotension during carotid artery surgery, among others), articles not in English and articles exclusively focusing on cardiac surgery (n = 1 197), 22 articles met the inclusion criteria. After assessment of full text, another six articles were excluded. Most of these articles focused on hypotension outside the

Table I. — Search strategy and MeSH terms.

Acute kidney injury
PubMed: ((“Hypotension”[Mesh]) OR “Low Blood Pressure”) AND “Acute Kidney Injury”[Mesh] (*n* = 407) Embase: ‘hypotension’/exp AND ‘perioperative period’/exp AND ‘kidney injury’/exp (*n* = 71) Web of Science Core Collection: TS=(“hypotension” AND “perioperative period” AND “kidney injury”) (*n* = 11)
Myocardial injury
PubMed: ((“Hypotension”[Mesh]) OR “Low Blood Pressure”) AND “Myocardial Ischemia”[Mesh] AND (“postoperative”[tiab] OR “perioperative”[tiab] OR “preoperative” [tiab]) (*n* = 100) Embase: ‘hypotension’/exp AND ‘perioperative period’/exp AND ‘heart muscle ischemia’/exp (*n* = 179) Web of Science Core Collection: TS=(“hypotension” AND “ischemia”) AND TI=(“*operative”) (*n* = 126)
Cerebral ischemia
PubMed: ((“Hypotension”[Mesh]) OR “Low Blood Pressure”) AND “Stroke”[Mesh] AND (“postoperative”[tiab] OR “perioperative”[tiab] OR “preoperative” [tiab]) (*n* = 33) Embase: ‘hypotension’/exp AND ‘perioperative period’/exp AND ‘cerebrovascular accident’/exp (*n* = 230) Web of Science Core Collection: TS=(“hypotension” AND (“cerebrovascular accident” OR “Stroke”)) AND TI=(“*operative”) (*n* = 140)
Delirium
PubMed: ((“Hypotension”[Mesh]) OR “Low Blood Pressure”) AND “Delirium”[Mesh] (*n* = 50) Embase: ‘hypotension’/exp AND ‘perioperative period’/exp AND ‘delirium’/expa (*n* = 109) Web of Science Core Collection: TS=(“hypotension” AND “perioperative period” AND “delirium”) (*n* = 4)

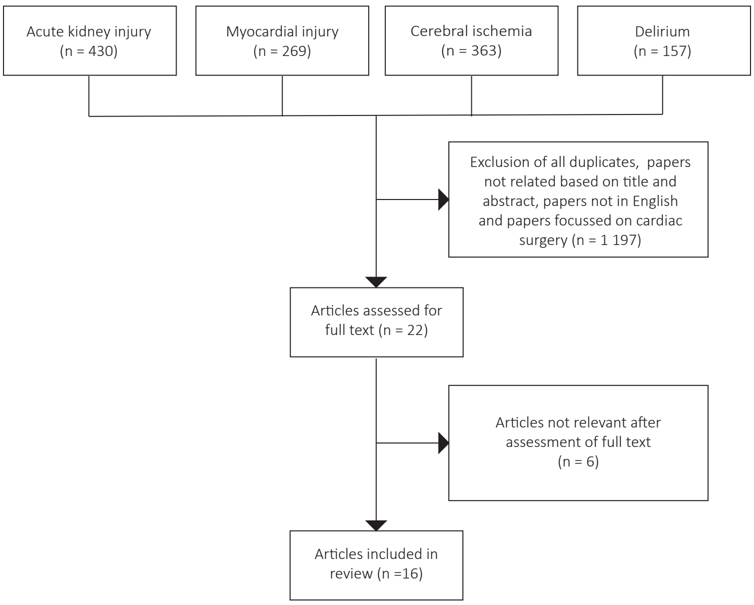

Fig. 1 — Flow chart of included papers.

Table II. — Summary of cohorts investigating AKI – MAP: mean arterial pressure

Study	No. of patients	Age range (years)	Type of surgery	Definition hypotension	AKI	Outcome
Mathis et al. (2020)	138 021	18 – 80+	Non-cardiac surgery	Absolute: MAP < 64 mmHg OR Relative: 20% below baseline	12,431 (9%)	Correlation between absolute IOH and AKI only in patients with high preoperative risk. Weak correlation between relative IOH and AKI.
Tang et al. (2019)	4 952	18-60	Non-cardiac, non-urological surgery	Absolute: MAP < 64 mmHg	186 (3.76%)	Considerably increased risk of AKI if MAP < 55 mmHg for more than 10 min.
Jang et al. (2019)	248	65-97	Femoral neck surgery	Absolute: MAP < 60 mmHg OR Systolic < 80 mmHg	44 (17.7%)	IOH is an independent risk factor for development of AKI.
Maheshwari et al. (2018)	42 825	18 – 80+	Non-cardiac, non-urological surgery	Absolute: MAP < 65 mmHg	2,328 (5%)	IOH is associated with development of AKI.
Hallqvist et al. (2018)	470	58-74	Non-cardiac, non-pheochromocytoma surgery	Relative: 40-50% below baseline for > 5 min	127 (27%)	IOH is associated with an elevated risk of AKI.
Sun et al. (2015)	5 127	18 – 80+	Non-cardiac, non-urological surgery	Absolute: MAP < 65 mmHg	324 (6.3%)	IOH increased the risk for AKI.

intraoperative period (on the ward or intensive care unit). A summary of these results can be found in figure 1.

The summary of the articles can be found in the tables included with this paper. Table II summarizes articles found regarding AKI and IOH. Table III summarizes articles found regarding myocardial injury and IOH. Table IV summarizes articles found regarding cerebral ischemia and IOH. Lastly, Table V summarizes articles found regarding postoperative delirium and IOH.

Discussion

IOH is a common problem with profound effects on many organ systems. We noticed that it was hard to

Table III. — Summary of cohorts investigating myocardial ischemia.

Study	No. of patients	Age range (years)	Type of surgery	Definition of hypotension	Myocardial ischemia	Outcome
Van Waes et al. (2016)[9]	890	60+	Vascular surgery	Absolute: MAP < 60 mmHg OR Relative: 40% below baseline more than 30 min	29% (n=131, IOH) vs 20% (n=87, non-IOH)	Association between IOH for > 30 min and myocardial ischemia. No association when IOH < 30 min
Hallqvist et al. (2016)[10]	300	57-74	Non-cardiac, non-pheochromocytoma surgery	Relative: 50% below baseline more than 5 min	30% (n=90)	Association between IOH for > 5 min and myocardial ischemia
Roshanov et al. (2019)[11]	955	45-80+	Non-cardiac surgery	Absolute: systolic blood pressure < 90 mmHg	7.7% (n=74)	IOH is independently associated with cardiovascular events
Roshanov et al. (2019)[11]	955	45-80+	Non-cardiac surgery	Absolute: systolic blood pressure < 90 mmHg	7.7% (n=74)	IOH is independently associated with cardiovascular events

Table IV. — Summary of cohorts investigating cerebral ischemia. MACCE: Major adverse cardiac and cerebrovasculair events.

Study	No. of patients	Age range (years)	Type of surgery	Definition of hypotension	Cerebral ischemia	Results
Bijker et al. (2012)(3)	48 241	18-80+	Non-cardiac, non-neurological surgery	Relative: > 30% below baseline	0.09% (n=42)	Duration of IOH is statistically associated with ischemic stroke.
Hsieh et al. (2016)(4)	106 337	18-80+	Non-cardiac, non-neurological, non-carotid surgery	Absolute: MAP < 70 mmHg	0.1% (n=104)	No statistically significant or clinically important relationship between IOH and stroke.
Mazzefi et al. (2021)(5)	9 816	17-89	Non-cardiac, non-neurological, non-trauma, non-emergency, non-transplant surgery	Absolute: MAP < 65 mmHg	0.3% (n=34)	MAP < 60 mmHg for more than 30 min increased odds for ischemic stroke.
Gregory et al (2021)(6)	368 222	18-80+	Non-cardiac, non-caesarian surgery	Absolute: MAP < 75 mmHg OR relative: MAP > 40% below baseline	Non given	For all absolute MAP thresholds, and under 40% baseline, IOH is associated with MACCE.

Table V. — Summary of cohorts investigating postoperative delirium.

Study	No. of patients	Age range (years)	Type of surgery	Definition of hypotension	POD	Results
Hirsch et al (2015)(7)	594	64-94	Non-cardiac	Absolute: MAP < 50 mmHg OR relative: > 20% below baseline	30% (n=178)	No significant association between IOH and POD. Association between fluctuation in BP and POD.
Radinovic et al (2019)(8)	277	60+	Hip fracture surgery	Absolute: MAP < 80 mmHg	53% (n=148)	Low MAP or high DMAP is an independent risk factor for POD.
Maheshwari et al. (2020)(9)	1083	18-80+	Non-cardiac surgery admitted to ICU	Absolute: MAP < 65 mmHg	35% (n=377)	Both IOH and postoperative hypotension are associated with POD.

compare the different studies since the definition of IOH is not well defined and there is a lot of variety between the study populations. A group by Bijker et al. did a literature study of four prominent journals of anesthesia and found 130 articles mentioning hypotension, providing 140 different definitions of hypotension[10].

Depending on which definition used, IOH has an incidence between 5 and 99%[10].

Definitions can be absolute, for example systolic blood pressure < 90 mmHg, or relative, for example decrease in systolic blood pressure > 20% from baseline. The etiology of IOH is multifactorial. Possible causes include vasodilation (anesthetics, systemic inflammation), low cardiac output (low stroke volume, bradycardia), hypovolemia, high intra-thoracic pressure, blunted autonomic response, external compression by surgeons or preoperatively taken medication such as angiotensin-converting enzyme inhibitors or alpha-2 agonists[1].

Several risk factors have been identified such as high American Society of Anesthesiologists (ASA) score, general anesthesia with propofol, combinations of general and regional anesthesia, male sex, older age, duration of surgery and emergency surgery[11].

Acute kidney injury

AKI is a common problem with severe consequences. A recent review in The Lancet estimates the incidence around 10-15% of all in-hospital patients and up to more than 50% in all ICU patients[12]. Furthermore, AKI is associated with a higher risk of coagulopathy, need for mechanical ventilation, sepsis and anemia. All this results in an increased mortality compared to patients without AKI, even if there is a complete renal recovery[13].There is a wide range in the incidence for developing AKI after noncardiac surgery, ranging between 5% and 27%[14,15]. A possible explanation for this is the great diversification are the inclusion criteria. For example, while Masheshwari et al. exclude all patients with pre-existing renal failure and all patients undergoing urological surgery, Hallqvist et al. does include these and only excludes patients undergoing pheochromocytoma resection. Furthermore, Jang et al. only includes patients that underwent femoral neck fracture surgery, a subpopulation which is already burdened with a high morbidity and mortality. Mathis et al. is the only study that does a subgroup analysis based on the a priori preoperative risk. They use a weighted risk score multivariable logistic regression model using predictors of AKI (the most important being: ASA-status, age, medical history, and pre-existing renal injury) to stratify patients in quartiles based on their risk of developing AKI. They found that only in the two highest quartiles (high and highest risk of developing AKI postoperatively) there was an association between IOH and AKI. They also found that this correlation is strongest between absolute rather than relative hypotension[16].

The results provide sufficient high-quality evidence that IOH is an independent risk factor for developing AKI in the postoperative period. Most articles regarding this subject use a MAP between 60 and 65 mmHg as cutoff for defining IOH, so keeping an MAP higher than 65 mmHg might have protective effect on developing AKI. The mechanism behind this is likely tissue hypoperfusion which results in tissue hypoxia and ischemia. However, there is some evidence that this model alone is not sufficient for explaining AKI after an episode of sepsis. Sepsis is accompanied by a hyperdynamic state and as such, renal blood flow usually remains intact. It is therefore postulated that it is the systemic inflammation which leads to tubular injury[17].

Myocardial injury

Intra-operative hypotension can cause myocardial injury due an imbalance between oxygen supply and demand in the myocardium. This can be identified with the use of high-sensitivity troponin T (hsTnT). The VISION Study, which published its results in 2017, followed 21.842 patients after major non-cardiac surgery and determined hsTnT in the days after surgery. They found a mortality of 1.2% (n=266) and an association between peak hsTnT levels and mortality, even if there were no other signs of myocardial injury[18]. The first thing we noticed is the high incidence of myocardial injury, up to 30%. However, it must be noted that the majority of the cases, up to 94%, might not be recognized because there are no other associated signs or symptoms[18].

The differences in the incidence of myocardial injury between the studies can be explained when further examining the cohorts. Van Waes et al. only includes patients after major vascular surgery and over 60 years of age[19]. Hallqvist et al. include all patients, except those after pheochromocytoma resection[20]. Finally, Roshanov et al, who has the lowest incidence of myocardial injury, only included people with a previous history of coronary artery disease (CAD) or congestive heart failure[21]. However, their definition of myocardial injury not only included elevation of hsTnT, but at least one other marker of ischemia (ECG changes, imaging abnormalities or other signs/symptoms), which might explain their much lower incidence.

All studies we found show an association between the two but are unable to define it as an independent risk factor. The group by Van Waes even write that the occurrence of IOH could merely be a marker for other events that could cause myocardial injury[22]. The group by Hallqvist find the association between IOH and myocardial injury defined by an increased hsTnT, but cannot prove a causality between IOH and hard endpoints like myocardial infarction or death[20].

While strictly beyond the scope of this article, it is worth mentioning that postoperative hypotension also plays its role in development of myocardial injury. A recently published article by Liem et al. found that postoperative hypotension (defined by a MAP < 75 mmHg) occurs in 8-48% of patients within the first 24 hours after surgery and is independently associated with myocardial ischemia[23].

Cerebral ischemia

Cerebral ischemia is a severe complication which can increase the mortality up to eightfold[24]. It occurs in approximately 0.54% of all surgical cases, but this can increase up to 1.9% in the high-risk population[25].

While many risk factors have been identified for the development of perioperative cerebral ischemia (for example: old age, history of atrial fibrillation, renal disease, smoking, hypertension, and others), there is still much debate on whether IOH plays an important role in development of cerebral ischemia[25]. While Hsieh et al. find no statistically significant relationship, some other studies do. A possible explanation might be the use of a lower threshold for defining IOH in the studies by Bijker et al. and Mazzefi et al. Although Gregory et al.

do use a higher threshold for defining IOH, they do not differentiate further between cardiac and cerebrovascular events[3-6]. Both Bijker et al. and Mazzeffi et al. do find an association, neither do find a causality though. It is even stated that cerebral ischemia based solely on hypoperfusion is uncommon and counts for only 9% of all perioperative stroke[27].

Delirium

There are well known risk factors that precipitate postoperative delirium (POD), for example: old age (> 60 years), pre-existing cognitive impairment, history of alcohol abuse, polypharmacy and low education level[28]. There were only three studies evaluating the association between IOH and POD. The data regarding POD and IOH are conflicted. Hirsch et al. finds no correlation between POD and IOH, though he does notice a larger variance in blood pressure fluctuations in the group that developed POD[7]. Radinovic et al. do find a correlation between the lowest intraoperative MAP and POD. However, they only included elderly patients after hip fracture surgery and find that a MAP higher than 80 mmHg has a protective effect on developing POD. They suggest this might be because these patients were already hypertensive and a MAP of 80 mmHg may effectively be hypotension for this specific population[8].

The most recent study, by Maheshwari et al., also find an independent association between both intra- and postoperative hypotension and POD. However, they only included critically ill patients which were admitted to the surgical intensive care unit after surgery[9].

Another clinical entity, closely related to POD is postoperative cognitive dysfunction (POCD). This is defined as a change of Z-score (the number that indicates how many standard deviations a score deviates from the mean value) or a pre-defined change in absolute test scores from either preoperative scores from the patient or from test scores from healthy individuals. A recent systematic review by van Zuylen et al. only find 9 relevant articles regarding a possible association between IOH and POCD. They find that the quality of evidence provided by four of these is low. They conclude that there are no statistically significant differences in the occurrence of POCD between hypo- and normotensive groups[29].

Lastly, it must be noted that the duration of IOH also plays in important role in developing postoperative complications. The studies by Van Waes et al. and Mazzefi et al. both find a correlation between IOH and different postoperative outcomes (myocardial injury and cerebral ischemia respectively) only when the duration of IOH exceeds 30 minutes[5,22].

Conclusion

There seems to be sufficient evidence that episodes of IOH might be associated with both AKI and myocardial ischemia. The data regarding IOH and cerebral ischemia and POD however are inconsistent. There are a lot of methodological differences between studies regarding both the definition of IOH and the study population, no hard conclusion can be drawn from this review. In the future, further research is needed to identify the true impact of IOH on the various organ systems. It would also be useful if there was an international consensus regarding the definition of hypotension, so comparison between the different studies becomes possible.

Until there is a unanimous consensus regarding the association between IOH and the several postoperative complications, remains important to diagnose and promptly treat IOH. Anesthesiologist should be aware of this importance of IOH and use caution and their clinical judgement to prevent IOH.

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doi.org/10.56126/73.S1.34