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CASE REPORT

Angiotensin II for the Treatment of Vasodilatory Shock during Percutaneous Hepatic Perfusion Cases: A Case Report

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Percutaneous hepatic perfusion (PHP) is an effective treatment for isolated liver metastases from uveal melanoma. Intraoperative anesthetic management is challenging due to extreme hemodynamic fluctuations associated with the venovenous bypass circuit, hemofiltration system, and hepatic artery chemotherapy delivery. Patients often require maximal doses of multiple vasopressors to maintain adequate perfusion. The mechanism of intraoperative hypotension is hypothesized to be due to catecholamine filtration, though literature supporting this mechanism is limited. The following report describes the successful use of angiotensin II for hypotension management during a PHP procedure, supporting the potential for an alternative mechanism for this profound vasoplegia. (A&A Practice. 2026;20:e02141.)

Percutaneous hepatic perfusion (PHP) is an advanced therapeutic strategy for the treatment of liver malignancies. PHP is performed by an interventional radiologist and involves the delivery of the chemotherapeutic agent, melphalan hydrochloride, directly to the liver via a hepatic artery catheter, then drainage of all blood from the liver via an inferior vena cava catheter to an extracorporeal circuit. The drained blood is filtered to remove melphalan, then returned to the patient, effectively exposing only the liver to chemotherapy and minimizing systemic exposure[1] (Figure 1). PHP is appropriate for patients with unresectable primary hepatic malignancies or isolated hepatic metastases from extrahepatic malignancies. It is currently approved for use in Europe to treat ocular melanoma, cholangiocarcinoma, colorectal cancer, hepatocellular carcinoma, and pancreatic cancer, among others.[2] The best-studied and most efficacious use of melphalan PHP is for the treatment of ocular melanoma metastatic to the liver. PHP gained Federal Drug Administration (FDA) approval for use in treating ocular melanoma in the United States in 2023 after a phase III clinical trial showed significantly increased objective response rate and progression-free survival compared to best alternative care.[3]

During the procedure, a profound shock state develops with patients often requiring maximal doses of vasopressors to treat hemodynamic perturbances. The hypotension associated with PHP significantly worsens when blood in the extracorporeal circuit is diverted through the filters. It has been hypothesized that the filter used to remove chemotherapy also removes catecholamines, leading to systemic hypotension. Catecholamine levels were reduced by the filter in a study of three patients undergoing PHP with an earlier filter derivative and in a separate study of three pigs undergoing PHP with the current (second generation [GEN2]) filter, but this phenomenon has not been studied using the modern PHP filter system in humans.[4,5] Although reduced preload due to diversion of blood flow through the veno-veno bypass circuit explains some degree of hypotension, the explanation does not account for the degree of hypotension or the worsening that occurs once blood is passed through the charcoal filters. The subsequent vasoplegia may be caused by anaphylactic or anaphylactoid reactions, calcium depletion, or activation of vasoactive mediators, such as bradykinins. We hypothesized that bradykinin activation may play a role in the hypotension experienced during PHP and that the use of angiotensin II would help counteract the effect of circulating bradykinins and reduce vasopressor use during PHP cases.

Our manuscript follows the 2013 CAse REport (CARE) Guidelines. The patient provided written Health Insurance Portability and Accountability Act (HIPAA) authorization for the publication of this case report.

CASE DESCRIPTION

We present a case of a 68-year-old man, 175.3 cm in height and weighing 122 kg (ideal body weight 71 kg), with a medical history of stage IV choroidal malignant melanoma of the right eye with liver metastases, who was scheduled for his fifth PHP treatment. Despite treatment with tebentafusptebn, a CD3 T-cell engager used to treat HLA-A*02:01-positive patients with unresectable or metastatic uveal melanoma, he had ongoing growth of multiple liver lesions on imaging, without extrahepatic disease.

The patient had intravenous (IV) access and invasive blood pressure monitoring obtained and received aprepitant 32 mg IV for postoperative nausea and vomiting (PONV) prophylaxis before entering the procedural room. He was monitored continuously with pulse oximetry, electrocardiography, capnography, and invasive blood pressure monitoring as general endotracheal anesthesia was established via IV induction with propofol, fentanyl, lidocaine, and rocuronium. After induction, processed electroencephalography (EEG) and neuromuscular blockade monitoring were added. Anesthesia was maintained with inhaled sevoflurane and rocuronium infusion.

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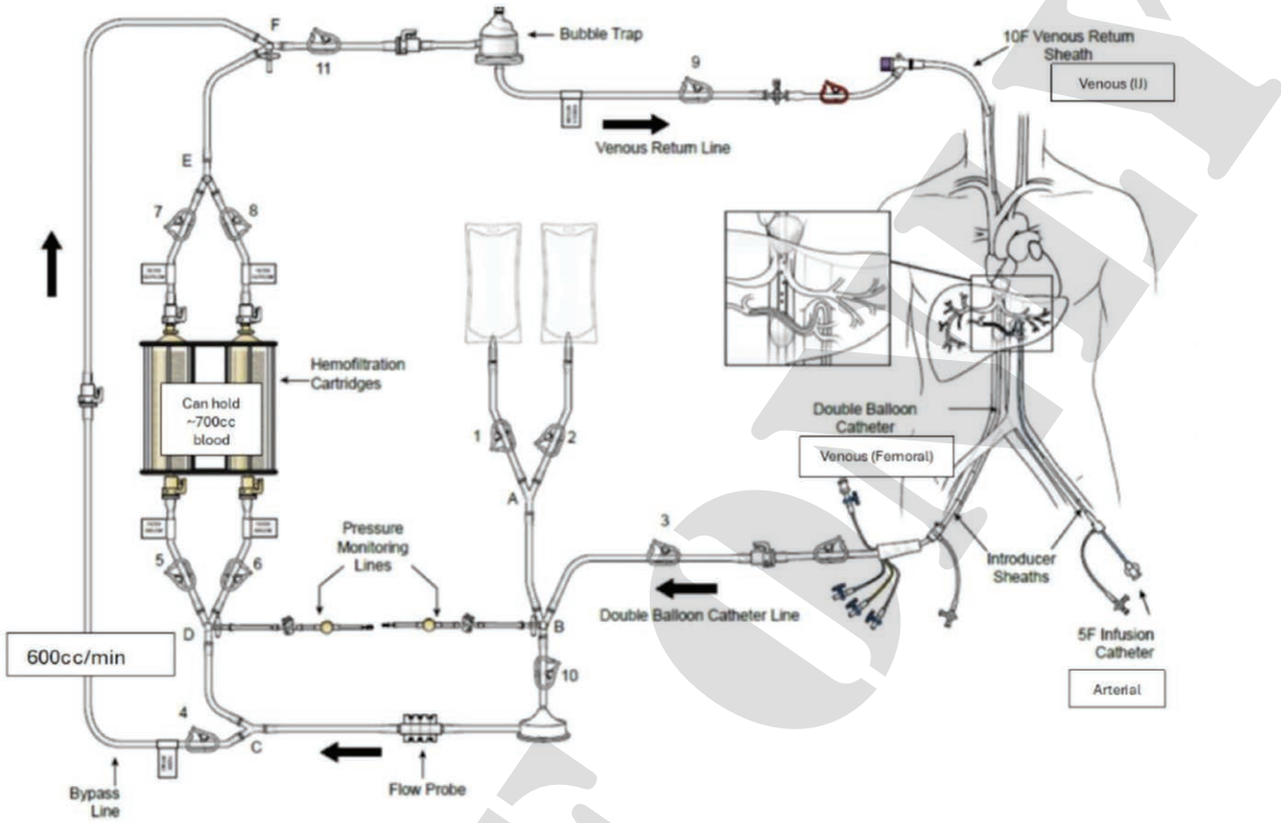

Figure 1. Melphalan-Percutaneous Hepatic Perfusion Circuit. Used with permission from Delcath Systems, Inc. The circuit is used to transport hepatic venous blood from the fenestrated lumens of the double balloon catheter in the inferior vena cava through the hemofiltration cartridges and back to the patient through the 10F venous return sheath in the internal jugular vein. The charcoal hemofiltration cartridges rapidly adsorb melphalan to limit systemic exposure. Hepatic venous blood is diverted through the hemofiltration cartridges during a 30-min infusion of melphalan and a subsequent 30-minute washout period.

The patient did not require vasopressors during placement of the central venous catheter, inferior vena cava drainage catheter, return catheter, and hepatic artery catheter by the procedural team. In preparation for veno-venous bypass, a norepinephrine infusion and angiotensin II (ATII) were initiated at 10 µg/min and 2.5 ng/kg/min, respectively, to increase the systolic blood pressure to a target of 180 mm Hg. The patient responded briskly, and the team proceeded to initiate bypass, inflate the cephalad and caudad IVC occlusion balloons, engage the charcoal filters, and clamp the filter bypass line. During initiation of bypass, the patient experienced one episode of transient hypotension with a subsequent rapid increase in central venous pressure from 10 to 30. Under fluoroscopy, the team identified that the central venous catheter was malpositioned in the azygous vein, and the hypotension and central line measurements quickly returned to baseline by applying a small amount of traction to the catheter.

During the filtration process, the patient required a low-dose norepinephrine infusion and angiotensin II infusion to maintain a mean arterial pressure (MAP) >65 mm Hg. The total norepinephrine equivalent dose (inclusive of angiotensin II dose) during this procedure was 0.28 µg/kg/min.[6] This contrasts with the patient's four previous PHP procedures, in which the patient required a mean of 0.87 µg/kg/min total norepinephrine equivalents to maintain a target MA >65 mm Hg. Other procedural and anesthetic factors, including chemotherapy drug, dosage, and infusion rate; duration of filtration; maintenance anesthetic choice (inhaled sevoflurane); and fluid administration, were similar. Compared with the patient's previous treatments, arterial blood gas analysis during and after this case revealed a similar degree of lactic acidosis with prompt resolution early in the postprocedural phase. The patient similarly experienced transient hypocalcemia for which he received calcium supplementation postprocedurally (Table).

Postprocedurally, the patient received ondansetron and haloperidol for PONV prophylaxis and was extubated and transferred to the Post Anesthesia Recovery Unit (PACU), awake and hemodynamically stable without pharmacologic support. His postprocedural course was unremarkable, and he was discharged home on the first postprocedural day. On telephone follow-up, the patient reported less orthostatic hypotension and less fatigue postprocedurally compared to previous treatments. He had no known procedural complications, including no known periprocedural thrombotic events, and he was scheduled to return for subsequent PHP treatment.

Table. Arterial Blood Gas Analysis During Serial Percutaneous Hepatic Perfusion (PHP) Procedures						
Procedure	**pH**	**Lactate (mmol/L)**	**Base deficit (mmol/L)**	**pCO2 (mm Hg)**	**pO2 (mm Hg)**	**Ionized calcium (mmol/L)**
1	7.32	2.0	4.5	43	158	1.09
2	7.21	5.1	12.2	38	175	1.34
3	7.39	2.1	1.9	39	290	1.05
4	7.32	2.4	4.2	43	348	0.87
5	7.28	4.3	5.9	45	148	0.91

DISCUSSION

PHP is a recently developed procedure with limited literature regarding anesthetic management. Phase III clinical trial results are promising, demonstrating increased hepatic and overall progression-free survival for patients with ocular melanoma and unresectable metastasis to the liver.[3] However, this therapy presents anesthetic challenges given the extreme hemodynamic disturbances requiring maximal vasopressor dosages.

In this case report, we observed a substantial hemodynamic response to modest doses of ATII, minimizing the need for additional vasopressors. Although some degree of hypotension is expected due to a reduction in preload associated with beginning veno-veno bypass, in our experience, patients typically experience a profound decrease in systolic blood pressure later—during clamping of the filter bypass line with subsequent shunting of blood through the hemofiltration cartridges. Additionally, patients routinely experience a mild to moderate degree of hypocalcemia requiring repletion. During this critical period, patients require high doses of vasopressors with one center reporting norepinephrine infusions as high as 500 µg/min to maintain hemodynamic stability, despite an expected compensatory increase in patients' endogenous catecholamine secretion in response to procedural stress.[7] Angiotensin II substantially decreased this patient's vasopressor requirement.

ATII is an endogenous peptide hormone that acts at AT1 and AT2 receptors in the heart and the vascular smooth muscle, signaling calcium-dependent phosphorylation of myosin and contraction of vascular smooth muscle, raising systemic blood pressure.[8] ATII was studied in the ATHOS-3 trial of adult patients with vasodilatory shock requiring high dose (>0.2 µg/kg/min) norepinephrine infusion and was shown to effectively increase blood pressure by at least 10 mm Hg or to a MAP > 75 mm Hg. However, patients treated with ATII experienced a higher rate of severe or life-threatening thromboembolic events during the ATHOS-3

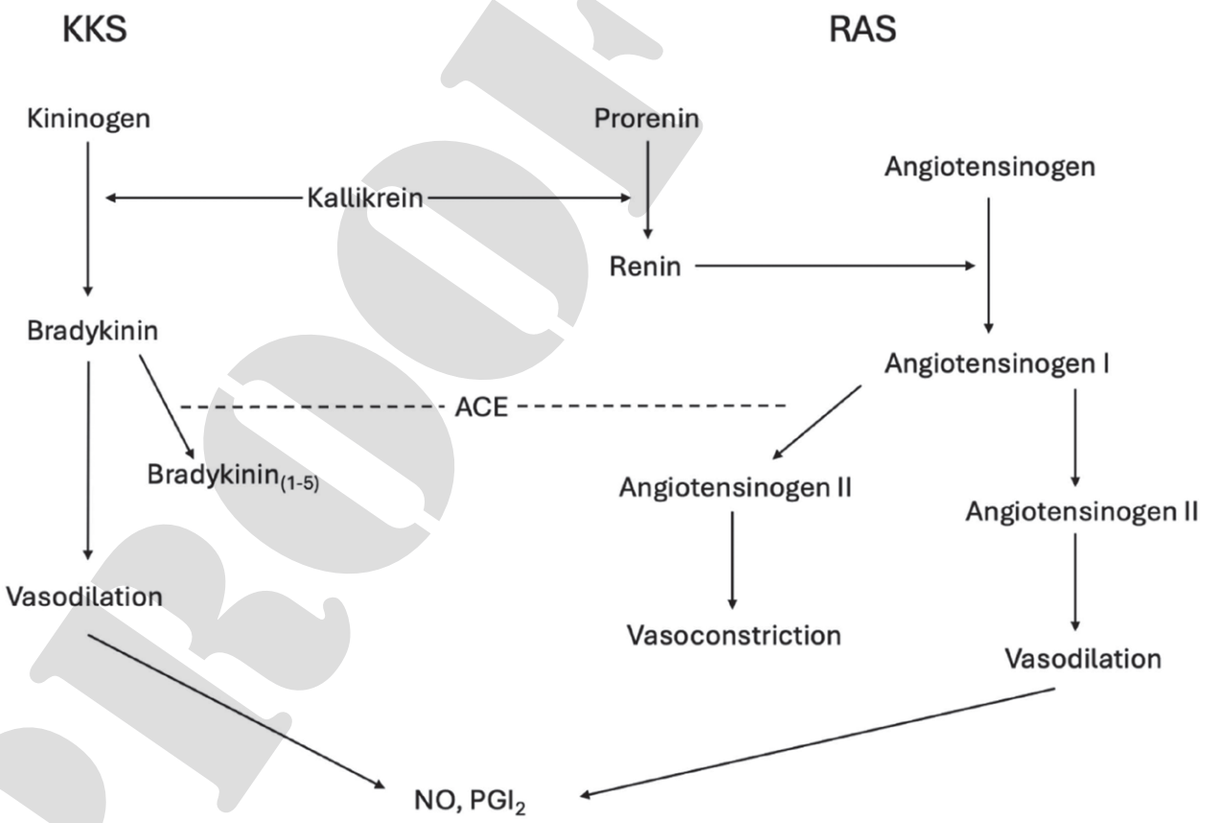

Figure 2. Interaction between the Kallikrein-Kinin System and Renin-Angiotensin-Aldosterone System. Used with permission from Schmaier, *Am J Physiol Regul Integr Comp Physiol*, 2003.[12] ACE indicates angiotensin-converting enzyme; KKS, Kallikrein-Kinin system; NO, nitric oxide; PGI2, prostacyclin; RAS, Renin-Angiotensin-Aldosterone System.

trial.[9] The propensity for thromboembolic events is hypothesized to be related to ATII stimulation of tissue factor and plasminogen activator inhibitor-1 (PAI-1). A more recent systematic review of seven studies encompassing 1,461 patients was unable to support or refute an association between ATII and venous or arterial thromboembolic events.[10] Venous thromboembolism prophylaxis is recommended during ATII treatment. Although the administration of IV heparin in preparation for veno-veno bypass far exceeds prophylactic doses of heparin (and its analogues), extreme vigilance to heparin re-dosing and activated clotting time (ACT) monitoring is necessary to prevent a potentially catastrophic thrombotic event during filtration. ATII has similarly been used safely during cardiac surgery where patients receive high-dose heparinization for cardiopulmonary bypass.[11] Beyond advancing clinical practice for this therapeutic procedure by improving hemodynamic stability, reducing the risk for perioperative cardiac events, acute kidney injury (AKI), and cerebral ischemia, this robust response provides preliminary support for the hypothesis that vasoplegia during PHP arises from activation of the kallikrein-kinin system (KKS), which opposes the renin-angiotensin-aldosterone system (RAAS), rather than catecholamine depletion (Figure 2). It is well established that leukoreduction filters used for blood transfusion cause kinin pathway activation, as well as implicated more recently in intradialytic hypotension during hemodialysis; thus, it is conceivable that a similar mechanism may underlie the vasoplegia associated with PHP filtration.[13–15] Angiotensin II may more selectively counteract the effects of KKS activation compared with catecholamine-based vasopressor regimens, accounting for the dramatic response seen in this case, although the interplay between the KKS and the RAAS is complex. Angiotensin II in this case may produce its clinical effect solely by activation of the known AT1 and AT2 receptors, through modulating bradykinin in the KKS, or through a combination of these and other intermediary mechanisms. Further studies to identify the biochemical changes induced by the filters during PHP are needed to fully elucidate the mechanism of hypotension associated with PHP. Additionally, patients' baseline levels of vasoactive intermediaries in the KKS and the RAAS may predict responsiveness to ATII and inform optimal hemodynamic management tailored to individual patients.

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