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Special Article

Vasopressor Therapy in Cardiac Surgery—An Experts' Consensus Statement

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Hemodynamic conditions with reduced systemic vascular resistance commonly are observed in patients undergoing cardiac surgery and may range from moderate reductions in vascular tone, as a side effect of general anesthetics, to a profound vasodilatory syndrome, often referred to as vasoplegic shock. Therapy with vasopressors is an important pillar in the treatment of these conditions. There is limited guidance on the appropriate choice of vasopressors to restore and optimize systemic vascular tone in patients undergoing cardiac surgery. A panel of experts in the field convened to develop statements and evidence-based recommendations on clinically relevant questions on the use of vasopressors in cardiac surgical patients, using a critical appraisal of the literature following the GRADE system and a modified Delphi process.

The authors unanimously and strongly recommend the use of norepinephrine and/or vasopressin for restoration and maintenance of systemic perfusion pressure in cardiac surgical patients; despite that, the authors cannot recommend either of these drugs with respect to the risk of ischemic complications. The authors unanimously and strongly recommend against using dopamine for treating post-cardiac surgery vasoplegic shock and against using methylene blue for purposes other than a rescue therapy. The authors unanimously and weakly recommend that clinicians consider early addition of a second vasopressor (norepinephrine or vasopressin) if adequate vascular tone cannot be restored by a monotherapy with either norepinephrine or vasopressin and to consider using vasopressin as a first-line vasopressor or to add vasopressin to norepinephrine in cardiac surgical patients with pulmonary hypertension or right-sided heart dysfunction.

Key Words: cardiac surgery; hemodynamic therapy; vasodilation; vasoplegic shock; distributive shock; vasopressor therapy

HEMODYNAMIC CONDITIONS with reduced systemic vascular resistance (SVR) commonly are observed in patients undergoing cardiac surgery and may range from slight-to-moderate reductions in vascular tone as a side effect of general anesthetics[1] and inodilators[2,3] to a profound vasodilation, often referred to as vasoplegic shock[2] or vasoplegic syndrome,[3] which has a reported incidence ranging from 9% to 44%.[4-6] Profound vasodilation leads to arterial hypotension and is associated with an increased risk for subsequent organ failure, especially acute kidney injury (AKI), and increased mortality.[2,3,7,8]

Defining Vasoplegia

Vasoplegia is a state of arterial hypotension despite normal or high cardiac output and adequate fluid resuscitation that is characterized by markedly low SVR.[3] Numerous definitions of absolute and relative arterial hypotension can be found in the literature; however, mean arterial pressure (MAP) of 60-to-65 mmHg is a frequently used cutoff value below which a patient is regarded as hypotensive. Prolonged vasoplegia necessitating treatment has been reported to be associated with a mortality rate of up to 25%.[3] Mortality may even be greater in the case of catecholamine-refractory vasoplegia.[9]

Mechanisms Involved in Vasoplegia

The etiology and the pathophysiology of perioperative vasoplegia are multifactorial, and to date no unique definition of vasoplegic shock has been published. Contributing factors include hypothermia; duration of cardiopulmonary bypass (CPB); total cardioplegic volume infused; preoperatively or perioperatively reduced cardiac function; preoperative treatment with calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin-receptor blockers; perioperative treatment with inodilators, and a systemic inflammatory response syndrome (SIRS).[3,10]

On the vascular level, activation of several intrinsic vasodilatory pathways and a vascular hyporesponsiveness to adrenergic vasopressors have been observed.[11] Activation of adenosine triphosphate-sensitive potassium channels in the plasma membrane of vascular smooth muscle, activation of the inducible form of nitric oxide (NO) synthase, increased plasma concentrations of hydrogen sulfide and reactive oxygen species, and a relative or absolute deficiency of arginine-vasopressin are believed to be prime culprits responsible for derailment of vascular tone, the resistance to vasopressors, and vasodilatory shock.[2,10-13]

Treating Vasoplegia in Cardiac Surgical Patients: Unmet Questions

Vasopressor agents commonly are administered to restore vascular tone and to treat vasodilation-associated arterial hypotension. Unfortunately, sparse guidance is available of when to use a vasopressor, at which dosage, and when to start and stop this treatment.

Herein the authors attempt to provide clinicians with information on the following six relevant aspects/questions regarding the treatment of cardiac surgical patients with vasopressors: (1) Which vasopressors should be used in cardiac surgery? (2) What are the optimal dosage and the optimal time to start and stop vasopressor treatment? (3) Are there differences among vasopressors in the incidence of new-onset atrial fibrillation? (4) Are there differences among vasopressors in the incidence, progression and severity of acute kidney injury? (5) Which vasopressor should be used in pulmonary arterial hypertension (PAH) and/or right-sided heart failure? (6) Are there differences among vasopressors in the incidence of ischemic complications?

Methods

Consensus Group and Process

A group of 22 experts from eight European countries convened to develop statements and evidence-based

recommendations on clinically relevant questions about the use of vasopressors in cardiac surgical patients, following the GRADE system[14] and a modified Delphi process. The initiative for this process was originated by prominent (Amomed Pharma, Vienna, Austria) European Association of Cardiothoracic Anaesthesiology members, and the organization of the consensus meeting was supported by a pharmaceutical company. The GRADE system is a simplified system for evidence-based medical recommendations that uses a binary system of either strong or weak recommendations toward or against an intervention based on the balance between desirable and undesirable effects; quality of evidence, values, and preferences; and resource allocations. The process consisted of two consensus meetings (in December 2018 in Vienna, Austria [13 attendants] and in September 2019 in Ghent, Belgium [13 participants]); active electronic discussions; and a final electronic voting on recommendations and statements ("agree" *versus* "disagree") from October–December 2019. One expert ultimately refrained from coauthoring the manuscript, and another expert did not vote. The agreement on the statements and recommendations was reported as the percentage of positive votes.

Literature Search

Methodology

PubMed (including the Medline and Cochrane databases) was searched with agreed MeSH terms. The drugs specifically addressed were norepinephrine, epinephrine, dopamine, vasopressin, terlipressin, methylene blue (MB), and angiotensin II (AT II). A detailed description of the pharmacologic properties is presented in the Supplementary Material (Supportive Information 1).

After applying a filter (human and adult patients, clinical studies, systematic reviews, meta-analysis), the remaining references and their abstracts were reviewed by an independent medical consultant and selected based on relevance regarding the list of the aforementioned six questions. Furthermore, the Scopus database was searched, and a hand search of references of more than 50 publications was performed. After removing duplicates and the selection criteria (discussed in the following section), a table with all selected items was created, checked, and approved by the authors of this publication.

Selection Criteria

The inclusion criteria were as follows: full-text publications (one exception: Dominick et al.[15] because of relevance and because no publication is yet available), adult patients, English language, and a publication date not older than 30 years at the time of the literature search. The exclusion criteria included non-human studies, case reports, case series with fewer than ten patients, editorials, and letters to the editor.

Selected MeSH terms were as follows: Cardiac Surgical Procedures; Coronary Artery Bypass; Heart Valve Prosthesis Implantation; Cardiac Valve Repair; Aortic Aneurysm, Thoracic; Cardiac Output, Low; Cardiac Output, High; Shock, Surgical; Vasoplegia; Shock, Cardiogenic; Vasoconstrictor Agents; Vasopressin; Arginine Vasopressin; Deamino Arginine Vasopressin; Terlipressin; Lypressin; Felypressin; Ornipressin; Catecholamines; Norepinephrine; Dobutamine; Dopamine; Epinephrine; Angiotensin II; Methylene Blue; Perioperative Period; Preoperative Period; Intraoperative Period; Postoperative Period; Atrial Fibrillation; Atrial Flutter; Acute Kidney Injury; Renal Insufficiency; Hypertension, Pulmonary; Heart Failure; Adverse Drug Event; Complications; Ischemia

Results

Based on the aforementioned search strategy and criteria, the authors identified 132 clinical studies, systematic reviews, and meta-analyses (Fig 1ES and Tables 1ES and 2ES). These included 38 randomized controlled trials (RCTs) investigating vasopressor agents. To ensure the best possible level of evidence, the 2016 revised Cochrane risk-of-bias tool was applied on the selected RCTs (Table 3ES).

RCTs Investigating Vasopressors

Catecholamines (Norepinephrine, Epinephrine, Dopamine)

Fourteen RCTs, several reviews/meta-analyses, and some retrospective or prospective uncontrolled studies investigating various catecholamines in cardiac surgery patients were identified (see Table 1ES). However, none of the RCTs was performed specifically in patients with vasodilatory hypotension/post-cardiac surgery shock. In addition, all trials investigating dopamine used doses <10 μg/kg/min, implying that predominantly inotropic effects of dopamine rather than its vasopressor activity may have been investigated.[16] Furthermore, there may be substantial variability in receptor specificity for dopamine among patients; thus, these studies were not taken into further consideration. In addition, as noted by others,[17] treatment of hypotension/shock in cardiac surgery patients with catecholamines is mostly empirical and not substantiated by evidence.

Vasopressin

Fifteen RCTs, 15 reviews/meta-analyses primarily evaluating vasopressin, and 18 retrospective or prospective controlled or uncontrolled studies in cardiac surgery patients were identified. The majority of these publications evaluated patients with vasodilatory syndrome/vasodilatory shock (see Table 1ES). Five RCTs[18-22] investigated patients with vasodilatory shock. In four of these,[18,19,21,22] vasopressin was used in addition to catecholamines, and the comparator was placebo in one trial and norepinephrine in two trials. In one trial,[20] vasopressin was used first line with norepinephrine as a comparator.

Argenziano et al.[18] included ten patients with vasodilatory shock after left ventricular assist device placement. Vasopressin increased MAP significantly versus placebo and led to a marked decrease in norepinephrine requirement. The majority of patients had an absolute vasopressin deficiency, but all patients responded to vasopressin administration. Dünser

et al.[19] compared concomitant administration of vasopressin and norepinephrine with norepinephrine alone in patients with advanced vasodilatory shock (19 of 48 patients after cardiac surgery). Vasopressin patients had a significantly lower heart rate, norepinephrine requirements, and incidence of new onset tachyarrhythmias than did norepinephrine patients. MAP was significantly higher and gastrointestinal perfusion was better preserved in the vasopressin group versus the norepinephrine group. Luckner et al.[21] evaluated the effect of concomitant administration of vasopressin and norepinephrine versus norepinephrine alone on microcirculation in 18 patients with advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome. During the study period, there were no differences in either cutaneous reactive hyperemia or the oscillatory pattern of vascular tone between groups. Torgersen et al.[22] compared two vasopressin dose regimens in 50 patients with vasodilatory shock requiring norepinephrine >0.6 μg/kg/min (six of 50 patients after cardiac surgery) and concluded that a vasopressin infusion of 0.067 IU/min restored vascular tone more effectively than vasopressin at 0.033 IU/min without any difference in the occurrence of adverse events. Hajjar et al.[20] analyzed the effects of a monotherapy with vasopressin or norepinephrine in 300 patients with a vasoplegic syndrome after cardiac surgery. The primary endpoint was a composite of mortality or severe complications within 30 days, which occurred in 48 vasopressin patients (32%) and 74 norepinephrine patients (49%), mainly triggered by a significantly lower incidence of AKI in vasopressin-treated patients versus norepinephrine-treated patients. In addition, significantly fewer vasopressin-treated patients developed atrial fibrillation (AF) compared with norepinephrine-treated patients. Length of intensive care unit (ICU) and hospital stay were significantly shorter in vasopressin patients, as was the duration of study during infusion and the duration of inotropic support with dobutamine. The mean vasopressin dose administered in the study was 0.04 IU/min. It is notable that the study has been criticized because the primary endpoint was changed after the trial already had enrolled some patients.[23]

Five trials evaluated the prophylactic use of vasopressin in patients undergoing cardiac surgery. Papadopoulos et al.[24] examined prophylactic infusion of low-dose vasopressin (0.03 IU/kg/min) versus placebo until four hours after bypass for prevention of vasoplegic shock in patients preoperatively treated with ACEIs and a low ejection fraction. The incidence of vasodilatory shock was significantly lower (8% *v* 20%) in the vasopressin group versus the placebo group. In the vasopressin group, fewer patients were treated with norepinephrine and with a lower mean dose and fewer patients were additively treated with epinephrine. Vasopressin administration was associated with a higher 24-hour urine output. Morales et al.[25] investigated whether vasopressin (0.03 IU/min) versus placebo administered before CPB would reduce post-CPB hypotension and catecholamine use in patients receiving ACEI. Vasopressin did not change pre-CPB MAP or pulmonary artery pressure (PAP). After CPB, the vasopressin group (n = 13) had a significantly lower peak norepinephrine dose than the placebo group (n = 14), a shorter period on catecholamines, fewer hypotensive periods, and a shorter ICU length of stay. Hasija et al.[26] compared the effects of continuation versus discontinuation of the ACEI ramipril and assessed the efficacy of prophylactic vasopressin infusion on hemodynamic stability and vasoactive drug requirements in 47 patients undergoing coronary artery bypass grafting (CABG). Main results of the study were that prophylactic low-dose vasopressin (0.03 IU/kg/min) prevented post-CPB hypotension in ACEI-treated patients. Jahangirifard et al.[27] compared vasopressin (0.03 IU/kg/min) and placebo in 80 patients undergoing CABG. Vasopressin significantly reduced the number of patients treated with dopamine and mean dose of this drug immediately after CPB separation and later in the ICU. Duration of mechanical ventilation, 24-hour urinary output, and heart rate were significantly lower in the vasopressin group versus the placebo group. The incidence of arrhythmias did not differ between groups. Elgebaly et al.[28] investigated the hemodynamic effects of preemptive vasopressin (0.03 IU/min) versus placebo applied during and up to 60 minutes after CPB in 20 patients with mild-to-moderate systolic dysfunction undergoing CABG. Cardiac output and SVR were significantly higher in the vasopressin group after CPB. Epinephrine was required in seven placebo-administered patients but in none of the vasopressin-administered patients on initial separation from CPB.

The remaining five RCTs[29-33] investigated various effects of vasopressin in cardiac surgery patients. In four of these trials, vasopressin was used first line.[29,30,32,33] Hasanpour et al.[29] compared vasopressin (0.02 IU/min) and norepinephrine (0.05-0.5 μg/kg/min) with respect to their effect on renal function in 120 patients undergoing CABG and found a significantly higher creatinine clearance in the norepinephrine group versus the vasopressin group but no differences in sodium, potassium, urea, and creatinine levels. Jeon et al.[30] compared vasopressin (0.02-0.16 IU/min) and norepinephrine (2-16 μg/min) in 50 patients undergoing CABG and receiving milrinone. Vasopressin and norepinephrine were titrated until MAP was increased by 20%. Milrinone infusion reduced both SVR and pulmonary vascular resistance (PVR). Both vasopressin and norepinephrine increased SVR and PVR; however, only vasopressin significantly decreased the PVR/SVR ratio. Park et al.[32] compared the effects of vasopressin (0.033 IU/min) and norepinephrine (1.33 μg/min) on internal thoracic arterial flow in 41 patients after off-pump CABG. Study drugs were titrated in order to maintain a 20% increase in MAP throughout the study. With norepinephrine, grafted internal thoracic arterial flow increased significantly relative to baseline, whereas it remained unchanged with vasopressin. The SVR index increased in both groups, whereas the PVR index remained unchanged in the norepinephrine group but significantly decreased in the vasopressin group. Yimin et al.[33] compared the hemodynamic effects of vasopressin and norepinephrine in 20 patients undergoing CABG. During surgery there were no differences in MAP, heart rate, central venous pressure, pulmonary capillary wedge pressure (PCWP), and SVR between the groups. PAP increased in both groups but significantly more in the norepinephrine versus the

vasopressin group. PVR increased in the norepinephrine but not in the vasopressin patients. Metoprolol usage was significantly lower in the vasopressin group (5.9 mg) versus the norepinephrine group (11.2 mg). Okamoto et al.[31] investigated the relationship between intraoperative vasopressin infusion and postoperative myocardial necrosis markers in 92 patients undergoing cardiac surgery. After anesthesia induction, the study drug (vasopressin 0.03 IU/min or placebo) was administered, along with catecholamines, to patients requiring hemodynamic support. There were no differences in postoperative myocardial necrosis markers.

Terlipressin

One RCT in cardiac surgery patients and no review dedicated to only terlipressin was found. Abdelazziz et al.[34] compared terlipressin with norepinephrine in 40 cardiac surgery patients with PAH to prevent milrinone-induced systemic vascular hypotension. Both drugs increased MAP to a similar extent, but the mean PAP was significantly lower in the terlipressin group compared with the norepinephrine group ($p < 0.05$ at skin closure and 24 hours postoperatively, respectively). Terlipressin is included in several reviews/meta-analyses and 2 retrospective studies discussing vasopressors (see Table 1ES).

MB

Four RCTs, seven reviews, one meta-analysis of RCTs, and some retrospective or prospective uncontrolled studies were identified (see Table 1ES). Most of them investigated patients with vasoplegic shock. Maslow et al.[35] examined the hemodynamic effects of MB versus placebo administered during CPB in 30 patients taking ACEIs and undergoing cardiac surgery. MB increased MAP and SVR and reduced the need for phenylephrine and norepinephrine. Furthermore, serum lactate levels were lower in MB patients. Levin et al.[7] randomly assigned 56 patients with vasoplegic syndrome after cardiac surgery to either MB or placebo. Patients treated with MB showed significant reductions in morbidity and mortality compared with placebo. In addition, the duration of vasoplegia was significantly shorter in the MB group versus the placebo group. However, this study has been criticized due an astonishingly low complication rate in the MB group. Özal et al.[36] studied whether preoperative administration of MB prevents the occurrence of vasoplegic syndrome in 100 cardiac surgery patients at high risk for perioperative vasodilation (eg, patients treated with

Table 1
Summary of Statements and Recommendations

Statement/Recommendation	Grade of Recommendation	Quality of the Evidence	Agreement
A vasopressor is necessary in patients undergoing cardiac surgery to optimize systemic vascular tone, if systemic perfusion pressure cannot be restored and/or maintained after optimization of fluid status and cardiac function.	n/a Statement	n/a	100%
We recommend using norepinephrine and/or vasopressin for restoration and maintenance of systemic perfusion pressure in cardiac surgical patients.	Strong	Moderate	100%
We recommend against using methylene blue for other purposes than as a rescue therapy for treating post-cardiac surgery vasoplegic shock.	Strong	Low	100%
We recommend against using dopamine for treating post-cardiac surgery vasoplegic shock.	Strong	Moderate	100%
There is insufficient evidence to make a recommendation on the use of terlipressin in cardiac surgical patients.	n/a Statement	n/a	100%
There is insufficient evidence to make a recommendation on the use of angiotensin II in cardiac surgical patients.	n/a Statement	n/a	100%
There is insufficient evidence to make specific recommendations of optimal doses for norepinephrine or vasopressin.	n/a Statement	n/a	100%
We recommend that clinicians consider early addition of a second vasopressor (norepinephrine or vasopressin) if adequate vascular tone cannot be restored by a monotherapy with either norepinephrine or vasopressin.	Weak	Low	100%
We recommend to start or add vasopressin to restore vascular tone if adverse effects attributable to sympathoadrenergic drug infusion are observed.	Strong	Moderate	95.2%
We recommend that clinicians consider to wean vasopressin as the last vasopressor in cardiac surgical patients with vasoplegic shock.	Weak	Very low	100%
We recommend clinicians to consider the use of vasopressin as a first-line vasopressor or to add vasopressin to norepinephrine to prevent atrial arrhythmias in cardiac surgical patients.	Weak	Moderate	95.2%
There is insufficient evidence to make a recommendation for preference of a specific vasopressor to reduce the incidence of acute kidney injury in cardiac surgical patients.	n/a Statement	n/a	100%
We recommend clinicians to consider use of vasopressin as a first-line vasopressor or to add vasopressin to norepinephrine in cardiac surgical patients with pulmonary hypertension and/or right-sided heart dysfunction	Weak	Very low	100%
We cannot recommend norepinephrine or vasopressin with respect to the risk of ischemic complications.	Strong	Moderate	100%

ACEIs). The incidence of vasoplegic syndrome was significantly lower in the MB compared with the control group. In addition, ICU and hospital stay were significantly shorter in the MB group versus the control group. Ribeiro et al.[37] investigated the hemodynamic and inflammatory responses of MB versus no MB in 60 patients undergoing CABG. MB administration resulted in a higher SVR, lower tumor-necrosis factor α (TNFα) concentrations, fewer leukocytes and neutrophils, and lower levels of NO.

AT II

Four RCTs (including one post-hoc analysis of one of the other trials) and one review were identified (Table 1ES). Only one trial explicitly studied cardiac surgery patients with vasoplegic shock, whereas the others included patients with vasodilatory shock as a result of various reasons. Bennet et al.[38] compared AT II with phenylephrine in 20 patients scheduled for cardiac surgery who had been taking ACEIs for at least six months and examined the effect on renal function after surgery. Neither drug caused renal impairment.

Discussion and Recommendations

Question 1: Which Vasopressors Should Be Used in Cardiac Surgery?

Although a mild degree of vasodilation is observed in almost every cardiac surgical patient upon induction of general anesthesia and during CPB,[1] a relevant number of patients present with moderate or even profound vasodilation and accompanying arterial hypotension that, in the most severe form, has been entitled "vasoplegic shock".[2,7] Moreover, treatment of myocardial dysfunction with inodilating drugs also may dose-dependently decrease SVR.[34] Consequently, after optimization of fluid status and myocardial function, drugs with vasoconstrictory properties often are inevitable to restore and maintain an adequate arterial perfusion pressure in cardiac surgical patients.

- A vasopressor is necessary in patients undergoing cardiac surgery to optimize systemic vascular tone if systemic perfusion pressure cannot be restored and/or maintained after optimization of fluid status and cardiac function (statement – agreement 100%).

The present systematic review of the literature revealed that there is overall sparse scientific evidence on the use of vasopressors in this field. Catecholamines traditionally have been used for increasing vascular tone and still are used as first-line agents in many European heart centers.[39,40] However, their use for this indication must be regarded as empirical because no larger study showing an outcome benefit of norepinephrine or dopamine (in vasopressor doses) compared with non-catecholaminergic vasopressors is available. Several meta-analyses have shown equivalence[41] or even superiority[42] of non-adrenergic vasoconstrictory drugs, such as vasopressin or terlipressin, in terms of reductions in mortality and morbidity compared with catecholamines in vasodilatory states. In line with this, when comparing first-line administration of norepinephrine with first-line administration of vasopressin in patients with vasoplegic shock after cardiac surgery,[20] vasopressin was superior to norepinephrine with respect to a combined primary outcome of 30-day mortality and severe complications, the incidence of AKI and AF, and significantly shortened ICU and hospital stays. In addition, first-line therapy with vasopressin has proven effective in the treatment of milrinone-induced hypotension[30] and in patients with a reduced ejection fraction in maintaining hemodynamic stability without increasing PAP.[27,28] Thus, vasopressin seems to be an effective alternative for first-line therapy. This is pathophysiologically plausible based on the observations that vasoplegic shock may be associated with a relative vasopressin deficiency; adrenergic hyposensitivity; a loss of responsiveness to the vasopressor effects of catecholamines[12,43]; and that high doses of catecholamines may lead to significant adverse effects such as arrhythmias, organ ischemia, and increased mortality.[44,45]

Nonetheless, several recent surveys have delineated that norepinephrine is still the most frequently used vasopressor, at least in Europe,[39,40] and thus may be regarded as the present standard of care. The authors recommend using norepinephrine and/or vasopressin for restoration and maintenance of systemic perfusion pressure in cardiac surgical patients ([strong recommendation, moderate quality of evidence]; agreement 100%).

In contrast to the use of vasopressin, which was more or less unequivocally associated with improved outcomes in terms of mortality or morbidity,[42,41] data on the use of MB for severe vasodilatory states in patients undergoing cardiac surgery are controversial. Whereas an RCT in 58 patients after cardiac surgery showed that MB in addition to norepinephrine versus placebo reduced mortality and duration of vasoplegia;[7] a retrospective study of 75 of 226 patients with vasoplegia treated with MB was associated with increased postoperative morbidity and mortality.[46] In a meta-analysis of five RCTs (n = 174), Pasin et al.[47] concluded that MB versus control modestly but significantly increased arterial blood pressure without an adverse effect on mortality. Several reviews[48,49] that included prospective and retrospective observational studies mentioned the lack of high-quality data and demonstrated the role of MB in case of catecholamine-resistant vasoplegia or as last-resort therapy if other vasopressors failed because no consistent improvement in morbidity and mortality could be demonstrated. The authors recommend against using methylene blue for other purposes than as a rescue therapy for treating post-cardiac surgery vasoplegic shock ([strong recommendation, low quality of evidence); agreement 100%).

No recent evidence is available regarding the efficacy and safety of dopamine acting as a vasopressor. In a recent systematic review on the use of vasopressors for hypotensive shock, Gamper et al.[50] stated that dopamine increased the risk of arrhythmia compared with norepinephrine and might increase mortality. Likewise, De Backer et al.[51] reported a greater incidence of arrhythmias in the dopamine versus norepinephrine

group in their trial, and Sakr et al.[52] concluded in their observational study that dopamine might be associated with increased mortality in patients with shock of any cause. Thus, it is difficult to provide guidance on the use of dopamine for the treatment of hypotension or vasoplegic shock in cardiac surgery patients. The authors recommend against using dopamine for treating post-cardiac surgery vasoplegic shock ([strong recommendation, moderate quality of evidence]; agreement 100%).

The majority of trials investigating terlipressin were conducted in patients with septic shock or hepatorenal syndrome. One RCT compared the effects of terlipressin and norepinephrine in patients with milrinone-induced hypotension and observed that both drugs increased MAP to a similar extent, but the mean PAP was significantly lower in the terlipressin group compared with the norepinephrine group. Treatment of catecholamine-refractory hypotension after cardiac surgery was only evaluated in two retrospective studies[53,54] that did not reveal conclusive results. Therefore, it is difficult to judge the efficacy of terlipressin in cardiac surgery patients. There is insufficient evidence to make a recommendation on the use of terlipressin in cardiac surgical patients (statement – agreement 100%).

AT II seems to be an alternative to phenylephrine in patients on ACEIs and may be considered in patients who fail to respond to conventional vasoconstrictors[38]; however, only sparse data are available for this drug. The largest trial investigating AT II was conducted by Khanna et al.[55] (ATHOS-III), but only 19 of 321 patients with circulatory shock receiving a study intervention experienced postoperative vasoplegic shock. However, a recent post-hoc analysis in 16 cardiac surgical patients showed fewer treatment-emergency serious adverse events and no difference in thrombotic events in patients treated with AT-II compared with patients treated with placebo.[56] There is insufficient evidence to make a recommendation on the use of angiotensin II in cardiac surgical patients (statement – agreement 100%).

Question 2: What Is the Optimal Dosage and the Optimal Time to Start and Stop Vasopressor Treatment?

There are neither clear guidelines nor well-established treatment strategies available to support clinicians in deciding on dosage, treatment start, and duration of vasopressor therapy. This fact becomes visible when the different treatment regimens used in the studies selected for the present article are examined (see Table 1). There is insufficient evidence to make specific recommendations of optimal doses for norepinephrine or vasopressin (statement – agreement 100%).

Usually, vasopressor therapy is started if MAP remains low despite adequate volume substitution and optimization of cardiac function. In clinical studies, the threshold for MAP as an inclusion criterion usually is set at <50 up to <70 mmHg.[2,7] Preoperative use of ACEIs, calcium channel blockers, reduced cardiac function, treatment with inotropic substances, such as milrinone or levosimendan during surgery, and long duration of CPB are some of the factors that increase the risk for the development of severe hypotension and/or vasoplegic shock.

Treatment start with second-line non-adrenergic vasopressors differed considerably among the trials and was based on MAP and norepinephrine requirements. The threshold for the norepinephrine doses varied between 0.1 μg/kg/min and 0.7 μg/kg/min and the one for MAP between 55 mmHg and 70 mmHg.

Treatment duration with vasopressors depends on the hemodynamic condition of the patient. Vasoplegic shock can last from several hours up to a few days. Jochberger et al.[43] reported a mean duration of vasoplegic shock of 9.9 ± 6.9 days. Treatment start and duration should be based on the clinical situation of each individual patient. It is reasonable to wean vasopressor therapy as soon as vascular tone is restored (statement – agreement 100%).

Several studies have shown a clear and dose-dependent association between the doses of betamimetic catecholamines and adverse outcomes.[45,57] The addition of a non-adrenergic vasopressors, such as vasopressin[19] or AT II[55] in patients on high-dose norepinephrine therapy, allows for the immediate reduction of the norepinephrine dose to improve MAP and stroke volume and to avoid the myocardial toxicity associated with high doses of norepinephrine.[57] However, some of these studies were performed in critically ill patients with a vasoplegic syndrome outside the field of cardiothoracic surgery, were monocentric, or included only a small number of patients. The authors recommend that clinicians consider early addition of a second vasopressor (norepinephrine or vasopressin) if adequate vascular tone cannot be restored by a monotherapy with either norepinephrine or vasopressin ([weak recommendation, low quality of evidence]; agreement 100%).

Because of its betamimetic properties (Supplementary Material, see Supportive Information 1), treatment with high doses of norepinephrine (and even more epinephrine) may be associated with clinical signs of a severe stress response such as tachycardia, tachyarrhythmia, hyperglycemia, and type B lactacidosis.[58] In addition, a high sympathetic tone may trigger AF that not only often prolongs ICU and hospital stay, but also may be associated with increased morbidity and mortality.[59] Evidence from large observational trials,[60] sound pathophysiologic reasoning, and moderately sized RCTs[20] support the avoidance of sympathoadrenergic overactivation (see also the following section). The authors recommend to start or add vasopressin to restore vascular tone if adverse effects attributable to sympathoadrenergic drug infusion are observed ([strong recommendation, moderate quality of evidence]; agreement 95.2%).

In a statement of dissent, the coauthor (U.S.), who did not agree on this specific recommendation, noted that a reasonable patient management always should aim to avoid a complication instead of treating it; and, thus, from his perspective, vasopressin should be started or added before adverse effects attributable to sympathoadrenergic drug infusion are observed.

There are sparse data guiding the weaning sequence in case more than one vasopressor is applied in patients after cardiac surgery. The discontinuation schemes described in the

available literature are heterogeneous and often are not reported at all. Order of discontinuation does not seem to be relevant if MB is added to catecholamines because it usually is given over a short period. Dominick et al.[15] conducted a retrospective analysis comparing 54 patients in whom vasopressin was discontinued first with 35 patients in whom vasopressin was weaned off after other vasopressors. They observed an increased incidence (50% *v* 17%) of clinically significant arterial hypotension if vasopressin was discontinued first, without other morbidity. There were no significant differences in vasopressin duration, use of rescue therapy, length of stay in both the ICU and hospital, or in-hospital mortality. The authors recommend that clinicians consider to wean vasopressin as the last vasopressor in cardiac surgical patients with vasoplegic shock ([weak recommendation, very low quality of evidence]; agreement 100%).

Question 3: Are There Differences Among Vasopressors in the Incidence of New-Onset AF?

The incidence of AF has been reported as high as 10% among ICU patients presenting with vasodilatory shock,[61] 15% to 40% after CABG surgery, and up to 60% after combined CABG and valve surgery.[62,63] In all clinical scenarios, AF independently has been associated with morbidity, mortality, and lengths of ICU and hospital stay. Vasopressor requirements,[61] postoperative fluctuations in autonomic tone, postoperative sympathetic activation,[59] inflammation, increased catecholamine release, and variable-length atrial refractory periods—termed "dispersion of refractoriness" [64]—have been identified as risk factors.

Whereas one RCT comparing dopamine versus placebo found no differences in the incidence of AF in patients after CABG,[65] three retrospective studies[59,64,66] reported that the use of dopamine or dobutamine were independent predictors for AF after cardiac surgery and increased the risk up to 74%.[64]

Comparably, norepinephrine doses of >0.5 μg/kg/min were associated with an increased risk for AF.[57,67] Dünser et al.[19] and Okamoto et al.[31] showed a significant reduction in the occurrence of AF when vasopressin was added to norepinephrine versus norepinephrine therapy alone in vasoplegic critically ill or cardiac surgical patients, respectively. Hajjar et al.,[20] who compared first-line therapy of vasopressin and norepinephrine, reported a significant difference in the occurrence of AF in favor of vasopressin in vasoplegic cardiac surgical patients. These results are supported by two recent meta-analyses[60,68] that demonstrated a significant reduction in the risk of AF in cardiac surgery patients when vasopressin was added to norepinephrine or given first line versus norepinephrine monotherapy (RR 0.77 [95% confidence interval 0.67-0.88]; odds ratio [OR] 0.42 [95% confidence interval 0.21-0.82], respectively). Robust evidence is lacking for AT II and MB. Only Levin et al.[7] mentioned a reduction of supraventricular arrhythmias when MB was added to norepinephrine in vasoplegic cardiac surgical patients. Thus, a potential role for MB reducing AF needs to be explored further. The authors recommend clinicians to consider the use of vasopressin as a first-line vasopressor or to add vasopressin to norepinephrine to prevent atrial arrhythmias in cardiac surgical patients ([weak recommendation, moderate quality of evidence]; agreement 95.2%).

In a statement of dissent, the coauthor (U.S.), who did not agree on this specific recommendation, noted that this sentence could be interpreted as a recommendation to use vasopressin as a first-line vasopressor in all cardiac surgical patients, taking into account the high incidence of AF in this specific population.

Question 4: Are There Differences Among Vasopressors in the Incidence, Progression, and Severity of AKI?

AKI develops in 5% to 30% of patients undergoing cardiac surgery and is associated with increased extra-renal morbidity and short- and long-term mortality.[69-72] Thus, any deterioration of renal function in patients after cardiac surgery should be avoided.

Norepinephrine, as the physiologic mediator of renal sympathetic nervous activity, reduces renal perfusion and increases tubular reabsorption of sodium by preferentially binding to α-receptors on renal afferent arterioles and activates the renin-angiotensin-aldosterone system via β_1-receptors.[73] Consequently, norepinephrine, especially at higher doses, may negatively affect renal function. In contrast, binding of vasopressin to V_1 receptors may lead to efferent glomerular vasoconstriction, thereby increasing the glomerular filtration rate.[74] In addition, V2 receptor–mediated renal vasodilation may counteract this vasoconstrictor response and increase renal blood flow.[75] Vasopressin also acts on the V3 receptors, promoting adrenocorticotropic hormone (ACTH) release, and, thus, stimulation of the adrenal gland. Therefore, endocrine effects in regulation cannot be excluded. MB counteracts the effects of NO and other nitrovasodilators in endothelium and vascular smooth muscle.[76] Specific effects on efferent and afferent arterioles in the kidney have not been investigated.

The results of several small RCTs investigating the effect of vasopressors on kidney function in cardiac surgery are heterogeneous and inconclusive.[29,31,33] In a direct comparison of vasopressin and norepinephrine in patients with vasoplegic shock,[20] vasopressin significantly reduced the occurrence of AKI and the need for renal replacement therapy (RRT) compared with norepinephrine (10.3% *v* 35.8%; $p < 0.0001$). In a direct comparison of AVP and NE in patients with vasoplegic shock,[16] AVP significantly reduced the occurrence of AKI compared to NE (10.3% vs. 35.8%; $p < 0.0001$). In addition, significantly less patients in the AVP group needed renal replacement (RRT) therapy in comparison with the NE group. However, the initiation of RRT was not standardized or protocolized. These results were in line with a meta-analysis reviewing the evidence concerning the effects of vasopressin and its analogs compared with other vasopressors in distributive shock[74] that showed that patients treated with vasopressin or its analogs had a reduced need for RRT (OR 0.59 [0.37-0.92]) and a lower AKI incidence (OR 0.58 [0.37-0.92]).

However, these results should be interpreted with caution because of excessive heterogeneity. Dünser et al.[68] showed in their meta-analysis that vasopressin significantly reduced the pooled OR of perioperative complications, including AKI in patients undergoing cardiac surgery. When only AKI was examined, no statistically significant difference was found.

The majority (11 of 13) of participants of the second consensus conference demonstrated a potential beneficial effect of vasopressin for kidney function in cardiac surgery patients. However, the available evidence was considered to be insufficient to make a recommendation.

Sparse data investigating the renal effects of AT II in cardiac surgical patients are available. Bennet et al.[38] compared phenylephrine with AT II in cardiac surgery patients who received ACEIs preoperatively and found that neither drug caused renal impairment using creatinine clearance as a measure of the rate of glomerular filtration. However, the study was not powered adequately to allow for assumptions on the safety of this approach. A subgroup analysis of the ATHOS-III study in patients treated with RRT upon inclusion revealed a higher likelihood of renal recovery and improved survival in patients treated with AT II compared with placebo, suggesting a beneficial effect of AT II in kidney function.[77] If this observation may be explained by effects of AT II itself or by the withdrawal of vasopressors mediating adverse effects on the kidney needs to be explored in future studies. There is insufficient evidence to make a recommendation for preference of a specific vasopressor to reduce the incidence of acute kidney injury in cardiac surgical patients (agreement 100%).

Question 5: Which Vasopressor Should Be Used in PAH and/or Right-Sided Heart Failure?

Preexisting PAH is a major risk factor for increased mortality and morbidity in patients undergoing cardiac surgery.[78] Severe right ventricular failure has been reported to occur in approximately 0.1% of patients after cardiac surgery and in 20% to 30% of patients requiring left ventricular assist devices,[79,80] and the in-hospital mortality rate has been reported to range between 70% and 75%. However, subtle right ventricular dysfunction is a universal feature of many cardiac surgical procedures,[81] and the incidence of right-sided heart failure observed in clinical practice seems to be as high as 20%.[82] Common causes of the development of acute new-onset postoperative PAH include preexisting pulmonary hypertension, ischemia-reperfusion injury, pulmonary embolism, left ventricular failure, adverse protamine reactions, hypervolemia, and excessive blood transfusion.[79]

Sympathomimetic vasopressors, such as norepinephrine and phenylephrine, increase both SVR and PVR, with the latter potentially harming the already strained right side of the heart.[83] The potential adverse effects on PVR are likely to occur only at higher doses of norepinephrine (>0.5 μg/kg/min).[78] Dopamine administered at doses ≥10 μg/kg/min increases PCWP and PVR, whereas it does not change PCWP at doses <5 μg/kg/min.[84,85] Vasopressin has no clinically relevant vasoconstrictor effect on pulmonary vessels. Experimental studies have revealed vasodilating properties at low doses that include pulmonary vasodilation through an NO-dependent mechanism via V1 receptors, and it has been used safely in sepsis.[78] AT II acts on pre-capillary arterioles, but at normal doses it has little effect on the lung.[38] The authors of the present article did not find any data regarding the effect of AT II on patients with PAH or right-sided heart failure. MB has been shown to increase PAP and PVR, which could worsen PAH. The adverse pulmonary effects of MB may limit its use in patients with PAH, right ventricular dysfunction, or acute respiratory distress syndrome.[84,86]

Only a few RCTs reported on the effect of different vasopressors on pulmonary vascular reactivity. Kwak et al.[83] compared the ability of norepinephrine and phenylephrine to treat hypotension in 24 patients with chronic PAH undergoing cardiac surgery. Mean PAP and pulmonary vascular resistance index (PVRI) significantly increased in both groups. However, the ratio of mean PAP-to-mean systolic blood pressure was reduced significantly in the norepinephrine group but not in the phenylephrine group when systolic arterial pressure was increased to 30% above baseline values.

Thirteen studies investigating vasopressin in cardiac surgery patients reported pulmonary hemodynamic parameters. Two of these studies included patients with PAH and observed that the ratio between SVR and PVR was favorably altered.[87,88] The remaining 11 RCTs with vasopressin included cardiac surgery patients without preexisting pulmonary hypertension and reported on various hemodynamic parameters, such as mean PAP, PCWP, or PVR. None of these trials reported any deterioration of lung hemodynamics regardless of whether vasopressin was used for treatment first line[24,28,32,33] or second line on top of norepinephrine[18,19,43,22] or whether it was administered prophylactically[25,26,30] for prevention of hypotension or vasoplegic shock. Overall, the evidence for vasopressor treatment in cardiac surgery patients with PAH is scarce. The authors of the present article did not find any RCT comparing first-line treatment with a vasopressor versus placebo or active control in patients with PAH. The only drug that consistently did not show any negative effect on pulmonary pressures is vasopressin. Even in patients with preexisting PAH, vasopressin was used safely without deterioration of PAH. The authors recommend clinicians consider use of vasopressin as a first-line vasopressor or to add vasopressin to norepinephrine in cardiac surgical patients with pulmonary hypertension and/or right-sided heart dysfunction ([weak recommendation, very low quality of evidence]; agreement 100%).

Question 6: Are There Differences Among Vasopressors in the Incidence of Ischemic Complications?

Cardiac surgical patients who experience postoperative hypotension and vasoplegic shock are at high risk of ischemic complications. Higher doses of adrenergic vasopressors imply the risk of myocardial and tissue ischemia.[57] Higher doses of vasopressin (>0.06 IU/min) could increase the risk of mesenteric and skin ischemia.[89] Dopamine might increase myocardial oxygen consumption and provoke myocardial ischemia,[65]

and MB may lead to mesenteric vasoconstriction and compromised blood flow, usually occurring at doses >2 mg/kg.[86,90] Continuous peripheral infusion of MB for a prolonged duration may lead to local cutaneous necrosis.[91] Based on its mode of action, AT II also could be associated with adverse events. However, adverse events reported in the identified studies are very heterogeneous. Few investigators reported adverse events, some reported only serious adverse events, others listed special complications of interest, and many did not report at all. Thus, it is difficult to compare and draw any meaningful conclusions.

However, in the comparative studies, no clinically relevant statistical differences in the incidence of vasopressors were observed (for details, see Supplementary Material, Supportive Information 2). The authors cannot recommend norepinephrine or vasopressin with respect to the risk of ischemic complications ([strong recommendation, moderate level of evidence]; agreement 100%).

Limitations

Rare complications or specific conditions of cardiac surgical patients beyond vasoplegia that may influence the choice of a specific vasopressor were not addressed. For example, in patients with systolic anterior movement, a phenomenon after mitral valve reconstruction, or in patients with hypertrophic cardiomyopathy, the use of a vasopressor may not only be guided by the vasoconstrictive effect, but also by the lack of inotropic properties. Based on case reports, the use of phenylephrine may be superior to dopamine in these conditions.[92] However, no comparative studies with other vasopressors, such as AT II or vasopressin, are available.

Second, the term "vasoplegia" was used as a general description of a severe loss of vascular tone associated with arterial hypotension if left untreated. This is an oversimplification, taking into account the complex interplay of vascular impedance and cardiac function[93] and that a "severe loss of vascular tone" may be induced by different mechanisms, such as inflammation or the vasodilation induced by the application of an inodilator, and it is not known on which effector sites on the vascular level (conductance vessels, order of resistance vessels) these factors precisely act.

Third, the utility of catecholamines to support hemodynamics in cardiac surgery patients was established in the 1960s and 1970s. Because the literature search of this consensus document excluded studies published before 1990, the authors cannot rule out that articles supporting the use of classic catecholamines in cardiac surgical patients may have been missed.

Fourth, the majority of studies included in the present systematic review were small and monocentric. In addition, some studies did not exclusively focus on patients after cardiac surgery. Unfortunately, compared with other clinical fields (such as sepsis or heart failure), the cardiac surgical patient population is relatively small. In addition, most drugs of interest already have a generic status; consequently, public and industrial interest in supporting large and expensive RCTs in this field is rather low, and dedicated large multicentric trials with a focus on vasoplegia in cardiac surgical patients are hardly to be expected within the foreseeable future.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2020.11.032.

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