

Anesthetic Considerations and Management for the Percutaneous Hepatic Perfusion Procedure

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Uveal melanoma is the most common intraocular malignancy in adults, with an incidence of 5.1 to 6 per million.¹ It is an aggressive form of melanoma and metastases develop in approximately 25% to 31% of patients within 5 years, 34% to 45% within 15 years, and 49% within 25 years.^{2,3} More than 90% of metastases occur in the liver.⁴ Metastatic uveal melanoma has a poor prognosis. Once metastases are present, median survival is only 8 to 13 months; and median 2-year survival is 8%.⁵⁻⁸ There is some evidence correlating survival with control of hepatic metastatic disease, so liver-targeted therapy with minimal systemic toxic side effects became a research interest.³ Traditional treatment options for metastatic uveal melanoma include chemotherapy, radiation, immunotherapy, radiofrequency ablation, transarterial chemoembolization, surgical resection, and isolated hepatic perfusion (IHP), an open surgical procedure in which the liver is isolated from the systemic circulation and perfused with a chemotherapeutic agent. These modalities have had limited efficacy due to poor response rates, toxic side effects, and high rates of disease progression.⁹⁻¹¹ IHP is invasive, has been associated with high morbidity rates, and can be attempted only once.¹² Broad adoption of immunotherapies has been limited by minimal response rates and lack of evidence demonstrating improved survival.¹¹

The Percutaneous Hepatic Perfusion in Patients with Hepatic-dominant Ocular Melanoma (FOCUS) trial is a phase III randomized controlled multicenter study that compared percutaneous hepatic perfusion (PHP) using melphalan, an alkylating chemotherapeutic, with the best alternative care for metastatic uveal melanoma.¹³ It resulted in Food and Drug Administration approval of the HEPZATO KIT (Delcath Systems, Inc) for treatment of uveal melanoma with isolated hepatic metastases in August, 2023. The PHP

technique was first described in 1994.¹⁴ It is a minimally invasive liver-targeted therapy that facilitates high-dose chemotherapy administration directly to the liver while minimizing systemic exposure and toxicity. The procedure is performed in the interventional radiology (IR) suite under general anesthesia and requires collaboration between Medical Oncology, Surgical Oncology, IR, Anesthesiology, and Perfusion teams. Unlike IHP, PHP can be repeated for up to six treatments.¹² FOCUS demonstrated that PHP was superior to the best alternative care in multiple endpoints, including disease control rate and objective response rate. These translated to significantly longer progression-free survival for the PHP group. The objective response rate was almost three times greater in the PHP group compared to the best alternative care group (36.3% vs 12.5%). For PHP-treated patients, the median duration of response was 14 months, and the median overall survival was 20.5 months. Chemotherapy and non-PHP liver-directed therapies have reported median survival ranges from 10.2 months to 12.8 months. In the PHP group, overall survival was 80% at 1 year and 43% at 2 years; 7.7% of patients achieved a complete treatment response.¹³ A subsequent study demonstrated that patients who underwent melphalan-based PHP as either first- or second-line therapy had significantly longer progression-free survival compared with those who underwent immunotherapy or other liver-directed therapy. These findings suggest that first-line treatment with melphalan/PHP may contribute to improved survival, and that good disease control is still possible with PHP even in patients who have failed other treatment modalities.¹⁵ Contraindications to PHP include intracranial metastases or other brain lesions with bleeding risk, liver failure, portal hypertension, esophageal varices that may bleed, uncorrectable coagulopathy, surgery of the liver in the previous 4 weeks, history of heparin-induced thrombocytopenia, or inability to safely tolerate general anesthesia.¹⁶

PHP is a sophisticated procedure that incorporates complex anesthetic considerations, including utilization of an extracorporeal circuit, significant intraoperative hemodynamic fluctuations, and perioperative coagulopathy. There is a lack of data characterizing anesthetic management for this procedure,^{17,18} with the exception of a recent publication detailing one center's practice.¹⁹ Here, we describe our experience in the anesthetic management of PHP for treatment of uveal melanoma with hepatic-only metastases.

A small group of anesthesiologists who have completed training specific to this procedure staff the PHP cases at our hospital. Before initiating the PHP program, we worked closely with the IR and Medical Oncology teams to develop a perioperative care plan. The collaborative multidisciplinary environment was essential to safely navigate this new procedure. We created guidelines for preoperative

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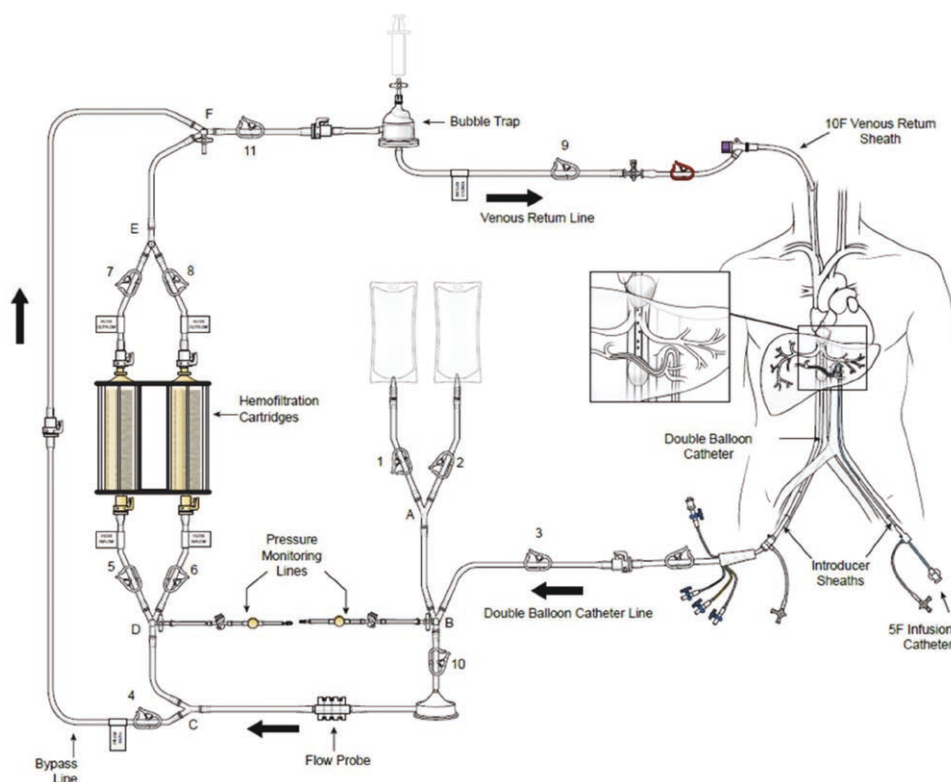


Figure. Fully assembled PHP delivery system including the femoral venous introducer sheath, double balloon catheter, 5 French arterial infusion catheter that delivers melphalan to the hepatic artery, two carbon hemofiltration cartridges, bypass line, and 10 French venous return sheath. The system is designed to administer high-dose chemotherapy to hepatic metastases while minimizing systemic chemotherapy exposure and toxic side effects. PHP indicates percutaneous hepatic perfusion.

evaluation and cardiovascular testing as a joint effort between Anesthesiology, IR, and Medical Oncology. Each prospective patient undergoes assessment of comorbid conditions, functional status, baseline coagulation parameters, hepatic and renal function, and electrocardiogram (ECG). We recommend preoperative stress testing in patients over the age of 50 years because of considerable intraoperative cardiovascular strain.

After induction of general anesthesia and placement of a radial arterial catheter for continuous blood pressure monitoring, we administer 40mg intravenous (IV) pantoprazole for gastrointestinal stress ulcer prophylaxis and 2g IV magnesium for arrhythmia prophylaxis. Anesthesia is typically maintained with volatile anesthetics for ease of titration, however, a propofol total IV anesthetic can be safely utilized with no change in medication dosage required even with hemofiltration.²⁰ The IR team places an 18 French femoral venous drainage catheter, a 10 French internal jugular venous return catheter, a 5 French femoral arterial catheter, and a 7 French internal jugular vein central venous catheter for vasoactive medication administration.¹⁶ 300 to 400 units/kg IV heparin is administered to achieve an activated clotting time (ACT) >450 seconds. Once the ACT is therapeutic, the 18 French femoral venous drainage catheter and 10 French internal jugular venous return catheter are connected to an extracorporeal hemofiltration circuit (EHC), similar in style to a venovenous bypass circuit. The ACT is checked every 30 minutes while circulating through the EHC. The femoral venous catheter is advanced

to the retro-hepatic inferior vena cava (IVC). It has two inflatable balloons and is also referred to as a double balloon catheter. The cephalad balloon is positioned above the highest hepatic vein, near the junction of the right atrium and IVC, and the caudal balloon is positioned below the lowest hepatic vein. The balloons are inflated to effectively isolate the liver from the systemic venous circulation. The femoral arterial catheter is advanced to the hepatic artery and is used to administer melphalan chemotherapy to the affected liver segments. The double balloon catheter contains fenestrations so that chemotherapy-saturated hepatic blood is aspirated and drained via the 18 French femoral venous catheter into the EHC. The EHC contains two activated carbon hemofilters, which remove more than 85% of the chemotherapeutic agent delivered to the liver. The filtered blood is then returned to the systemic circulation via the 10 French internal jugular vein catheter. Once the double balloon catheter is positioned and connected to the EHC, chemotherapy is administered to the liver via the hepatic artery catheter for 30 minutes. The administration period is followed by a 30-minute washout period to further reduce systemic toxicity.¹⁶ The Figure depicts the assembled hepatic delivery system.

There are three periods of significant hypotension during the procedure. Clear communication with the IR team is necessary to ensure the cadence of the procedural steps correlates with hemodynamic management. We believe that major hemodynamic fluctuations contribute to increased perioperative cardiovascular stress and injury, so

collaborative teamwork is crucial for optimal procedural success. The first period of hypotension correlates with inflation of the double balloon catheter due to preload loss. We preemptively administer 750 to 1000 mL 5% albumin and 1 to 2 L crystalloid after induction of anesthesia. This amount of volume administration has not resulted in major fluid overload-mediated complications, such as pulmonary edema necessitating prolonged mechanical ventilation. Before inflation of the balloons, vasopressor infusions are administered to obtain a goal systolic blood pressure of 150 to 160 mm Hg in preparation for preload loss; this typically requires vasopressin 0.04 units/min and norepinephrine 0.1 to 0.4 µg/kg/min. Inflation of the double balloon catheter is generally well tolerated if patients are adequately volume loaded.

Initiation of hemofiltration with exposure to the carbon-based filters signals the second period of hypotension. The etiology of hypotension is incompletely understood, but contributing factors likely include a substantial inflammatory response resulting in cytokine release and vasodilation, nitric oxide modulation, and removal of endogenous catecholamines by the hemofilters.^{21–23} We perform several interventions to mitigate the hypotension. All patients receive 100 mg IV methylprednisolone, 20 mg IV famotidine, and 50 mg IV diphenhydramine after induction of anesthesia to attenuate histamine release and the inflammatory response. Before blood exposure to the carbon filters, we initiate vasopressor infusions. Three to four minutes are required to fully saturate the first carbon filter with blood. We then ask the perfusionist to flow through the saturated filter for an additional 2–3 minutes, which appears to attenuate major hemodynamic fluctuations. The most significant hypotension occurs 3–4 minutes after blood exposure to each carbon filter, so we recognize there is a several-minute period between opening the first filter and the onset of precipitous hypotension. In contrast to Nahrwold et al,¹⁹ we use a lower target systolic blood pressure of 160 to 170 mm Hg before exposure to the first filter to avoid vasopressor-mediated “overshooting” of the blood pressure in an anticoagulated patient. Once the blood pressure begins to decline, typically 3–4 minutes after blood exposure to the first filter, we rapidly increase the vasopressor infusion rate. We repeat the same sequence with the second carbon filter. The vasopressor infusions are typically norepinephrine 0.5 to 2 µg/kg/min and vasopressin 0.04 units/min during this stage of the procedure; additional bolus doses of both norepinephrine and vasopressin are frequently required at this time. Despite high doses of vasopressors, it is common to experience systolic blood pressures in the 70s to 80s mm Hg for several minutes during this period.

The bypass line is an additional limb in the EHC that allows femoral venous drainage to bypass the carbon filters and return to the systemic circulation via the internal jugular vein. Clamping the bypass line diverts all femoral venous drainage through the carbon filters and causes further vasodilation. This step marks the third period of significant hypotension during the procedure. We instruct the perfusionist to partially clamp the bypass line, monitor for precipitous hypotension, and proceed with full clamping of the bypass line only once hemodynamic stability is ensured. Our method differs from previously published

data¹⁹ because we use a slow and controlled exposure to the bypass circuit and filters while accounting for the timing of major periods of hypotension (3–4 minutes after, rather than immediately following, blood exposure to the filters). We believe our method attenuates major hemodynamic fluctuations, thus limiting malignant hypertension and its deleterious effects, including end-organ injury (particularly myocardial injury) and bleeding in systemically anticoagulated patients. Norepinephrine infusion rates are typically increased to 2 to 2.5 µg/kg/min during this phase, and again bolus doses of norepinephrine and vasopressin are frequently required. Hepatic artery vasospasm is common at this time, which is treated by the interventional radiologist with direct administration of nitroglycerin into the hepatic artery. We believe that the ability to wean from high-dose norepinephrine may help to alleviate severe hepatic artery vasospasm. The interventional radiologist then administers chemotherapy to the isolated liver over a 30-minute period. As soon as there is blood pressure recovery, vasopressor infusions may be weaned to achieve normotension. Vasopressor requirements usually remain high but stable, with a norepinephrine infusion rate 0.3 to 0.8 µg/kg/min during chemotherapy administration and the 30-minute washout period.

After the washout phase, deflation of the double balloon catheter results in preload return and allows for further vasopressor weaning. Separation from the EHC is straightforward because its hemodynamic contribution is minimal, about 700 to 800 mL/min. Protamine is administered to reverse the effects of heparin, and the vascular access catheters are removed using percutaneous closure devices. Post-procedure arterial blood gas values are often consistent with a metabolic acidosis, hypocalcemia, and hyperglycemia, which are corrected. Most patients are weaned from vasopressor support and extubated in the procedure room. They recover in the intensive care unit for close hemodynamic monitoring and correction of coagulopathy. Hypofibrinogenemia, thrombocytopenia, and elevated INR are common after surgery since coagulation factors are removed by the carbon filters. Some groups routinely transfuse blood products to all patients.¹⁹ We use viscoelastic blood testing to guide postoperative coagulopathy management because of the recognized, albeit low, risk associated with blood product transfusions. We also strive to be mindful of unnecessary consumption of a valuable resource, particularly for patients who return for multiple procedures. Using viscoelastic testing, we have found that postoperative blood product transfusion requirements differ among our patients, and some patients have not required any transfusions. Other periprocedural complications include myelosuppression, hypersensitivity reactions, hemorrhage, hepatocellular injury, vascular injury, thromboembolic events due to intra-arterial administration of melphalan, nausea, vomiting, abdominal pain, and diarrhea.¹⁶

Many patients have a postoperative troponin elevation consistent with a type 2 non-ST-segment elevation myocardial infarction (NSTEMI). Intraoperative hypotension, hypertension, and tachycardia likely cause an imbalance in myocardial oxygen supply and demand.²⁴ We hypothesize that coronary artery vasospasm, related to high-dose vasopressor doses, may also occur. Despite the cardiovascular

stress associated with PHP, one analysis found that no patients had acute coronary syndrome, ECG changes suggestive of myocardial infarction, heart failure, unstable cardiac arrhythmias, or cardiac death. Importantly, there were no major adverse cardiac events at 90 days, and PHP treatment was not suspended or delayed for any patient with a postoperative type 2 NSTEMI.²⁴ The PHP-associated troponin elevation appears to be transient, asymptomatic, and clinically insignificant. Intraoperative tachycardia is common, likely as a result of the inflammatory response and perhaps related to beta-adrenergic receptor activation from high-dose norepinephrine requirements. Patients with preexisting atrial fibrillation or conduction abnormalities may have a higher propensity for intraoperative arrhythmogenicity, so careful patient selection and proactive pharmacologic management of arrhythmias is important. There are no published data, however, detailing cardiac arrhythmias that are contraindications to PHP. Early IV magnesium administration and control of excessive tachycardia using short-acting beta-blockade may reduce the negative effects of tachycardia and prevent unstable cardiac arrhythmias.

Melphalan/PHP produces a clinically meaningful response for aggressive uveal melanoma with hepatic metastases, which previously had limited treatment options. The intraoperative procedure requires advanced anesthetic considerations, including management of an extracorporeal circuit, coagulopathy, and major hemodynamic disturbances. Despite these complexities, there is a lack of published information to guide the anesthetic management. Here, we describe the anesthetic protocol for PHP procedures at our institution. A successful program requires a dedicated group of specially trained anesthesiologists as well as a multidisciplinary partnership with the IR and Medical Oncology teams. The team must periodically evaluate its process and make modifications for further improvement. Effective collaboration is crucial preoperatively to ensure appropriate patient selection for this high-risk procedure and intraoperatively to guarantee that the anesthesiologist and interventional radiologist work cohesively during the critical portions. ■■

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