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The Renin–Angiotensin–Aldosterone System in Cardiac Surgery and Angiotensin II Therapy for Vasoplegia

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Cardiac surgery remains associated with major complications, ranging from persistent postoperative vasoplegia, defined as a persistently low blood pressure due to a low systemic vascular resistance and normal cardiac output, acute kidney injury (AKI), and cardiovascular events to cognitive dysfunction.[1,2] The renin–angiotensin–aldosterone system (RAAS) plays a role in cardiopulmonary bypass (CPB) induced vasoplegia and is a potential target for interventions aimed at decreasing its associated complications.[3,4]

Cardiac surgery–associated vasoplegia affects up to one-third of patients, depending on the population considered, the type of surgery, and definitions used.[3,4] The management of hypotension during and after cardiac surgery includes the use of fluids to optimize intravascular filling and cardiac output, and the use of vasopressor drugs to restore arterial smooth muscle tone.[3] Vasopressors such as norepinephrine and vasopressin are typically used to restore and maintain the target mean arterial pressure when vasoplegia results. However, side effects of these agents include arrhythmias and end-organ ischemia. Recently, angiotensin II has been approved as a vasopressor agent for the treatment of vasoplegia.[1,5–10]

We report a state-of-the-art clinical update regarding the RAAS in patients undergoing cardiac surgery with a focus on the use of angiotensin II in cardiac surgery patients. Finally, we discuss the rationale for using exogenous synthetic angiotensin II as a vasopressor and provide guidance regarding the patient population in which angiotensin II is most likely to be effective.

PHYSIOLOGY OF THE RAAS

The RAAS is a hormone system that regulates fluid, and electrolyte balance, vascular resistance, and blood pressure, and systemic vascular resistance.

Renin is produced and secreted by juxtaglomerular cells in the afferent arterioles of the kidney. Renin secretion is upregulated by 4 different mechanisms in the kidney: (1) renal baroreceptor mechanism: decrease of blood pressure in the afferent arterioles; (2) macula densa mechanism: decrease of sodium chloride concentration in the distal tubule; (3) sympathetic nervous system: β_1-adrenergic receptor stimulation; and (4) feedback: low levels of angiotensin II. Plasma renin converts angiotensinogen into angiotensin I, which is subsequently converted to the active angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II has a short life (approximately 1 to 2 minutes) and is rapidly degraded into angiotensin III by angiotensinases. Angiotensin III increases blood pressure and induces aldosterone secretion from the adrenal cortex.

Angiotensin II is a potent vasopressor that causes vasoconstriction, resulting in increased blood pressure. In addition, angiotensin II also increases the secretion of aldosterone. Aldosterone triggers tubular sodium reabsorption, resulting in sodium retention and an increase in blood pressure. This effect increases the volume of extracellular fluid in the body, which also increases blood pressure.

THE PATHOPHYSIOLOGY OF THE RAAS IN CARDIAC SURGERY

Vasoplegia is a syndrome and a frequent complication of cardiac surgery, especially following CPB. It is defined as a state of shock (hypotension) in which cardiac output is normal or even high and vascular tone (systemic vascular resistance) is decreased.[3]

The RAAS, particularly angiotensin II, plays a role in maintaining or restoring vascular tone. In vasoplegia caused by CPB, the use of angiotensin II thus represents targeted therapy. During CPB, the pulmonary circulation is bypassed; therefore, the exposure of angiotensin I to ACE is limited, and hence, production of endogenous angiotensin II decreases.[11] As ACE and ACE2 are also located in the kidneys and renal blood flow is redistributed away from the kidneys during CPB, the RAAS is also activated. Though a vast majority of the ATHOS-3 trial patients had septic shock, a small subset of 17 patients had post-CPB vasoplegia, and 9 received angiotensin II. 89% of those patients exhibited an improvement in blood pressure compared to none in the placebo group (n=7).[10] These observations support the involvement of RAAS-asociated pathophysiological processes in cardiac surgery-associated vasoplegia.[12,13]

Preliminary biomarker data also suggest dysregulation of the RAAS after cardiac surgery, which may also be associated with poor postoperative outcomes.[12,13] In a 2021 study, Küllmar et al reported that high plasma renin concentrations, potentially indicating an angiotensin II deficit, were associated with a higher risk of vasoplegia and postoperative AKI after cardiac surgery.[13]

Existing evidence supports the relevance of angiotensin metabolism (higher angiotensin I/II ratio) in predicting the response to angiotensin II. In a 2022 study, patients with high plasma renin concentrations were more likely to show an increase in blood pressure in response to the infusion of angiotensin II after cardiac surgery than with norepinephrine.[12] Among patients enrolled in the ATHOS-3 trial, which recruited patients with vasodilatory shock (mostly sepsis), the median angiotensin I/II ratio was 1.63 (interquartile range (IQR) 0.98–5.25).[14] In a subgroup of patients with vasoplegia after cardiac surgery with CPB (n = 16), the authors reported a median angiotensin I/II ratio of 2.3 (0.6–3.3),[10] values much higher than in healthy controls (0.39 (IQR, 0.28–0.64)).[14] Patients in ATHOS III with severe AKI also had a higher angiotensin I/II ratio, suggesting a deficit in the conversion of angiotensin I to angiotensin II.[14] Patients undergoing cardiac surgery frequently receive chronic treatment with RAAS modulators (ie, ACEi or ARB) due to a history of arterial hypertension, diabetes, or ischemic cardiomyopathy. Chronic and perioperative exposure to RAAS inhibitors before cardiac surgery is associated with higher baseline plasma renin concentrations.[15]

RAAS-inhibiting agents affect the response to angiotensin II differently (Figure). In the ATHOS-3 trial,[9] patients exposed to ACEi showed full responsiveness in blood pressure to angiotensin II infusion, whereas those exposed to ARBs had a significantly attenuated response.[9,15] This discrepancy is consistent with known physiology and confirms that the receptor blockade induced by ARB can reduce responsiveness to both endogenous and exogenous angiotensin II. Of note, stopping RAAS inhibitors the day before noncardiac surgery does not alter postoperative outcomes.[16] Whether this relatively short time frame for drug withdrawal is sufficient to activate the RAAS is unclear and requires further investigation, as many compounds in these classes possess a half-life longer than 24 hours. In a pilot RCT (n = 121) of patients undergoing nonemergent cardiac surgery, discontinuation of ACEi or ARB 2 days before surgery vs. continuation did not change postoperative intravenous vasopressor use (78.3% in the continuation versus 75.4% in the discontinuation group, P = .703) or development of vasoplegic shock (31.7% vs 27.9% respectively, P = .648).[17] Altogether, RAAS dysregulation in the context of ACEi/ARB use and CPB exposure appears to play a key role in postcardiac surgery vasoplegia. Taken together, these data suggest that elevated renin itself may result from different mechanisms and that ACEi

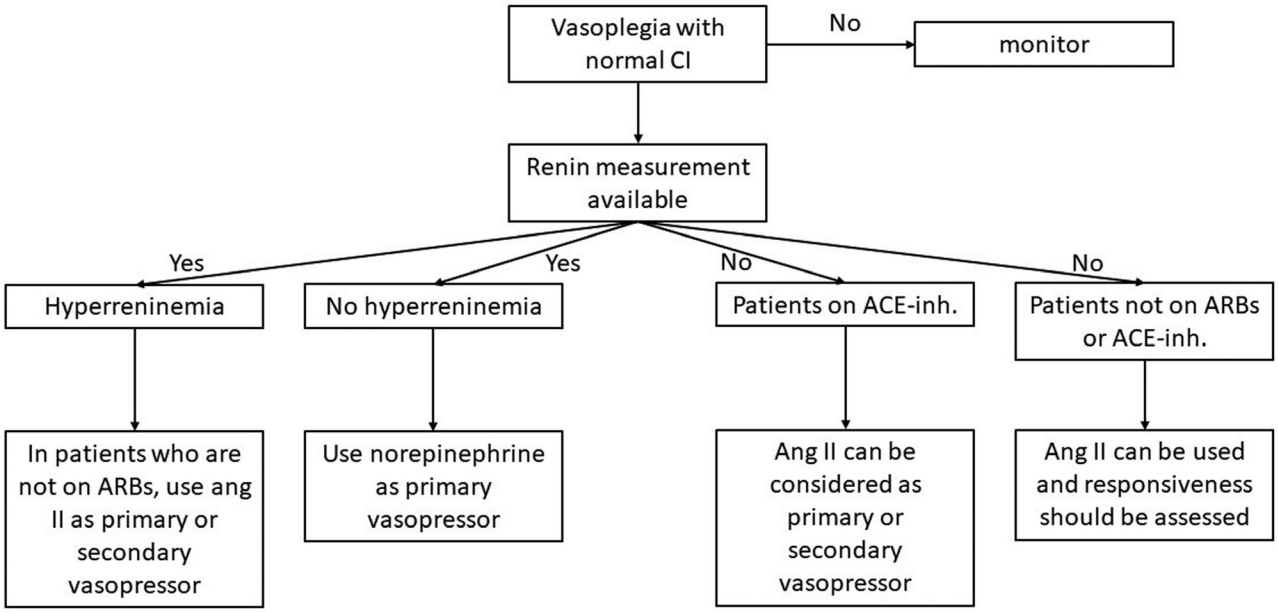

Figure. Suggested algorithm for cardiac surgery associated vasoplegia including angiotensin II. ACEi indicates angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; ARB, angiotensin receptor blocker; CI, cardiac index.

and ARBs act through completely different mechanisms to modulate the RAAS. ACEis increase the effect of angiotensin II, whereas ARBs significantly diminish the effects. Because of these considerations, several clinical trials focused on cardiac surgery have been conducted to compare angiotensin II infusion in cardiac surgery patients.[18,19]

VASOPRESSORS TO TREAT VASOPLEGIA: NOREPINEPHRINE, VASOPRESSIN, AND ANGIOTENSIN II

The most commonly used agent to restore and maintain target mean arterial pressure (MAP) is norepinephrine.[5] Norepinephrine causes vasoconstriction via stimulation of alpha receptors and also activates beta-receptors to augment myocardial contractility. However, norepinephrine may induce myocardial stress and has been associated with myocardial cell injury and a dose-dependent increased risk of arrhythmias, a complication that affects up to nearly half of patients undergoing cardiac surgery.[1] Accordingly, other vasopressor agents have been advocated to limit the dose of norepinephrine and decrease the frequency of such complications. One example is vasopressin, which acts on specific arginine vasopressin receptors to induce vasoconstriction.[6] Although vasopressin use is supported by some studies,[1] its use in cardiac surgery remains variable and center-dependent.[7] In this setting, the 2017 US Food and Drug Administration (FDA)[8] and European Medicines Agency (EMA) approval of angiotensin II for the treatment of vasodilatory shock introduces a new vasoconstrictive agent focusing on the RAAS. The potential for such an agent is relevant as many patients undergoing cardiac surgery are exposed to preoperative treatment with ACEi and ARB, which, amongst other factors (eg, CPB exposure, renal dysfunction), interfere with normal functioning of the RAAS.

CLINICAL STUDIES

The efficacy of angiotensin II as a vasoconstrictor agent in cardiac surgery-related vasoplegia has been documented by case reports,[20,21] and case series.[22–24] The reports have mostly focused on cardiac surgery in adult patients, and included heart transplant,[22–24] valve surgery,[24] and coronary artery bypass grafting (CABG) surgery[20,24] and do not allow any conclusions on outcome. Angiotensin II doses ranged from 20 to 80 ng/kg/min, and the duration of the administration was short in most cases,[20–22,24] with only few cases where the infusion lasted more than 24 hours.[23] The length of follow-up was short in all of these studies, and outcomes were limited to an increase in blood pressure and a reduction in the need of other vasopressors. While 10 publications involved only 72 patients treated with angiotensin II, more than 90% of these patients were responders in terms of increases in MAP,[20,23] decreases in the dose of other vasoactive agents,[22,24] and reductions in plasma renin concentrations.[21]

The association between angiotensin II and plasma renin concentrations in cardiac surgery has also been reinforced by a retrospective analysis of 40 high-risk AKI patients who received angiotensin II for the treatment of vasoplegia after CPB[12] and who had significant reductions of plasma renin concentrations after

administration of angiotensin II compared to norepinephrine administration alone. In addition, angiotensin II administration decreased the norepinephrine dose required to maintain the target MAP, with no increase in adverse events.[12]

Apart from the perioperative cardiac surgery setting, the use of angiotensin II has also been described in noncardiac surgery[25–28] and mechanical circulatory support.[29,30] Angiotensin II was effective and safe in maintaining MAP targets and decreasing catecholamine requirements in thoracic surgery,[24] thoracoabdominal aortic aneurysm repair,[25] liver transplant,[27] and pheochromocytoma resection.[26] The largest case series of angiotensin II during mechanical circulatory support, including mainly venoarterial extracorporeal membrane oxygenation or ventricular assist devices for cardiac failure, included a total of 50 patients.[30] In such patients, MAP increased from 60 to 70 mm Hg and the norepinephrine equivalent vasopressor dosage, including norepinephrine, decreased by 0.04 µg/kg/min in the first hour, with a further reduction by 0.16 µg/kg/min at 12 hours. Cardiac index and pulmonary artery pressures did not decrease in the first 12 hours of treatment. Another case series on angiotensin II administration during mechanical circulatory support (venoarterial/venovenous extracorporeal membrane oxygenation, and left ventricular assist devices) included 14 patients.[29] An MAP target ≥65 mm Hg was achieved in 36% of patients receiving angiotensin II at 3 hours, and the median norepinephrine dose requirement decreased accordingly. However, the included patients had refractory vasodilatory shock, evidenced by the high baseline norepinephrine dose. Authors observed a 78.6% in-hospital mortality rate, with 2 patients experiencing severe adverse drug events and one patient having a catastrophic thrombotic event. Previous papers[31] cautioned against the use of angiotensin II in patients on mechanical circulatory support, as the administration of angiotensin II may increase the incidence of thromboembolic events. Angiotensin II can provide a catecholamine-sparing effect in patients with refractory vasoplegic shock on mechanical circulatory support, but the adverse events reported in the case series emphasized the importance of careful monitoring and potential adjustments in these patients.[29]

Randomized evidence for the use of angiotensin II in cardiac surgery comes from 4 small RCTs.[10,19,32,33] The first study with angiotensin II was published in 2001.[33] This study compared the administration of phenylephrine versus angiotensin II in 20 patients undergoing cardiac surgery who had been taking ACEis during the 6 months before surgery. Authors found that angiotensin II effectively increased MAP. Further evidence for the use of angiotensin II in high risk patients undergoing cardiac surgery comes from a 2023 multicenter double blind RCT by Coulson et al which randomized 60 patients to receive either angiotensin II or norepinephrine to maintain an MAP between 70 and 80 mm Hg.[18,32] In their pilot (feasibility) study,[18] authors found that angiotensin II administration in high-risk cardiac surgery patients effectively treats vasoplegia while sparing other vasopressors and limiting fluid overload. In addition, when compared to norepinephrine angiotensin II did not increase the risk of AKI.[18,32] Norepinephrine significantly increased median plasma renin concentrations at ICU admission, while angiotensin II did not. In contrast, aldosterone levels increased with both vasopressors;[32] however, the aldosterone/plasma renin concentrations ratio were unchanged with norepinephrine, whereas it increased with angiotensin II, suggesting that exogenous angiotensin II in patients with an endogenous angiotensin II deficiency restores the RAA homeostasis.[32] Circulating dipeptidyl peptidase 3 (DPP3) levels also increased after cardiac surgery but did not show a differential response to angiotensin II infusion.[32] These results suggest that, unlike norepinephrine, angiotensin II effectively suppresses renin release while maintaining aldosterone levels.

The effect of angiotensin II on renal stress was further explored. In a follow-up 2024, a single-center, randomized trial in 63 adult patients with post-CPB vasoplegia, and increased plasma renin concentrations.[19] The study examined whether a 12-hour angiotensin II infusion targeting an MAP of ≥ 65 mm Hg could mitigate the severity of acute kidney stress measured by the 2 renal biomarker levels of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) ([TIMP-2]*[IGFBP7]) and found nosignificant difference in kidney stress between the 2 groups. However, patients receiving angiotensin II infusion required significantly less fluid, lower doses of norepinephrine, and experienced fewer serious adverse events compared to the placebo group.[19] This study suggested that a short-term, renin-guided approach to angiotensin II administration in the cardiac surgery setting was feasible.[34,35]

We summarize our opinions based on the currently available evidence.

CLINICALLY RELEVANT QUESTIONS

1. *Does angiotensin II restore blood pressure and decrease catecholamine requirements in post-cardiac surgery vasoplegia?*

Angiotensin II is a very potent vasopressor and can be used as a primary or secondary vasopressor to increase blood pressure and decrease catecholamine requirements in patients undergoing cardiac surgery.[10,12,18,19,32]

Table. Patient Selection

Angiotensin II can be considered
In patients with vasoplegia and one of the following: - Hyperreninemia - ACEi use - at risk for renal replacement therapy with or at risk for de novo atrial fibrillation - ongoing need for norepinephrine + vasopressin

Abbreviation: ACEi, angiotensin converting enzyme inhibitor.

Angiotensin II is part of the RAAS regulatory system. When ACE activity is decreased, angiotensin I is not converted in angiotensin II.[36] This change increases renin levels, which can be used as a biomarker.[13,37–39] Renin kinetics can predict the likelihood of developing AKI and vasoplegia after cardiac surgery.

It is important to underscore that both ACEi and ARBs increase renin levels, but do so via different mechanisms. These different effects have to be considered when assessing renin as a marker. ACEi increases the effect of angiotensin II on blood pressure, whereas ARBs significantly diminish the effects, suggesting that angiotensin II would have a greater effect in patients who are on ACEi.

2. *What phenotypes and/or endotypes of cardiac surgery-associated vasoplegia may benefit from angiotensin II administration?*

Pathophysiological reasoning and preliminary evidence from cardiac surgical studies suggest that the patients who can benefit most from angiotensin II are those who experience perioperative vasoplegia with hyperrenininemia caused by a reduced endogeneous angiotensin II production or the use of ACEi and who are at high risk of AKI.[13,37,38] If plasma renin concentrations assessment becomes widely available as a point of care test it may be possible to identify a subgroup of patients (those with hyperreninemia caused by a reduced endogeneous angiotensin II production or the use of ACEi or increased activation of the ACE2 pathway) who are most likely to respond to angiotensin II infusion (those who will have a rapid decrease of renin and satisfactory hemodynamic response).[37,38]

3. *What is a preferred treatment algorithm for cardiac surgery-associated vasoplegia?*

Evidence and pathophysiology suggest angiotensin II may be particularly effective in patients taking ACEi before surgery.[17] In addition, patients with hyperreninemia, not caused by ARBs, and vasoplegia with a normal cardiac index in the perioperative period may also respond well to angiotensin II.[13] Angiotensin II might be used in patients with vasoplegia even in the absence of a renin measurement, and the responsiveness to the drug should guide which vasopressor should be continued.

The algorithm shown in the Figure and the Table could guide the adoption of angiotensin II as a vasopressor as well as patient selection.

LIMITATIONS AND FUTURE DIRECTIONS

Angiotensin II was recently approved by the FDA and EMA and is now widely available in Europe and the United States. The costs for the treatment with this drug depend on several factors, including the required dose, the duration of the treatment, and the country specific price, but are at least 10-fold (eg, in Germany) higher compared to norepinephrine. As costs of angiotensin II are higher compared to other vasopressors, it should only be used in selected patient populations until more evidence is available. Future trials will need to include health economic analyses and safety concerns. Like other vasopressors, angiotensin II might cause hypertension and peripheral ischemia. In addition, thromboembolic events have been described with angiotensin II use both in case reports (30) and in the ATHOS-3 trial compared to placebo (21 (12.9%) vs 8 (5.1%)).[9]

Much current research is focused on the efficacy and safety of angiotensin II in the perioperative setting, either as monotherapy or as a catecholamine-sparing agent, and on identifying high-risk populations in which angiotensin II might be particularly effective relative to other vasopressors.[34,35] Current studies do not allow any conclusion on patient-centered outcomes. Measurement of renin levels at the bedside may facilitate the identification of patient populations likely to respond to angiotensin II. Future studies should be targeted towards identifying the patient populations that benefit most from the use of angiotensin II, and also whether angiotensin II can modify patient-centered outcomes and is cost-effective.

We conclude that angiotensin II may be a useful vasopressor for treating vasoplegia in patients undergoing cardiac surgery. Benefits from the administration of exogenous angiotensin II would be most evident in patients with an endogenous angiotensin II deficiency (based on a decreased ACE activity during cardiopulmonary bypass), and patients on ACEi. Angiotensin II can be used as a primary or secondary vasopressor in this patient population, and future studies will need to assess whether the use of angiotensin II can improve patient-centered outcomes, including organ function, long-term kidney function, length of ICU and hospital stay, mortality, and is cost-effective. ■

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