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Editorial Board Member of *World Journal of Cardiology*, Anshuman Darbari, FACS, MBBS, MCh, MS, Additional Professor, Department of Cardiothoracic Vascular Surgery, All India Institute of Medical Sciences, Rishikesh 249203, Uttarakhand, India. darbarianshu@gmail.com

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Effect of preoperative renin-angiotensin system blockade on vasoplegia after cardiac surgery: A systematic review with meta-analysis

Jean Jacques Noubiap, Brice Nouthé, Ying Tung Sia, Marco Spaziano

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Jean Jacques Noubiap, Centre for Heart Rhythm Disorders, The University of Adelaide, Adelaide 5000, South Australia, Australia

Brice Nouthé, Department of Medicine, University of British Columbia, Vancouver V6T 1W5, Canada

Ying Tung Sia, Department of Medicine, Regional Trois-Rivières Hospital (CIUSSS-MCQ), Trois-Rivières 5000, Canada

Marco Spaziano, Department of Cardiology, McGill University Health Centre, Montréal QC H4A 3J1, Canada

Corresponding author: Jean Jacques Noubiap, MD, MMed, Academic Research, Senior Editor, Statistician, Centre for Heart Rhythm Disorders, The University of Adelaide, Port Road, Adelaide 5000, South Australia, Australia. noubiapjj@yahoo.fr

Abstract

BACKGROUND

Vasoplegia is a common complication of cardiac surgery but its causal relationship with preoperative use of renin angiotensin system (RAS) blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB)] is still debated.

AIM

To update and summarize data on the effect of preoperative use of RAS blockers on incident vasoplegia.

METHODS

All published studies from MEDLINE, EMBASE, and Web of Science providing relevant data through January 13, 2021 were identified. A random-effects meta-analysis method was used to pool estimates, and post-cardiac surgery shock was differentiated from vasoplegia.

RESULTS

Ten studies reporting on a pooled population of 15672 patients (none looking at ARBs exclusively) were included in the meta-analysis. All were case-control studies. Use of ACEIs was associated with an increased risk of vasoplegia [pooled

adjusted odds ratio (Aor) of 2.06, 95%CI: 1.45-2.93] and increased inotropic/vasopressor support requirement (pooled aOR 1.19, 95%CI: 1.10-1.29). Post-cardiac surgery shock was increased in the presence of left ventricular dysfunction (pooled aOR 2.32, 95%CI: 1.60-3.36; I^2 49%) but not increased by the use of beta blockers (pooled aOR 0.78, 95%CI: 0.36-1.69; I^2 77%). Two randomized control trials (RCTs), not eligible for the meta-analysis, did not show an association between continuation of RAS blockers and vasoplegia.

CONCLUSION

Preoperative continuation of ACEIs is associated with an increased need for inotropic support postoperatively and with an increased risk of vasoplegia in observational studies but not in RCTs. The absence of a consensus definition of vasoplegia should lead to the use of perioperative cardiovascular monitoring when designing RCTs to better understand this discrepancy.

Key Words: Vasoplegia; Cardiac surgery; Coronary artery bypass graft; Angiotensin converting enzyme inhibitors

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Core Tip: Vasoplegia is a common complication of cardiac surgery but its causal relationship with preoperative use of renin angiotensin system blockers, mainly angiotensin converting enzyme inhibitors (ACEIs), is still debated. The meta-analysis of observational studies suggests that preoperative continuation of ACEIs is associated with an increased risk of vasoplegia and of the use of inotropic support postoperatively. However, these associations were not observed in two included randomized controlled trials with limited power. These findings support the potential benefit of holding ACEIs prior to cardiac surgery to reduce the risk of vasoplegia and associated adverse outcomes. However, well-powered randomized controlled trials using a consensus definition of vasoplegia are still needed to properly assess management strategies of RAS blockers in the perioperative setting.

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INTRODUCTION

Shock is a frequent complication of major cardiac surgery, occurring in approximately a quarter of procedures, especially those with cardiopulmonary bypass (CPB)[1-3]. Vasoplegia is a form of distributive shock characterized by persistent hypotension, reduced systemic vascular resistance (SVR) with normal or elevated cardiac output[1]. It is due to reduced vascular smooth cell contraction resulting from several mechanisms including the alteration of the endothelial glycocalyx, impaired receptor signaling, changes in endothelial cell metabolism, and depletion and decreased response to endogenous vasopressors[1,4]. This impairment of vascular reactivity is worsened by a systemic inflammatory response to surgical trauma, ischemia-reperfusion syndrome, and exposure of blood to the foreign surfaces during extracorporeal circulation[1,4]. The use of some medications prior to surgery is also thought to contribute to inappropriate vasodilatation in vasoplegia[1,4].

The association of continuation of renin angiotensin system (RAS) blockers and vasoplegia following cardiac surgery is still a matter of debate[2,5-7]. Preoperative administration of ACEIs has been associated with poor outcomes including acute kidney injury and increased mortality[8]. This systematic review and meta-analysis aimed to comprehensively summarize data on the effect of preoperative use of RAS blockers on vasoplegia in patients undergoing cardiac surgery.

MATERIALS AND METHODS

This review is reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology guidelines[9]. It was registered with PROSPERO (CRD42017072923).

Literature search

PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science were searched to identify all cohort studies, case-control studies or randomized controlled trials (RCTs) reporting primary data on the association between ACEIs or ARBs and the incidence of vasoplegia after cardiac surgery, published by January 13, 2021 (date of the last search), without language restriction. The search strategy used a combination of terms or their synonyms related to vasoplegia, a detailed list of cardiac surgical procedures, and names of ACEIs or ARBs (Supplementary Table 1). The reference lists of relevant research and review articles were also screened to identify potential additional data sources.

Study selection

We included: (1) Cohort studies, case-control studies or RCTs; (2) With 30 participants or more; and (3) Reporting on risk of vasoplegia associated with ACEIs or ARBs, or studies with enough data to compute these estimates. We excluded studies: (1) Which included patients undergoing non-cardiac surgery; (2) Lacking explicit description of the perioperative follow-up of patients; and (3) Not reporting primary data (reviews, commentaries, editorials). For duplicate publication of the same group/cohort of patients, we included the single most comprehensive report with the largest sample size. Two investigators (JJN and BN) independently selected records from bibliographic searches based on titles and abstracts screening. Full texts of articles deemed potentially eligible were retrieved and screened independently by the same investigators for final inclusion. Disagreements were resolved *via* discussion and consensus.

Data extraction and management

Data were extracted using a standard data abstraction form by one investigator (JJN) and cross-checked by a second investigator (BN). We collected data on study characteristics, type of cardiac surgery, definition of vasoplegia, sample size, mean or median age, sex proportion, proportion of patients with co-morbidities such as hypertension, diabetes, heart failure, or previous cardiac surgery, proportion of patients taking relevant medications (ACEIs, ARBs, beta blockers, calcium channel blockers, nitrates, number of participants with vasoplegia, and risk estimate [odds ratio (OR) or relative risk (RR)] with the 95% confidence interval (95%CI) for the association between vasoplegia and ACEIs or ARBs. We also extracted adjusted risk estimates (from multivariable regression analysis) for other risk factors for vasoplegia as complementary information. We assessed the risk of bias using the tools for case-control studies and randomized controlled trial developed by the CLARITY group at McMaster University[10, 11]. We separated studies with or without perioperative cardiac index monitoring in an attempt to further differentiate post-cardiac surgery shock from vasoplegia.

Statistical analysis

Analyses were conducted with R statistical software (version 3.6.2, The R Foundation for statistical computing, Vienna, Austria). The generic inverse variance method was used to pool adjusted risk estimates (OR or RR) and their standard errors with the random-effects meta-analysis model using the *metagen* function. Heterogeneity was assessed by the χ^2 test on Cochrane's Q statistic, which was quantified by I^2 values, assuming I^2 values of 25%, 50% and 75% respectively representing low, moderate and high heterogeneity[12]. We assessed the presence of publication bias related to small study effect by funnel plot inspection and by linear regression test of funnel plot asymmetry (Egger's test)[13]. All statistical tests were two-tailed and statistical significance defined as P value ≤ 0.05 .

RESULTS

Study selection and characteristics

Bibliographic searches retrieved 8076 records and 12 articles were finally included[2,5-7,14-21]. Ten studies were included in the meta-analysis[2,5-7,14-19] and 2 were summarized narratively[20,21]. The study selection is summarized in Figure 1. The observational studies included in the meta-analysis reported data from a pooled sample of 15672 patients undergoing a cardiac surgery. Half of them focused on patients undergoing coronary artery bypass (CABG)[6,7,15,18,19], while the other studies included patients undergoing various procedures including CABG or valvular surgery[2,5,14,16,17]. All observational studies were case-control studies, with data collection done prospectively in most of them [5-7,14-17,19]. The two studies summarized narratively were RCTs[20,21]. The characteristics of the included studies are presented in the appendix (Supplementary Table 2). Most of the studies had a low risk of bias in the majority of assessment items (Supplementary Tables 3 and 4).

The definition of vasoplegia varied across studies (Table 1). Nine studies were considered having acceptable definitions of vasoplegia[2,5-7,14-17,20]. In the remaining three studies, the need for inotropic support was the outcome variable and the definition of vasoplegia seemed to encompass other causes of shock[18,19,21]. We therefore separated studies reporting on vasoplegia and those reporting on post-cardiac surgery shock. The proportions of patients who developed post-cardiac surgery shock

Table 1 General characteristics of included studies

Ref.	Design	Procedure	Definition of vasoplegia	Total sample	Vasoplegia (%)	ACEI (%)
Tuman <i>et al</i> [14]	Case-control	Coronary artery and/or valve surgery requiring CPB	Post-CPB ≥ 2 vasoconstrictors with adequate cardiac output	4301	4.5	12.1
Bruce <i>et al</i> [16]	Case-control	Cardiac surgery requiring CPB	MAP ≤ 50 mmHg, indexed SVR ≤ 1400 dynes s/cm ⁵ /m ² , cardiac index ≥ 2.2 L/min/m ² , requiring norepinephrine infusion	188	34.0	42.0
Carrel <i>et al</i> [17]	Case-control	CABG or AVR	SVR < 600 dynes s/cm ⁵ with adequate cardiac output	800	7.5	43.1
Mekontso-Dessap <i>et al</i> [7]	Case-control	CABG	MAP < 70 mmHg, indexed SVR ≤ 1400 dynes s/cm ⁵ /m ² , normal cardiac output, requiring vasoconstrictor	108	33.3	31.5
Sun <i>et al</i> [15]	Case-control	CABG	MAP ≤ 70 mmHg, indexed SVR ≤ 1400 dynes s/cm ⁵ /m ² , cardiac index ≥ 2.5 L/min/m ² , and central venous pressure ≥ 10 mmHg	696	4.7	38.5
Levin <i>et al</i> [2]	Case-control	Cardiac surgery	Epinephrine/norepinephrine (≥ 150 ng/kg/min), dopamine (≥ 10 μ g/kg/min) or vasopressin (≥ 4 U/h)	2823	20.4	19.7
Shahzamani <i>et al</i> [6]	Case-control	CABG	MAP < 65 mmHg, normal cardiac output, requiring vasoconstrictor	300	17.0	64.0
Radaelli <i>et al</i> [19]	Case-control	Cardiac surgery	3 of these 4: MAP < 65 mmHg, indexed SVR ≤ 1600 dynes s/cm ⁵ /m ² , cardiac index ≥ 2.5 /min/m ² , and requirement of norepinephrine (> 0.03 μ g/kg/min) or vasopressin	3139	32.5	52.1
Suga <i>et al</i> [5]	Case-control	CABG	Inotropic support post-CABG	562	11.7	9.1
Miceli <i>et al</i> [18]	Case-control	CABG	Inotropic support post-CABG	2655	43.5	51.0
Pigot <i>et al</i> [21]	RCT	CABG	Inotropic support post-CABG	40	15.0	100
van Diepen <i>et al</i> [20]	RCT	CABG or valve surgery	MAP < 60 mmHg requiring vasopressor administration for at least 4 h and a central venous pressure ≥ 8 mmHg	121	29.8	76.9

ACEI: Angiotensin; AVR: Aortic valve replacement; CABG: Coronary artery bypass graft; CPB: Cardiopulmonary bypass; MAP: Mean arterial blood pressure; RCT: Randomized controlled trial; SVR: Systematic vascular resistance.

varied from 4.5% to 34.0% (Table 1). The proportion of patients who used ACEIs preoperatively varied from 9.1% to 64.0% in observational studies. Data on the use of other medications such as ARBs, beta blockers, calcium channel blockers, and nitrates are reported in the appendix (Supplementary Table 2), along with the distribution of co-morbidities across study populations. One of the 2 RCTs reported on an aggregated use of ACEIs and ARBs[20].

Association between angiotensin converting enzyme inhibitors and vasoplegia

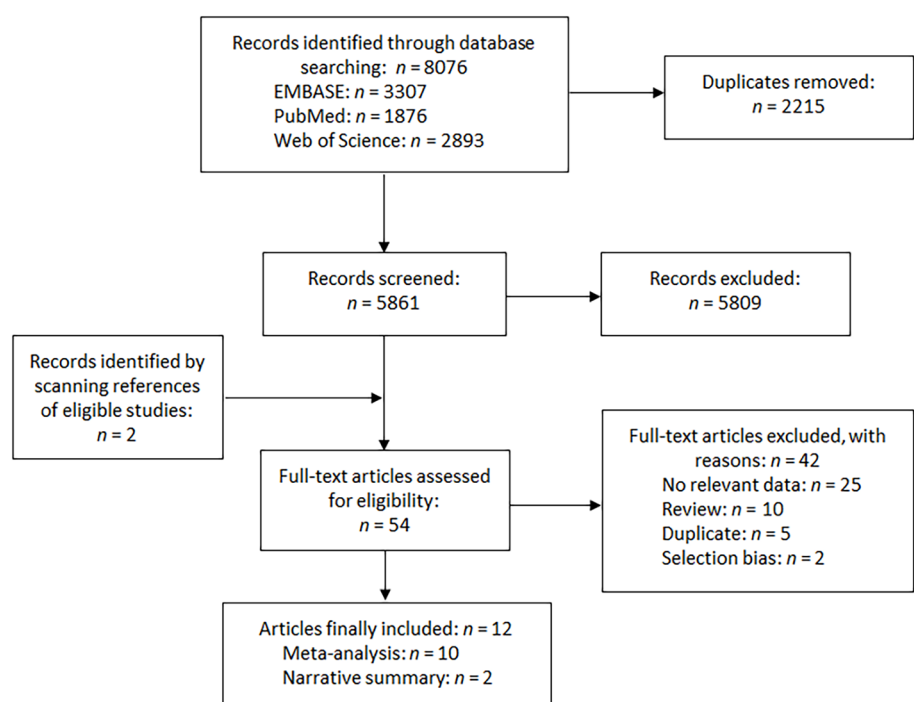
From the 10 observational studies selected, 1076 out of 9778 patients had post-cardiac surgery shock (Figure 2A). In the 6 studies with perioperative cardiac monitoring, 755 patients (12.0%) developed vasoplegia and the risk was increased by preoperative continuation of ACEIs [pooled adjusted odds ratio (aOR) 2.06, 95%CI: 1.45-2.93] (Figure 2B). Considering the high heterogeneity ($I^2 = 80\%$), we performed influencer analysis using a leave-one-out approach. Omission of the study by Carrel *et al*[17] resulted in a pooled aOR that changed to 1.61 (95%CI: 1.41-1.85) (Supplementary Figure 1). There was no evidence of small study effect on funnel plot inspection (Supplementary Figure 2), and according to the Egger's test ($P = 0.906$).

Association between angiotensin converting enzyme inhibitors and inotropic support

Three studies reported data on the association of omitting ACEIs with the need of inotropic support (use of at least one inotropic drug). A total of 4226 (31.1%) patients required inotropic support from a pooled population of 13595 patients undergoing cardiac surgery. Preoperative continuation of ACEI was associated with an increased risk of inotropic support requirement (pooled aOR 1.19, 95%CI: 1.10-1.29) (Figure 3). There was no heterogeneity ($I^2 = 0$), and no evidence of publication bias both on funnel plot inspection (Supplementary Figure 3) and based on the Egger's test ($P = 0.2$).

Risk factors for post-cardiac surgery shock

There was no association between beta-blockers and post-cardiac surgery shock (pooled aOR 0.78, 95%CI: 0.36-1.69; I^2 77%) (Figure 4A). The presence of left ventricular dysfunction (ejection fraction $<$



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Figure 1 PRISMA flow chart of study selection.

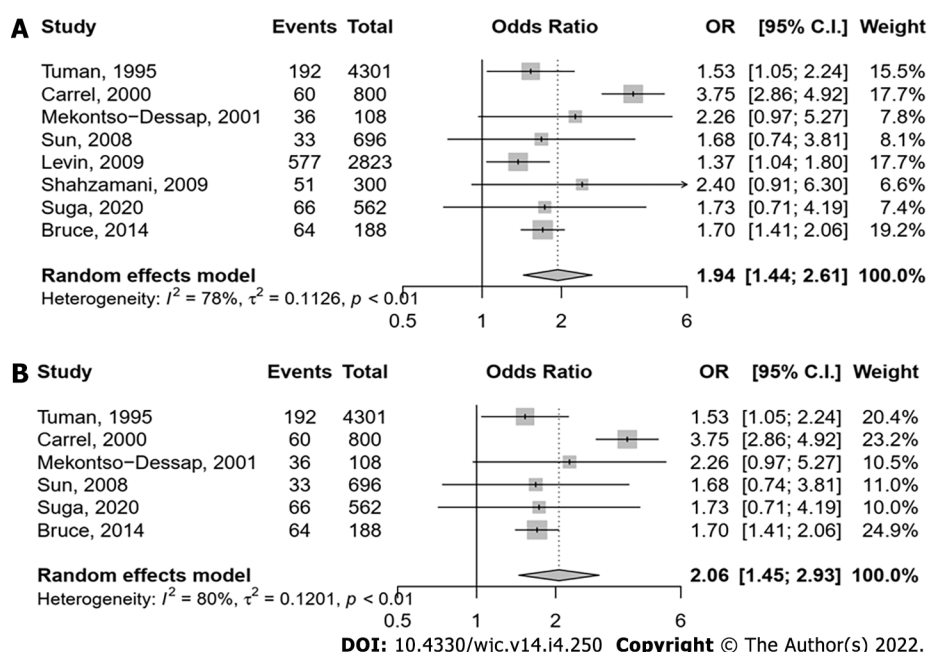


Figure 2 Association between angiotensin converting enzyme inhibitors adverse vascular outcomes. A: Post cardiac surgery shock; B: Vasoplegia.

40%) increased the risk of post-cardiac surgery shock (pooled aOR 2.32, 95%CI: 1.60-3.36; I^2 49%) (Figure 4B). The risk of post-cardiac surgery shock increased with CPB time (pooled aOR 1.012 per 1 min increase, 95%CI: 1.003-1.021, $P = 0.008$; I^2 0%) (Figure 4C). There was no significant association between age and post-cardiac surgery shock (pooled aOR 1.02 per 1 year increase, 95%CI: 1.00-1.04, $P = 0.052$; I^2 0%) (Supplementary Figure 4). There was no evidence of publication bias on funnel plot inspection (Supplementary Figures 5 and 6), and according to the Egger's test for studies reporting on the association between beta blockers and vasoplegia ($P = 0.906$), and between left ventricular dysfunction and vasoplegia ($P = 0.193$).

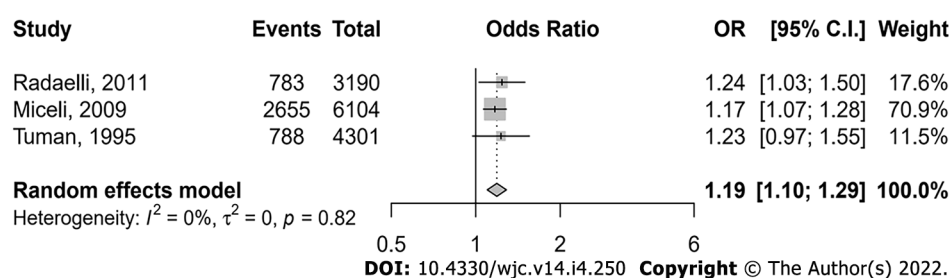


Figure 3 Association between angiotensin converting enzyme inhibitors and need for inotropic support.

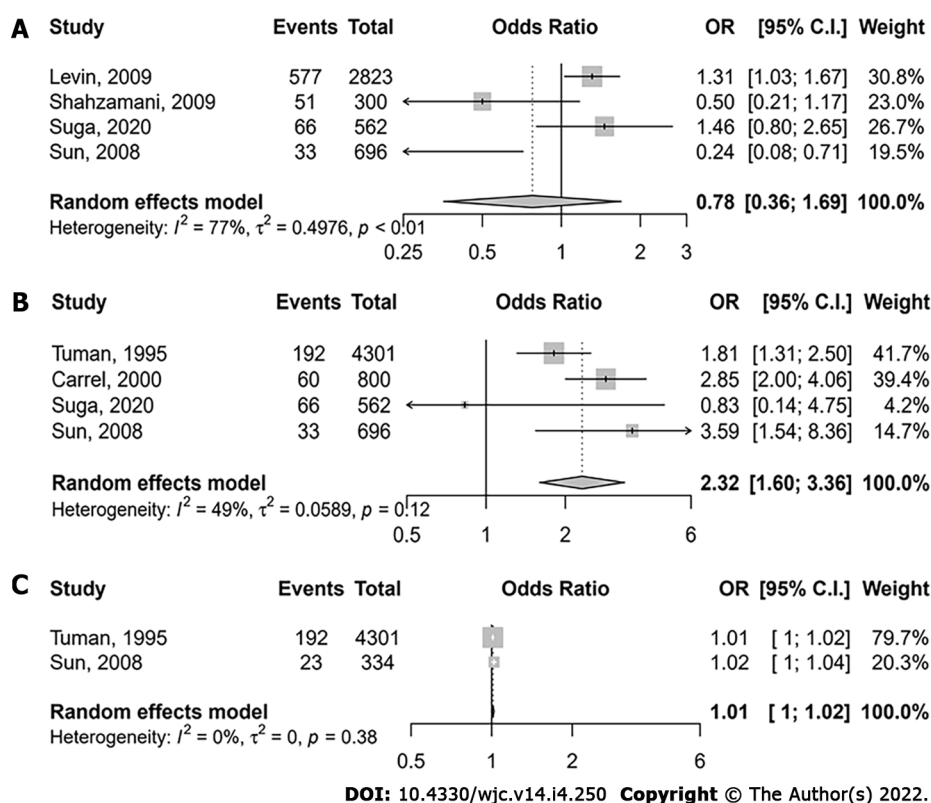


Figure 4 Association between other variables and post cardiac surgery shock. A: Beta blockers; B: Left ventricular dysfunction (EF < 40%); C: Cardiopulmonary bypass time (in minute).

Clinical trials on continuation of ACEIs and vasoplegia

Two RCTs reported on the risk of refractory hypotension with preoperative use of ACEIs[20,21]. The study by van Diepen *et al*[20] included perioperative cardiac monitoring in their definition of vasoplegia and had a larger sample size (61 patients taking RAS blockers)[21]. Incidence of post-cardiac surgery shock was 5%-15% in the study by Pigott *et al*[21] and in the RCT by van Diepen *et al*[20], vasoplegia was found in 29.8% of patients. Preoperative continuation of ACEIs (RAS blockers) was not associated with an increased risk of vasoplegia.

DISCUSSION

This study aimed to summarize data on the effect of preoperative use of ACEIs on incident vasoplegia in patients undergoing cardiac surgery using all relevant studies. Higher odds of vasoplegia (even when defined using perioperative cardiac monitoring) and more frequent use of inotropic support postoperatively were observed in patients who did not discontinue ACEIs. Other factors associated with the risk of post-cardiac surgery hypotension included left ventricular dysfunction and longer duration of CPB, whereas beta blockers use preoperatively was not. Interestingly, the 2 RCTs which evaluated the risk of vasoplegia and continuation of ACEIs (RAS blockers) before cardiac surgery did not show any association.

Hypotension is very common in cardiac surgery, especially with CPB. In response to reduced systemic blood pressure, the kidneys release renin that cleaves angiotensinogen to yield angiotensin I, further converted into angiotensin II by the angiotensin-converting enzyme which causes systemic vasoconstriction. It also increases the secretion of arginine vasopressin and aldosterone, and potentiates the release of norepinephrine by direct action on postganglionic sympathetic fibers. The increased risk of vasoplegia attributable to preoperative ACEI use reported in our study is also consistent with the evidence supporting a hemodynamic benefit of treatment with angiotensin II in patients undergoing cardiac surgery. For instance, a post-hoc analysis of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) multinational, randomized, double-blind trial showed that patients with vasoplegia after cardiac surgery with CPB rapidly responded to angiotensin II, reducing significantly vasopressor use[22].

Whether RAS blockers and specifically ACEIs should be held or not before cardiac surgery has been a matter of debate for more than two decades. The benefits of ACEIs and ARBs in patients with cardiovascular disease are well-established[23]. These positive effects are particularly prominent in the long-term management of patients with ischemic heart disease, especially those undergoing CABG, as evidenced in the QUinapril On Vascular Ace and Determinants of Ischemia (QUO VADIS) RCT[24]. A meta-analysis of 29 studies, mostly retrospective, showed that preoperative use of RAS blockers was associated with increased odds of postoperative acute kidney injury and mortality in patients undergoing cardiovascular surgery[25]. Despite the theoretical favorable mechanisms for RAS blockers in reducing post-operative atrial fibrillation, an increased incidence of post-operative atrial fibrillation has been shown in patients on preoperative RAS blockers, with an adverse effect on survival[26]. These data have motivated the recommendation to omit ACEIs or ARBs before cardiac surgery as a rational strategy to reduce the risk of postoperative vasoplegia and other adverse outcomes[27]. The two RCTs included in this review did not confirm an increased risk of vasoplegia, increased inotropic use or acute kidney injury when ACEIs (RAS blockers) were not discontinued before cardiac surgery[20,21]. However, these trials were not well-powered to be conclusive. They highlight the importance of conducting large multicenter randomized trials to examine the impact of preoperative RAS blockers discontinuation and of its timing on postoperative hemodynamic and clinical outcomes. A previous review already mentioned the weakness of the association between ACEIs and post-cardiac surgery vasoplegia, but a causal relationship has been widely accepted in some cardiovascular anesthesiology communities[28].

This study has some limitations. The definition of vasoplegia was not exactly the same across studies, thereby introducing a potential bias. This is probably due to the fact that there is still no consensus definition of vasoplegia. To address this issue, we pooled together data from studies that used similar definitions and as a result, the level of heterogeneity was low in most analyses. Next, it is possible that the effect of RAS blockers on vasoplegia and inotrope use were confounded by LVEF. Patients receiving RAS blockers are more likely to have low LVEF as these drugs are guideline-recommended in this population. As patients with low LVEF are more likely to have a more complicated post-operative course, it is possible that it is the low LVEF that drove the results, rather than the use of RAS blockers. Unfortunately, stratified analyses by LVEF were not available in the included studies. Moreover, there was no standardized perioperative medication management across studies. It is unclear whether patients reportedly not on ACEI ever took one, or whether some of them were chronically on ACEI but stopped few days before surgery. Another limitation is the relatively low number of eligible studies, which makes some of our estimates less robust. Furthermore, the association between vasoplegia and other factors such as age, CPB time, left ventricular dysfunction or preoperative beta blockers were not preplanned. These variables were not specifically included in the search strategy. Therefore, it is possible that some studies reporting on their attributable risk of vasoplegia were missed. Our findings related to these variables should therefore be interpreted with caution. Despite these limitations, our study is the first to systematically present the discrepancy between observational studies and RCT's on the effect of preoperative RAS blockage and the risk of vasoplegia.

CONCLUSION

Our meta-analysis shows that preoperative continuation of ACEIs is associated with an increased risk of vasoplegia and of the use of inotropic support postoperatively. These findings support the potential benefit of holding ACEIs prior to cardiac surgery to reduce the risk of vasoplegia and associated adverse outcomes. A consensus definition of vasoplegia may help future RCTs properly assess management strategies of RAS blockers in the perioperative setting.

ARTICLE HIGHLIGHTS

Research background

Vasoplegia is a common complication of cardiac surgery. The use of some medications prior to surgery is thought to contribute to inappropriate vasodilatation in vasoplegia. The causal relationship between preoperative use of renin angiotensin system (RAS) blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARB)] between vasoplegia is unclear.

Research motivation

If perioperative use of RAS blockers is associated with vasoplegia, withholding these medications in patients undergoing cardiac surgery might help preventing vasoplegia after cardiac surgery.

Research objectives

To update and summarize data on the effect of preoperative use of RAS blockers on incident vasoplegia.

Research methods

The authors performed a systematic review of the literature, and summarized available data using a random-effects meta-analysis.

Research results

Ten studies reported on a pooled population of 15672 patients were included in the meta-analysis. Use of ACEIs was associated with an increased risk of vasoplegia and increased inotropic/vasopressor support requirement. Left ventricular dysfunction increased the risk of post-cardiac surgery shock. There was no association between continuation of RAS blockers and vasoplegia in the two included randomized control trials (RCTs) .

Research conclusions

Preoperative continuation of ACEIs is associated with an increased risk of the use of inotropic support postoperatively and vasoplegia in observational studies but not in RCTs.

Research perspectives

Further studies are needed to clarify the relationship between perioperative use of RAS blockers and vasoplegia after cardiac surgery. Such studies should use a consensus definition of vasoplegia and conduct appropriate perioperative cardiovascular monitoring.

FOOTNOTES

Author contributions: Nouthe B, Noubiap JJ, Spaziano M and Sia YT contributed to the conception and design; Nouthe B, Noubiap JJ, and Spaziano M contributed to the search strategy; Nouthe B and Noubiap JJ contributed to the studies selection, data analysis and synthesis, data interpretation; Noubiap JJ contributed to the manuscript drafting; Nouthe B, Noubiap JJ, Spaziano M and Sia YT contributed to the manuscript revision, and approval of the final manuscript.

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Country/Territory of origin: Australia

ORCID number: Jean Jacques Noubiap 0000-0002-7722-9757; Marco Spaziano 0000-0002-9762-9133.

Corresponding Author's Membership in Professional Societies: World Heart Federation; Heart Rhythm Society.

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