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Point-of-Care Ultrasonography to Assess Portal Vein Pulsatility and the Effect of Inhaled Milrinone and Epoprostenol in Severe Right Ventricular Failure: A Report of Two Cases

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This article describes 2 patients with severe acute right ventricular failure causing circulatory shock. Portal vein pulsatility assessed by bedside ultrasonography suggested clinically relevant venous congestion. Management included cardiac preload reduction and combined inhalation of milrinone and epoprostenol to reduce right ventricular afterload. Portal vein ultrasonography may be useful in assessing right ventricular function in the acutely ill patient.   (A&A Case Reports. 2017;XXX:00–00.)

Patient 1 and next of kin of patient 2 provided written permission for publication of each report.

Right ventricular (RV) failure is associated with significant morbidity and mortality, namely in the postoperative setting.[1] Clinical suspicion must be high as rapid detection of RV failure is mandatory for appropriate hemodynamic management. We report the use of point-of-care ultrasonography to detect changes in portal vein (PV) pulsatility as a surrogate of venous congestion caused by RV failure and describe a combination of inhaled milrinone and epoprostenol to reduce RV afterload.

Case DESCRIPTIONS
Patient 1
An 83-year-old man presented with acute chest pain. Coronary angiogram showed severe coronary artery disease with a 90% left main coronary artery stenosis. Bedside transthoracic echocardiography (TTE) revealed a severely hypokinetic inferior left ventricular (LV) wall, an LV ejection fraction of 0.5, and moderate RV dysfunction.

The patient underwent urgent coronary artery bypass grafting with complete revascularization. Total intraoperative net fluid balance was 750 mL. At the end of the procedure, transesophageal echocardiography showed akinesia of the inferior LV wall, an LV ejection fraction of 0.35, and

a dilated and severely hypokinetic RV. Doppler flow signal was normal in all grafts. Weaning from cardiopulmonary bypass required high doses of norepinephrine (0.9 μg/kg/min), epinephrine (1.1 μg/kg/min), and vasopressin (6 units in total) and use of an intra-aortic balloon pump.

On arrival in the surgical intensive care unit (ICU), bedside TTE showed progressive RV dilation with diffuse hypokinesis, inferior vena cava (IVC) enlargement without respiratory variation, and abnormal PV flow pulsatility with diastolic flow reversal (Figure 1A and Supplemental Digital Content 1, Video 1, http://links.lww.com/AACR/A109). Pulmonary artery pressure (PAP) was 36/18 mm Hg while the mean arterial pressure (MAP) was 65 mm Hg, with a ratio of MAP to mean PAP of 2.6. Cardiac index was 1.85 L/min/m². At this point, the patient was anuric, and high doses of vasopressors and inotropes were required for hemodynamic support (Figure 2).

A continuous infusion of furosemide was started, and in an attempt to reduce RV afterload, epoprostenol (60 μg) and milrinone (4 mg) were administered via an ultrasonic nebulizer attached to the inspiratory limb of the ventilator as previously described.[2]

In the next hour, hemodynamic support was quickly tapered down (Figure 2). Focused TTE performed 45 minutes after the end of nebulization revealed normalization of PV flow which was now nonpulsatile throughout the cardiac cycle (Supplemental Digital Content 2, Video 2, http://links.lww.com/AACR/A110), although the IVC was still dilated and without respiratory variation and the RV still dilated and diffusely hypokinetic. As compared to before nebulization, PAP was now lower at 30/14 mm Hg and cardiac index was unchanged at 1.83 L/min/m² despite a significant reduction in epinephrine and norepinephrine infusion rate. Urine output began to rise. Administration of nebulized epoprostenol and milrinone was repeated 2 hours later. At 6 hours postoperatively, the patient was awakened and his trachea was extubated, further reducing right heart afterload by restoring spontaneous breathing and negative intrathoracic pressure.

Vasopressor support was rapidly weaned off and stopped 12 hours after ICU admission, and the intra-aortic balloon pump was removed. At that time, PAP was 20/10
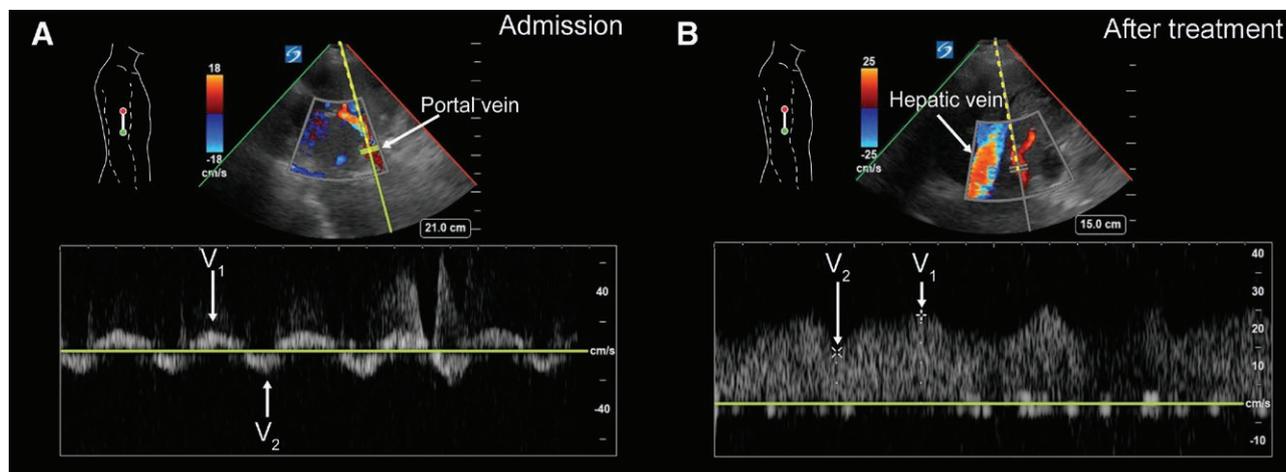
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Figure 1. (Case 1) A, Bedside transthoracic echocardiography on intensive care unit admission, with posterior axillary line interrogation of the portal vein using spectral Doppler tracing. An abnormal pulsatile portal waveform with transient diastolic flow reversal is seen (V1 indicates peak flow velocity; V2, through flow velocity; see Supplemental Digital Content 1, Video 1, http://links.lww.com/AACR/A109). B, Transthoracic echocardiography, postoperative day 1. Note the significantly reduced pulsatility of the spectral Doppler tracing of the main portal vein (see Supplemental Digital Content 3, Video 3, http://links.lww.com/AACR/A111).

mm Hg and the MAP/mean PAP ratio had risen to 4.6. Urine output was adequate without furosemide infusion, and creatinine levels were only mildly elevated as compared to preoperative values (83 vs 108 μmol/L) and did not rise further. Twenty-four hours after admission, repeat focused TTE revealed mildly phasic PV and normal IVC (Figure 1B and Supplemental Digital Content 3, Video 3, http://links.lww.com/AACR/A111). The patient was discharged from the ICU 36 hours after admission with a total net fluid balance of −2.4 L, and he was discharged home uneventfully on postoperative day 6.

Patient 2

A 49-year-old man had an unwitnessed out-of-hospital cardiac arrest. Initial rhythm was pulseless ventricular tachycardia. Emergency medical services provided prolonged resuscitation including cardioversion, which eventually resulted in return of spontaneous circulation after 43 minutes of resuscitation. On admission at a peripheral hospital, the electrocardiogram showed inferior S-T-segment elevation myocardial infarction, for which thrombolytic therapy was given. Overt cardiogenic shock developed, and the patient received more than 6 L of crystalloids during the initial resuscitation efforts. The patient was found to be unresponsive to painful stimuli. Anoxic brain death was diagnosed the next day and confirmed on arrival at our hospital to which the patient was transferred for stabilization before potential organ donation.

On arrival at our center, 48 hours after the initial cardiac arrest, the patient needed significant hemodynamic support (dobutamine 15 μg/kg/min, vasopressin 2.4 U/h, and epinephrine 1.2 μg/kg/min) and was severely hypoxemic (Sao$_2$ 91% at an Fio$_2$ of 1.0 during controlled ventilation with positive end-expiratory pressure 10 cm H$_2$O) and anuric. Cardiac ultrasonography showed severe RV dilation and hypokinesis with a normal LV and a highly pulsatile portal venous flow (Figure 3). Liver enzymes and creatinine were elevated and still rising 48 hours after the initial

cardiac arrest (ALT 711 U/L, bilirubin 31 μmol/L, creatinine serum concentration 406 μmol/L).

Epoprostenol (60 μg) and milrinone (4 mg) were simultaneously administered by nebulization through the inspiratory limb of the ventilator. One hour later, central venous pressure had decreased from 17 to 9 cm H$_2$O, and flow in the PV showed reduced pulsatility (Figure 3B).

Continuous venovenous hemofiltration was instituted, with a resultant net fluid balance of −2.8 L in 12 hours. After these interventions, ultrasonography showed a moderate improvement in RV contractility and reduced RV dilation. The flow in the PV was now phasic without significant pulsatility (Figure 3C). Hemodynamic support was tapered down (dobutamine 2.5 μg/kg/min, vasopressin 2.4 U/h, and norepinephrine 0.05 μg/min). The liver enzyme levels declined the next day (ALT 170 U/L and bilirubin 17.2 μmol/L). Approximately 48 hours after transfer to our institution, liver harvesting and subsequent transplantation were successfully performed.

Discussion

These cases highlight how point-of-care ultrasonography can be used to detect changes in PV pulsatility as a surrogate of venous congestion due to severe RV failure and, in conjunction with other echocardiographic and clinical parameters, help identify patients who might benefit from aggressive diuresis and RV afterload reduction. We also describe the combined administration of inhaled epoprostenol and milrinone in patients with severe RV failure and are the first to report their effect on PV pulsatility, which interestingly illustrates this finding's significance as a marker of RV function and load adaptability.

RV failure results in a decrease in cardiac output and systemic perfusion. Concomitantly, the increase in right heart filling pressure induces venous congestion and globally increases outflow pressures of vital organs such as the brain, kidney, and liver, thus further reducing tissue perfusion.[1,3] In such situations, administration of intravenous fluids will only exacerbate the phenomenon. This mechanism could
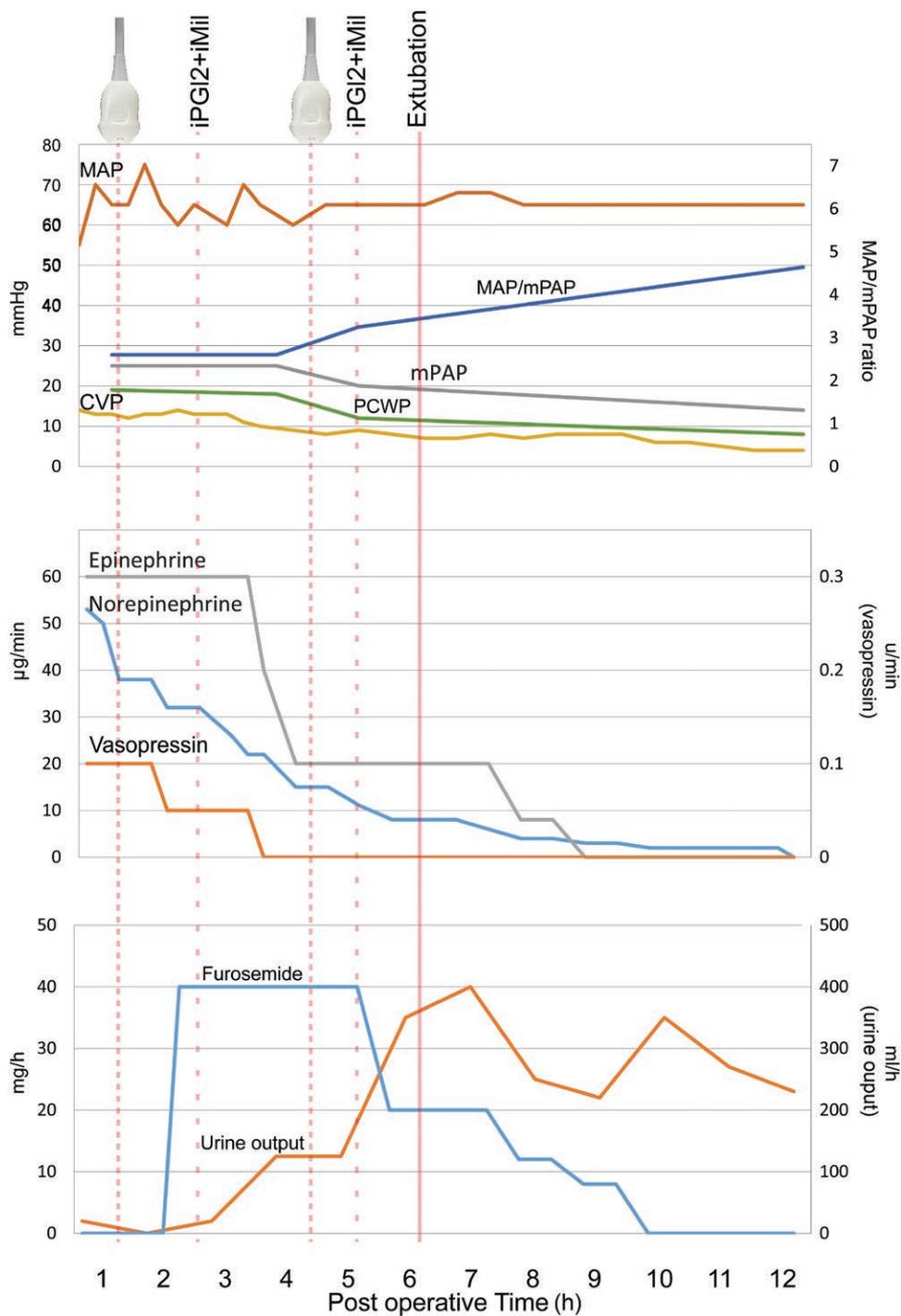
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Figure 2. (Case 1) Hemodynamic parameters, drug administration, and diuresis in the first 12 postoperative hours. Both administrations of inhaled epoprostenol (iPGI$_2$) and inhaled milrinone (iMil) were followed by gradual reduction in the pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (mPAP), and central venous pressure (CVP). The ratio of the mPAP on the mean systemic arterial pressure (mPAP/MAP) increased throughout this period. In addition, significant reduction in perfusion rate of inotropes and vasopressors was observed. Urine output was sustained after discontinuation of the furosemide perfusion. HR indicates heart rate; MAP, mean arterial pressure; TTE, transthoracic echocardiography.

partly explain why excessive fluid balance and elevated right atrial pressure have been associated with increased mortality in critically ill patients.[4]

Flow in the PV is normally hepatopetal (directed toward the liver) and exhibits small amplitude phasicity (typically less than 30%), reflecting partial transmission of hepatic venous waves through hepatic sinusoids.[5] During RV failure, higher right heart filling pressures are transmitted back to the hepatic veins and sinusoids, which reduce the compliance of these vessels, thus further facilitating retrograde transmission of pulsatile pressure waves from the

right atrium to the PV. The presence of PV pulsatility is defined as a pulsatility index above 50%, where the pulsatility index is the difference between peak flow velocity and through flow velocity divided by peak flow velocity (V1 – V2)/V1 (Figure 3). This finding has been clearly associated with elevated right atrial pressure, tricuspid regurgitation, and RV failure[5] and has also been described in cirrhotic and normal thin (body mass index <20 kg/m^2) patients, probably reflecting low abdominal and hepatic acoustical damping.[6] Eventually, when RV failure progresses and right atrial pressure exceeds portal venous pressure, partial
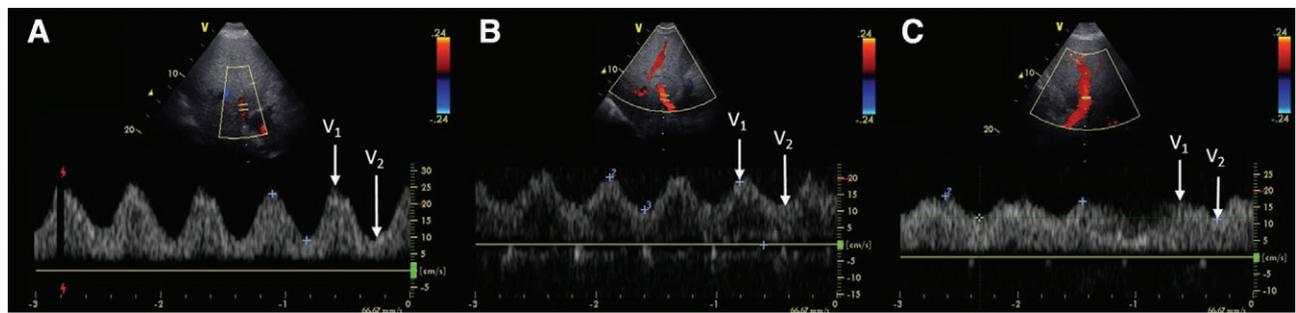
Figure 3. (Case 2) A, Echography of the portal vein using spectral Doppler tracing, showing strong waveform pulsatility (V1 indicates peak flow velocity; V2, through flow velocity; pulsatility index is defined as [V1 − V2]/V1 = 64%). B, Spectral Doppler interrogation of the portal flow after inhaled epoprostenol and milrinone. The pulsatility index is now 48%. C, After removal of 2.8 L of fluid, the pulsatility index is 29%.
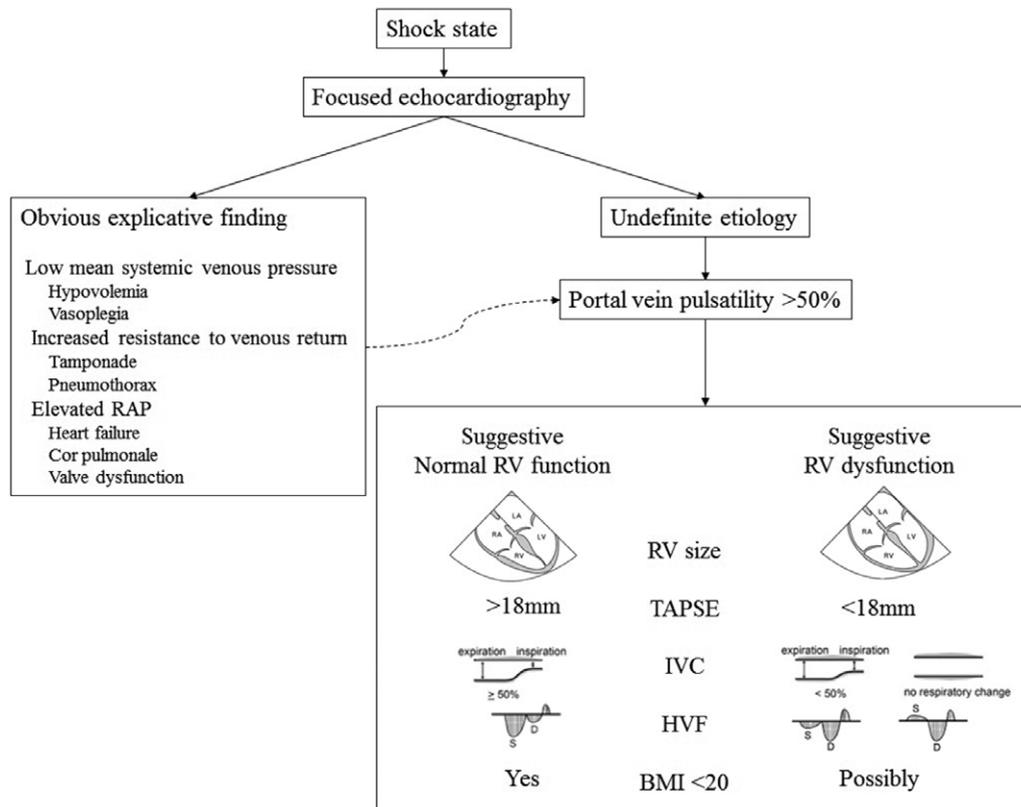

Figure 4. A suggested echocardiographic approach to the hemodynamically unstable patient. Portal vein interrogation can be pursued to confirm other findings and in case of poor echocardiographic views. In the presence of portal vein pulsatility, one must consider the possibility of a false positive finding and seek further confirmation with other ultrasonographic and clinical elements. BMI indicates body mass index; HVF, hepatic venous flow; IVC, inferior vena cava; RAP, right atrial pressure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion. Adapted from Refs. [8] and [10]. AQ8

or complete reversal of flow (hepatofugal) can occur,[5] as outlined in case 1. This finding reflects a severe venous congestion state that can be detrimental not only in the PV tributaries but also in other important organs such as the brain, gut,[7] or kidney.[3,8]

Conceptually, in the right clinical context, PV pulsatility therefore represents the indirect consequence of RV failure (whether systolic or diastolic), rather than direct signs of systolic dysfunction. In a recent series of 14 cardiac surgical patients with fluid overload and PV pulsatility, only 4 patients had direct echocardiographic signs of RV failure (hypokinesis and/or dilation).[9] Importantly, adequate bedside visualization of the portal flow is possible in virtually all patients (even in those with poor quality echocardiographic views) because of the location of the PV in the echogenic liver parenchyma.[9] This can prove the significant value when assessing the hemodynamic status of the unstable surgical patient, for instance, as an adjunct to other clinical and echocardiographic parameters (Figure 4). F4

In both patients, as PV pulsatility was associated with other signs of RV failure, it prompted us to induce pulmonary vasodilation using a combination of inhaled epoprostenol and inhaled milrinone. Because these 2 inhaled agents act on pulmonary vascular tone by 2 different mechanisms, combined administration offers additive effects and was associated with significant improvement in hemodynamic

parameters and reduction in vasoactive support during cardiac surgery.[2,11]

In summary, these 2 cases describe the assessment of PV flow with point-of-care ultrasound to detect signs of elevated RV filling pressures and to monitor response to therapy. It also outlines the use and effect of combined inhaled epoprostenol and milrinone, which resulted in rapid reduction of fluid overload and splanchnic congestion with resolution of PV pulsatility. Further research is warranted to further explore the role of this therapy as well as the role of PV pulsatility in the evaluation of the patient with suspected RV failure. ■

DISCLOSURES

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Contribution: This author helped instigate the report and revise the manuscript.
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REFERENCES

1. Denault AY, Haddad F, Jacobsohn E, Deschamps A. Perioperative right ventricular dysfunction. *Curr Opin Anaesthesiol*. 2013;26:71–81.
2. Laflamme M, Perrault LP, Carrier M, Elmi-Sarabi M, Fortier A, Denault AY. Preliminary experience with combined inhaled milrinone and prostacyclin in cardiac surgical patients with pulmonary hypertension. *J Cardiothorac Vasc Anesth*. 2015;29:38–45.
3. Beaubien-Souligny W, Bouchard J, Desjardins G, et al. Extracardiac signs of fluid overload in the critically ill cardiac patient: a focused evaluation using bedside ultrasound. *Can J Cardiol*. 2017;33:88–100.
4. Vincent JL, Sakr Y, Sprung CL, et al; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34:344–353.
5. McNaughton DA, Abu-Yousef MM. Doppler US of the liver made simple. *Radiographics*. 2011;31:161–188.
6. Gallix BP, Taourel P, Dauzat M, Bruel JM, Lafortune M. Flow pulsatility in the portal venous system: a study of Doppler sonography in healthy adults. *AJR Am J Roentgenol*. 1997;169:141–144.
7. Sundaram V, Fang JC. Gastrointestinal and liver issues in heart failure. *Circulation*. 2016;133:1696–1703.
8. Tang WH, Kitai T. Intrarenal venous flow: a window into the congestive kidney failure phenotype of heart failure? *JACC Heart Fail*. 2016;4:683–686.
9. Denault AY, Beaubien-Souligny W, Elmi-Sarabi M, et al. Clinical significance of portal hypertension diagnosed with bedside ultrasound after cardiac surgery. *Anesth Analg*. 2017;124:1109–1115.
10. Haddad F, Elmi-Sarabi M, Fadel E, Mercier O, Denault AY. Pearls and pitfalls in managing right heart failure in cardiac surgery. *Curr Opin Anaesthesiol*. 2016;29:68–79.
11. St-Pierre P, Deschamps A, Cartier R, Basmadjian AJ, Denault AY. Inhaled milrinone and epoprostenol in a patient with severe pulmonary hypertension, right ventricular failure, and reduced baseline brain saturation value from a left atrial myxoma. *J Cardiothorac Vasc Anesth*. 2014;28:723–729.

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