OPEN

Anaphylaxis to Machine Perfusion Substrate at Reperfusion: A Cautionary Tale

Amanda Liesegang, MD,[1] Janske Reiling, MD, PhD,[1,2] and Peter Hodgkinson, MBBS, FRACS[1]

INTRODUCTION

Hemodynamic instability during liver transplantation is not uncommon and can be attributed to postreperfusion syndrome (PRS). A rare but important differential when hypotension persists despite appropriate management is anaphylaxis.

Normothermic machine perfusion (NMP) in liver transplantation has regained popularity in recent years as an alternative preservation tool. It allows for functional assessment of donor organs before transplantation and preliminary evidence demonstrates that it may reduce the risk of early allograft dysfunction as well as PRS.[1] NMP is not yet widely utilized in Australasia, with our center being the first to successfully use the OrganOx *Metra* system (OrganOx Limited, Oxford, United Kingdom).[2] This letter describes a case of intraoperative anaphylaxis to epoprostenol (Flolan, GlaxoSmithKline, Victoria, Australia) on reperfusion, a substrate added throughout NMP to regulate vascular tone.

CASE DESCRIPTION

A 63-y-old male underwent a combined liver and kidney transplantation for end-stage liver and kidney disease. His liver disease was secondary to alcoholic liver disease, and his kidney disease was secondary to hepatorenal syndrome and diabetic nephropathy. At time of transplant, his model for end-stage liver disease score was 31. The patient had not yet commenced dialysis. His creatinine was 284 μmol/L immediately preoperatively. He had a known allergy to amoxicillin (diarrhea), peanuts (diarrhea), and dust mites (urticaria), however, no history of anaphylaxis.

A marginal liver graft from a 53-y-old deceased after circulatory death donor (donor risk index 1.93) was retrieved at a regional center and transported 1300 km to the recipient hospital using the University of Wisconsin solution. The graft sustained 27 min of warm ischemia, and the cold ischemia time was 7 h and 5 min. Standard back table preparation was performed. NMP was commenced on the Organox *Metra* at our center according to the manufacturer's instructions. Gelofusin and red blood cells were used as perfusate, and cephazolin, calcium gluconate, heparin, total parenteral nutrition, epoprostenol, sodium taurocholate, insulin, and sodium bicarbonate were added throughout the perfusion period. The graft underwent 9 h and 3 min of NMP. The functional and perfusion parameters can be seen in Figure 1. Preestablished viability criteria were met, and the liver was accepted for transplantation. The kidney graft underwent hypothermic perfusion (LifePort Kidney Transporter, Organ Recovery Systems).

The patient received basiliximab, methylprednisolone, and piperacillin-tazobactam preoperatively. Skin preparation was performed with 10% aqueous povidone iodine and a latex-free urinary catheter was inserted. Hemodynamic parameters remained within normal limits between induction and reperfusion.

The native liver appeared macronodular consistent with cirrhosis. Seven liters of the turbid ascitic fluid was evacuated. The liver graft was removed from the NMP device and flushed with 3 L of saline solution via the portal vein and hepatic artery. On reperfusion via the portal vein, 300 mL of reperfusion blood was vented via the open end of the donor inferior vena cava. At this point, the patient became acutely hypotensive and tachycardic. Mean arterial pressure (MAP) dropped from 68 mm Hg in the anhepatic phase to 32 mm Hg in the reperfusion phase. Compound boluses of adrenaline were required, as well as rapid escalation of vasopressor infusions and large volume fluid resuscitation, to maintain adequate blood pressure. A total of 13 units of red cells, 2 units of platelets, 16 units of fresh–frozen plasma, 11 L of albumin, and 40 units of cryoprecipitate were transfused intraoperatively. The hemodynamic parameters and vasoactive infusion escalation are demonstrated in Figure 2. An intraoperative transesophageal echocardiogram demonstrated severe underfilling and reduced afterload. There was no pulmonary embolus, pericardial effusion, aortic dissection, acute wall motion, or valvular

Received 14 September 2020. Revision received 10 February 2021.

Accepted 11 February 2021.

[1] *Queensland Liver Transplant Service, Princess Alexandra Hospital, Brisbane, QLD, Australia.*

[2] *Division of Medicine, University of Queensland, Brisbane, QLD, Australia.*

The authors declare no funding or conflicts of interest.

A.L. participated in writing of the paper, revision the draft critically, and final approval of the version to be published. J.R. and P.H. participated in revision of the draft critically, and final approval of the version to be published.

Correspondence: Amanda Liesegang, MD, 199 Ipswich Rd, Princess Alexandra Hospital, Brisbane, QLD, Australia. (amanda.liesegang@health.qld.gov.au).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001144

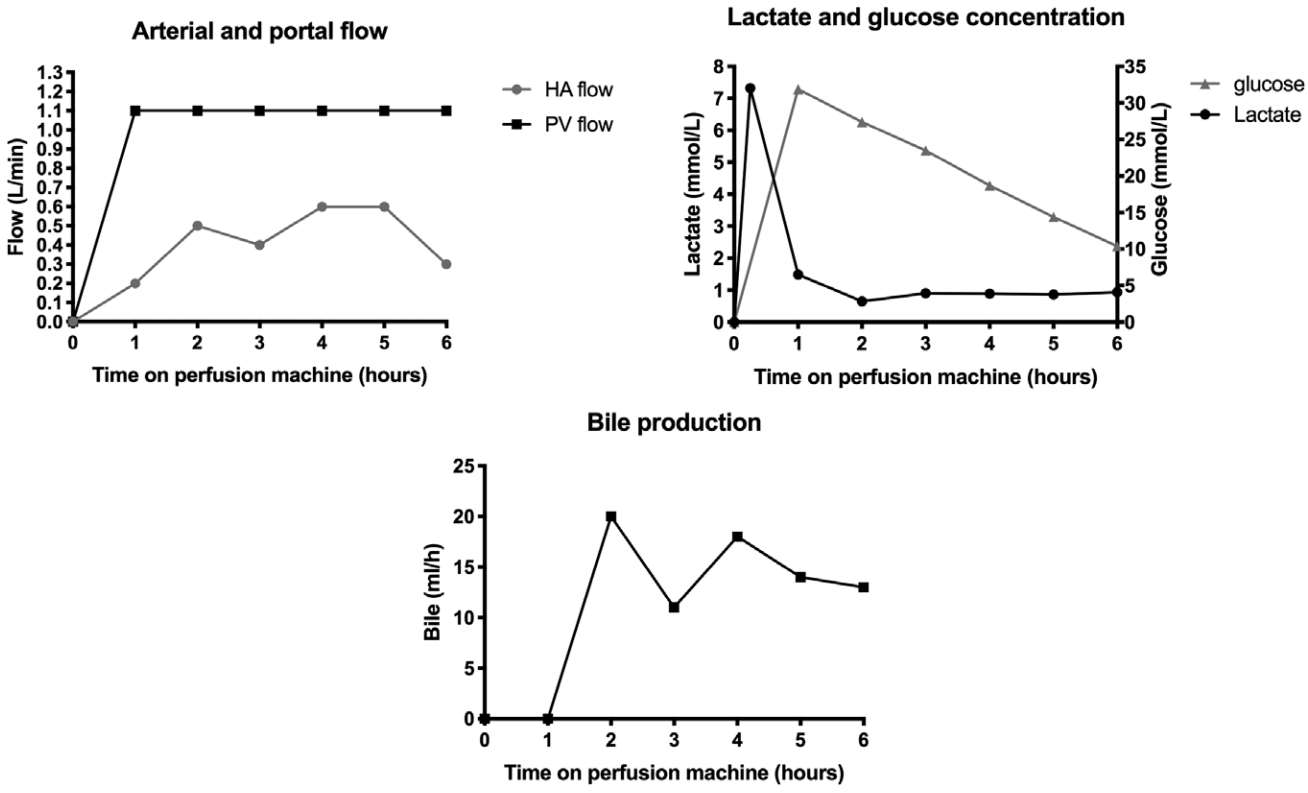

FIGURE 1. Function and perfusion parameters (arterial and portal flow, lactate and glucose concentration, and bile production) of the liver graft on normothermic machine perfusion over time (0–6 h)

abnormality to suggest cardiogenic shock. Throughout these resuscitative and investigative measures the surgical team continued to anastomose the hepatic artery and bile duct.

Toward the final stages of liver transplantation, 2 h and 35 min from reperfusion, the patient began to demonstrate hemodynamic recovery. A collaborative decision was made between the surgical and anesthetic teams to proceed with kidney transplantation that then began 9 h and 24 min from induction. The renal graft was transplanted uneventfully with cold ischemia time totaling 23 h and 8 min on removal from hypothermic machine perfusion.

Following an initially turbulent ICU stay, the patient was transferred to the ward day 3 posttransplantation. He required dialysis on day 5 because of delayed renal graft function. His liver graft demonstrated early allograft dysfunction based on peak aspartate transaminase alone (2890 U/L).

The patient underwent allergy testing 6 mo posttransplantation to assess for allergy to various medications that he may have been exposed to preceding the sudden hemodynamic instability. This included heparin, chlorhexidine, epoprostenol, povidone iodine, gelofusin, and cephazolin. The results demonstrated positive allergy to epoprostenol and negative reaction to all other substrates with appropriate positive and negative controls.

The patient remains well at his most recent review 17 mo posttransplantation with satisfactory liver and kidney function (bilirubin 24 μmol/L, ALT 22 U/L, aspartate transaminase 14 U/L, and creatinine 183 μmol/L).

DISCUSSION

This patient's sudden hemodynamic instability reflected a shocked state, the cause of which was critical to identify swiftly to facilitate appropriate management. Intraoperative echocardiogram enabled exclusion of cardiogenic or obstructive causes of shock. The volume of blood loss during the dissection and anhepatic phases was not felt to be excessive enough to cause hypovolemic shock. Consequently, the patient was treated for distributive shock with vasoactive drugs and fluid resuscitation. The etiology of his vasoplegic state, however, remained unclear during resuscitation. Anaphylaxis, PRS, and sepsis were equally viable differentials.

The differential of sepsis from bacterial peritonitis was considered because of the finding of turbid ascitic fluid. However, when ascitic fluid culture and blood culture demonstrated no bacterial growth, and as the patient remained afebrile postoperatively, this was improbable, and empirical antibiotics were ceased to no adverse effect. NMP sepsis was also considered as a recent report describes NMP fluid contamination utilizing the OrganOx *Metra*.[3] In this case, the patient did not demonstrate vasoplegia intraoperatively but became febrile and vasoplegic in the 24 h postoperatively. An identical microorganism was isolated in the NMP fluid and blood culture, and the patient clinically improved with antibiotics.[3] Not only did the onset and course of vasoplegia differ in our case, our patient was never pyrexic, demonstrated sustained stability post–early cessation of antibiotics, and most importantly NMP fluid and blood culture were sterile.

PRS was reasonably considered as the patient's presentation clearly satisfied its definition—a reduction in MAP by >30%, lasting >1 min during the first 5 min post–graft reperfusion.[4] A recent case series documents this phenomenon in the context of using NMP, and makes initial associations between PRS and hyperoxic perfusate.[5] NMP has been associated with a lower incidence of PRS overall,[4] as well as decreased

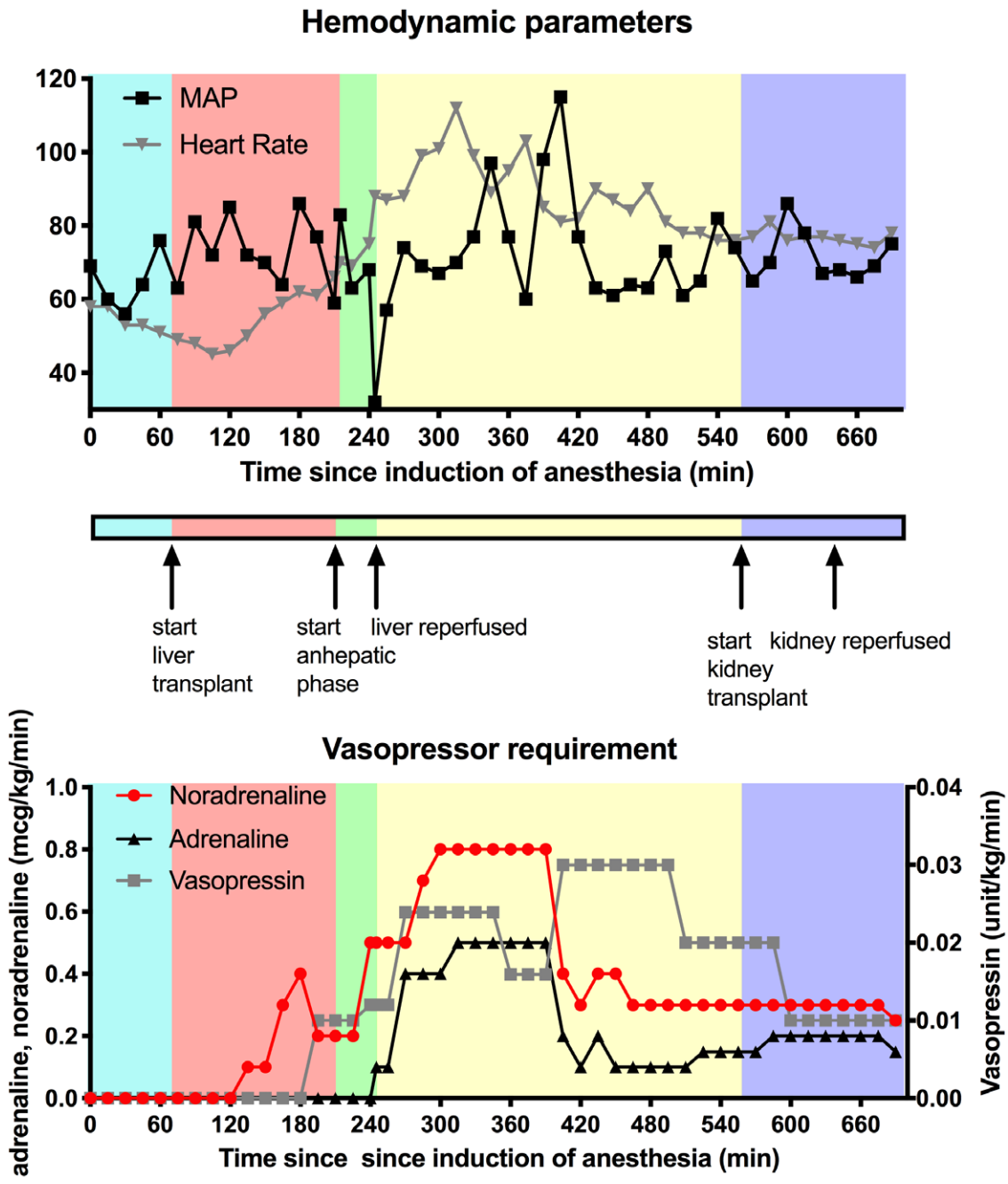

FIGURE 2. Hemodynamic parameters (MAP and heart rate) and vasopressor requirement (noradrenaline, adrenaline, and vasopressin) over time from induction of anesthesia to end of operation. MAP, mean arterial pressure.

vasopressor and blood product requirements when compared to static cold storage livers.[1] This patient required 34.8 L of total fluid resuscitation, which is 10 times more than the usual intraoperative requirement.[4] The demand for rapid succession of adrenaline boluses as well as sustained high-dose vasoactive infusions was also highly atypical for our center's experience with PRS. Although there is some evidence that PRS starts to convalesce on hepatic artery reperfusion,[6] our patient did not exhibit hemodynamic recovery for at least 1.5 h from hepatic artery reperfusion.

Anaphylaxis remained a differential, though this was not considered probable intraoperatively as no new medications were purposefully given at time of reperfusion. Though our patient did not demonstrate eosinophilia, with day 1 eosinophil count totaling 0.01 × 10^9/L, it is felt that preoperative immunosuppression may have inhibited this response. Ultimately, allergy testing identified a severe allergy to epoprostenol, a prostacyclin that is used to regulate vascular tone in the NMP system, and a medication that rarely elicits anaphylaxis. The identification of this allergy offered explanation to this case of refractory vasoplegia that was disproportionate to PRS, and was inconsistent with alternative causes of shock. In a report published of anaphylaxis postreperfusion triggered by exposure to the University of Wisconsin's fluid, tryptase was identified as highly specific for anaphylaxis and especially diagnostically useful when PRS remained a differential.[7]

Unfortunately, fixation bias on the more common PRS differential, as well as fatigue, likely contributed our initial oversight of anaphylaxis, which ultimately meant that tryptase levels were not taken in our case.

This report describes the first documented case, to our knowledge, of anaphylaxis to an NMP substrate postreperfusion. Though the concentration of substrates transferred from NMP perfusate to the patient is likely low, with the established understanding that anaphylaxis can be triggered from monomolecular exposure, it is felt that despite extensive graft flushing the risk of allergen exposure cannot be entirely eliminated. Further analysis is required to quantify formally if NMP substrates can be detected in a transplant liver after it has been flushed. As perfusate constituents are generally standardized, variation according to a recipient's known allergies may be required, a precaution that is not currently routinely considered. Although NMP remains useful as an alternative graft preservation tool, this case cautions that the use of NMP has the potential to introduce additional agents into the recipient circulation. In the event of severe distributive shock postreperfusion with an unclear etiology, tryptase levels, NMP culture, and blood culture have been demonstrated to be diagnostically useful in delineating between sepsis, PRS, and anaphylaxis. This case highlights some factors that influence intraoperative transplant hemodynamics, and how liver transplant surgeries can pose numerous causes for instability.

REFERENCES

1. Nasralla D, Coussios CC, Mergental H, et al; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature*. 2018;557:50–56.
2. Reiling J, Butler N, Simpson A, et al. Assessment and transplantation of orphan donor livers: a back-to-base approach to normothermic machine perfusion. *Liver Transpl*. 2020;26:1618–1628.
3. Hann A, Lembach H, Dassanayake B, et al. Severe sepsis mimicking primary nonfunction following liver transplantation: normothermic machine perfusion is a potential environment for bacterial overgrowth and transmission from donor to recipient. A case report. *Transplant Proc*. 2020;52:2781–2785.
4. Angelico R, Perera MT, Ravikumar R, et al. Normothermic machine perfusion of deceased donor liver grafts is associated with improved postreperfusion hemodynamics. *Transplant Direct*. 2016;2:e97.
5. Watson CJE, Kosmoliaptsis V, Randle LV, et al. Normothermic perfusion in the assessment and preservation of declined livers before transplantation: hyperoxia and vasoplegia-important lessons from the first 12 cases. *Transplantation*. 2017;101:1084–1098.
6. Fukazawa K, Yamada Y, Gologorsky E, et al. Hemodynamic recovery following postreperfusion syndrome in liver transplantation. *J Cardiothorac Vasc Anesth.* 2014;28:994–1002.
7. Anderson A, Eilers H, Yost CS. Anaphylaxis complicating graft reperfusion during orthotopic liver transplantation: a case report. *Transplant Proc.* 2010;42:1967–1969.