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Intravenous infusion of angiotensin II for treatment of cardiopulmonary bypass-induced vasoplegic shock after implantation of left ventricular assist device: a case report

We report on the first successful treatment of severe pharmacoresistant vasoplegic syndrome with angiotensin II acetate (ATII) in Croatia. ATII is a novel drug used to treat severe vasoplegic shock resistant to the administration of catecholamines or alternative vasopressors such as vasopressin or methylene blue. A 44-year-old patient with secondary toxic cardiomyopathy developed severe cardiopulmonary bypass-induced vasoplegic shock after scheduled implantation of a left-ventricular assist device. The cardiac output was maintained, but systemic vascular resistance (SVR) was extremely low. The patient had an inadequate reaction to the administration of high doses of norepinephrine (up to 0.7 $\mu\text{g}/\text{kg}/\text{min}$) and vasopressin (0.03 IU/min). At postoperative intensive care unit (ICU) admission, serum renin levels were unmeasurably high (>330 ng/L), and infusion of ATII 20 ng/kg/min was initiated. Soon after the start of the infusion, blood pressure increased. Vasopressin infusion was stopped, while the norepinephrine dose was decreased from 0.7 to 0.15 $\mu\text{g}/\text{kg}/\text{min}$. Serum lactate, mixed venous saturation, and glomerular filtration rate markedly improved. The patient was extubated 16 h after the ICU admission. Twenty-four hours after the start of the ATII infusion, serum renin dropped to 255 ng/L, and laboratory findings further improved. On postoperative day 3, the norepinephrine infusion was stopped. On day 6, renin further dropped to 136 ng/L, and the patient was hemodynamically stable and discharged from the ICU. In conclusion, ATII favorably affected the patient's vascular tone, enabling rapid hemodynamic stabilization and shortening the ICU and hospital stay.

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Vasoplegic syndrome is characterized by normal or increased cardiac output and reduced systemic vascular resistance (SVR), which warrants the administration of vasopressors to achieve adequate organ perfusion pressure (1). In up to 50% of patients, vasoplegia is caused by the use of cardiopulmonary bypass (CPB) and is marked by pathophysiologic mechanisms similar to those of sepsis (2). The most common drugs used for vasoplegia treatment are alpha-adrenergic catecholamines and vasopressin. When these options fail, clinicians may use angiotensin II acetate (ATII), a potent novel vasopressor. Pharmacoresistant vasoplegic syndrome often arises in the cardiac surgery setting, where the use of CPB, together with systemic inflammatory response, causes malfunctioning angiotensin converting enzyme (ACE). A reduced endogenous production of angiotensin II in vasoplegic patients may be explained by the preoperative use of ACE inhibitors and a significant reduction in pulmonary blood flow during CPB (3). In patients with mechanical circulatory support, ventricular-arterial coupling becomes dysregulated due to a loss of pulsatility, and sympathetic vascular tone usually increases immediately after surgery. If increase in vascular tone is inadequate, pressor support will be needed in the perioperative period to maintain MAP and organ perfusion. When catecholamines and vasopressin fail, ATII may be considered as a therapeutic option.

CASE REPORT

We report on a case of a 44-year-old man with secondary toxic cardiomyopathy due to a history of alcohol and cocaine abuse. He was scheduled for the implantation of a left ventricular assist device (LVAD). Other comorbidities were multi-organ failure, hypothyroidism, pulmonary emphysema, and the presence of a cardiac resynchronization therapy defibrillator.

One day before the surgery, the patient was transferred to the cardiac ICU, where a pulmonary artery catheter was inserted, and continuous infusion of levosimendan (0.05-0.1 µg/kg/min) was initiated as per the institutional LVAD pre-surgery preparation protocol.

In the operating theater, after induction of general anesthesia and preoperative transesophageal echocardiography (TEE), implantation of LVAD (Heartmate III, Abbott Cardiovascular, Abbott Park, IL, USA) and annuloplasty of the tricuspid valve were performed. The cumulative CPB duration was 130 minutes. After weaning off

CPB, the patient was extremely hypotensive, although TEE showed adequate right heart contractility (with continuous milrinone infusion of 0.6 µg/kg/min) and left-ventricular end-diastolic volume, correct cannula position, and adequate outlet cannula flow. According to the LVAD control console, cardiac output (CO) of 3 L/min was generated. It was determined that the culprit was loss of SVR, and infusion of norepinephrine was initiated (up to 1 µg/kg/min). Since it was impossible to achieve a mean arterial pressure (MAP) >50 mm Hg with infusion of norepinephrine alone, infusion of vasopressin was started at 0.03 IU/min with a gradual increase in MAP to 70 mm Hg. Norepinephrine infusion was gradually reduced to 0.7 µg/kg/min.

After hemodynamic stabilization, surgical hemostasis, and closure, the sedated and mechanically ventilated patient was transferred back to the cardiac ICU for further treatment and stabilization. At admission, he was hemodynamically unstable, with LVAD generating CO 3.1 L/min. Infusions of milrinone 0.6 µg/kg/min, norepinephrine 0.7 µg/kg/min, and vasopressin 0.03 IU/min were needed to achieve a MAP of 70 mm Hg. Initial lab results showed slightly reduced mixed venous saturation (SvO₂, 49.5%) and elevated serum lactate levels (4.8 mmol/L). Oliguria was also present, requiring the administration of furosemide to maintain diuresis and decreased glomerular filtration rate (GFR, 29 mL/min/1.73m²).

Since extremely high doses of norepinephrine and vasopressin were needed to achieve adequate perfusion pressures, serum renin levels were measured. The first value was unmeasurably high: >330 ng/L (automated chemiluminescence immunoassay, IDS-iSYS analyzer, Immunodiagnostic System Holdings, Boldon, UK). A decision was made to initiate ATII infusion at a 20 ng/kg/min rate (Giapreza, La Jolla Pharmaceutical, San Diego, CA, USA).

Within the first three hours after the start of the ATII infusion, MAP increased to 100 mm Hg. Vasopressin infusion was decreased to 0.01 IU/min and stopped after four hours. Norepinephrine dose was reduced from 0.7 µg/kg/min to 0.3 µg/kg/min, and then further to 0.15 µg/kg/min over the night. MAP was maintained between 70 and 90 mm Hg. On postoperative day (POD) 1, the patient was extubated. His serum lactate levels (2.2 mmol/L) normalized, serum renin was reduced to 255 ng/L after 24 h of ATII infusion, SvO₂ gradually increased (52.4%), and CO was preserved after a reduction in milrinone dose. ATII infusion was stopped in the evening of POD 1, 28 h after its start.

On POD 3, milrinone and norepinephrine infusions were stopped. CI was 2.2 L/min/m², SvO₂ (66%), serum lactate levels (0.7 mmol/L) normalized, and GFR was improved (38 mL/min/1.73m²).

On POD 6, serum renin further dropped to 136 ng/L, with complete normalization of GFR and marked improvement in serum transaminases and gamma glutamyl transferase. The patient was hemodynamically stable and discharged from the ICU. The timeline of relevant events is shown in Table 1.

DISCUSSION

CPB-induced vasoplegia is characterized by inducible nitric oxide synthase stimulation and increased release of nitric oxide caused by inflammatory response to surgical stress, synthetic materials in the circuit, hemolyzed blood cells, and postischemic reperfusion injury. Also, phosphorylation of adrenergic receptors impairs catecholamine binding, thus blunting the response to catecholamines. These factors, together with acidosis, depletion of endogenous arginine-vasopressin, and cell membrane hyperpolarization secondary to K_{ATP} channel stimulation, lead to severe vasoplegia refractory to high doses of α₁ agonists. Since the administered catecholamine dose is correlated with in-hospital mortality (4), several alternative options are available as adjuvant therapy to decrease norepinephrine requirements – vasopressin (5), methylene blue (6), and

angiotensin II (7). Angiotensin II is an active form of peptide hormone angiotensin I. ATII was approved by the US Food and Drug Administration in 2017 and by the European Medicines Agency in 2019. It has a positive inotropic and chronotropic effect, and increases aldosterone and vasopressin levels, as well as norepinephrine release and catecholamine sensitivity. Compared with norepinephrine alone, the use of ATII to treat catecholamine-resistant vasoplegic shock in combination with norepinephrine is associated with a higher probability of achieving a MAP of 75 mm Hg after three hours and a greater reduction of the cardiovascular subcomponent of the SOFA score (8).

Our decision to administer ATII was guided by elevated serum renin (9), and its kinetics showed the patient's favorable survival odds following ATII administration (10). There is still inconclusive evidence that ATII is superior to other vasopressors regarding hemodynamic response or decreased mortality (7,11), especially in the cardiac surgery setting, where there are only case reports or circumstantial evidence (3). However, this drug is considered safe (8) and can be used as a salvage vasopressor in vasoplegia.

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Ethical approval The patient provided consent for data publication.

Declaration of authorship AŠ, DB, JP conceived and designed the study; VM, IP, DM acquired the data; AŠ analyzed and interpreted the data; AŠ drafted the manuscript; VM, IP, DB, DM; JP critically revised the manuscript for important intellectual content; all authors gave approval of the version to be submitted; all authors agree to be accountable for all aspects of the work.

TABLE 1. The timeline of events*

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| 22 days before surgery (November 2022) | <ul style="list-style-type: none"> • Patient admitted to department of cardiology due to heart failure presenting as dyspnea • Left ventricular ejection fraction 10%, diastolic dysfunction grade 4, severe mitral regurgitation, moderate pulmonary regurgitation due to pulmonary hypertension, and moderate to severe tricuspid regurgitation with complete atrioventricular block |
| 1 day before surgery/ admitted to the cardiac ICU | <ul style="list-style-type: none"> • Insertion of pulmonary artery catheter, central venous catheter, arterial cannula • Levosimendan infusion initiated |
| Day of surgery | <ul style="list-style-type: none"> • Severe vasoplegia after LVAD implantation and weaning off CPB; milrinone, norepinephrine, and vasopressin initiated in the operating room • Serum renin unmeasurably high • ATII started after ICU admission, vasopressin stopped after 4 hours, NE dose reduced |
| POD 1 | <ul style="list-style-type: none"> • Patient extubated, normalization of lactate levels, increase in SvO₂, ATII infusion stopped in the evening, further reduction of NE dose • Serum renin started dropping |
| POD 3 | <ul style="list-style-type: none"> • Norepinephrine and milrinone stopped • Gradual improvement in SvO₂ and GFR |
| POD 6 | <ul style="list-style-type: none"> • Further reduction of serum renin levels and improvement in GFR, liver function tests, and SvO₂ • Patient discharged from ICU and transferred to cardiac surgery department |
| POD 10 | <ul style="list-style-type: none"> • Patient transferred from cardiac surgery ward to cardiology department |
| POD 46 | <ul style="list-style-type: none"> • Patient discharged from the hospital |

*Abbreviations: POD - postoperative day; LVAD - left ventricular assist device; CPB - cardiopulmonary bypass; ATII - angiotensin II acetate; ICU - intensive care unit; NE - norepinephrine; SvO₂ - venous oxygen saturation; GFR - glomerular filtration rate.

Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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