First step toward uncovering perioperative congestive encephalopathy

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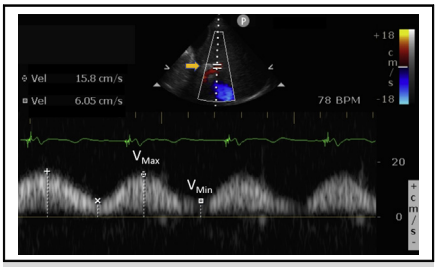

Portal flow pulsatility detected using transthoracic pulsed wave Doppler imaging.

CENTRAL MESSAGE

Cerebral venous congestion could be a mechanism leading to delirium in some patients after cardiac surgery. Portal flow assessment is a promising tool to identify significant congestion.

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See Commentary on page 154.

Continuous advances in perioperative care during past decades resulted in a substantial decline in mortality rate after cardiac surgery. However, acute complications such as postoperative delirium (POD) still occur and do so with a high frequency in elderly patients undergoing cardiac surgery.[1] The burden of POD is both important from the perspective of the patient and of the healthcare system. This complication is associated with adverse outcomes, including patient-centered outcomes such as discharge to a nonhome health care facility, a decline in functional status, and increased risk of subsequent postoperative neurocognitive disorder.[2,3] Clinicians often feel powerless when confronted with persistent postoperative delirium. The precise mechanism that leads to this state is often not readily apparent. Although there are considerable data suggesting that the systemic inflammatory response triggered by cardiopulmonary bypass may directly induce cognitive dysfunction,[4] a myriad of intraoperative and post-operative factors may be contributors to variable degrees. However, it might be challenging to detect them and determine which are clinically significant enough to merit intervention. When the arterial blood pressure targets are met, blood gases are satisfactory, and the cardiac output appears adequate, what can be done to improve patients who remain confused? We have yet to find an intervention to reliably prevent or treat POD in all cardiac surgery patients.[5] This may result from our inability to reliably identify major contributors to cognitive dysfunction that may vary greatly between individuals. Precision medicine precepts holds that identifying subphenotypes with common biologic contributors could allow us to study and apply more specific management strategies.[6]

AN OVERLOOKED THREAT

The concept of detrimental venous congestion is not new. Animal experiments dating back to 1913 demonstrated the progressive impairment of mammalian kidney function upon a rise in the pressure in the renal vein in a controlled setting.[7] More recent evidence provides compelling arguments regarding similar adverse effects on the liver,[8] the gastrointestinal tract,[9,10] soft tissues,[11,12] and the myocardium.[13,14] Data on how venous congestion might affect the brain are scarcer. However, it is unlikely that an organ contained in a nonexpandable cavity (eg, the cranium) could be the sole left unaffected by interstitial edema,

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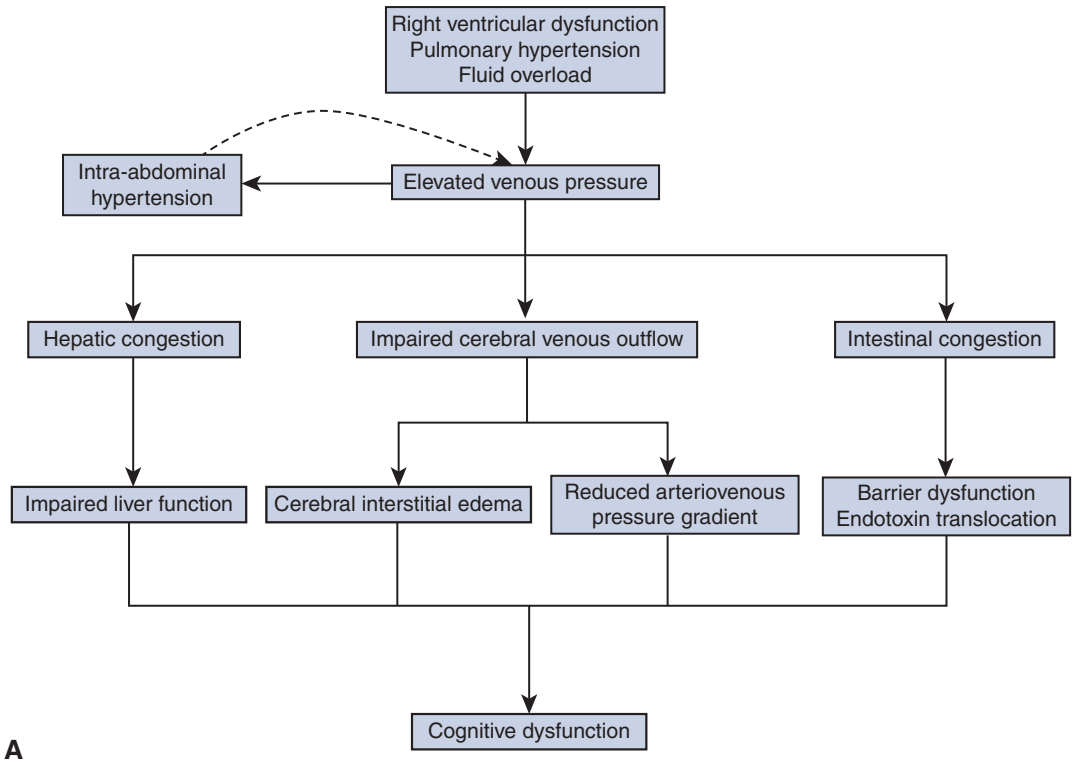
particularly in the setting of prolonged recumbent position necessary in the perioperative period. Subclinical cerebral edema has been shown to occur in a proportion of patients undergoing cardiac surgery.[15] Additionally, the release of blood–brain biomarkers suggesting subclinical cerebral injury has been described in patients with disturbance of venous outflow resulting in high jugular venous bulb pressure (>12 mm Hg) during surgery.[16] The degree of cerebral venous pressure elevation is correlated with intra-abdominal pressure and central venous pressure (CVP).[17] Data from an animal model of intra-abdominal hypertension suggests that the increase in jugular venous pressure in this setting may induce histologic changes suggestive of cerebral ischemia.[18] Furthermore, the influence of cerebral congestion has been noted in other settings. Neurocognitive outcomes appear to be worse in critically ill patients with evidence of venous congestion after cardiac arrest[19] or with a significant positive fluid balance in the setting of shock.[20] Despite these preliminary findings, much is left to learn because this mechanism of brain injury has largely been overlooked so far.

Undetected venous congestion may contribute significantly to cognitive dysfunction in a subgroup of patients undergoing cardiac surgery. Although higher CVPs have been associated with an increased risk of complications in multiple acute care settings, including cardiac surgery,[21] the CVP threshold above which harm occurs remains uncertain. This might be in part due to imprecisions in CVP monitoring, particularly in critical care settings. Accurate CVP measurements rely on adequate transducer placement and minor variations can result in important discrepancies, even in experienced operators.[22] Furthermore, invasive monitoring is discontinued early during the postoperative course and may be unavailable when POD becomes apparent, usually from 24 to 72 hours after cardiac surgery.

Apart from the potential direct effect of venous congestion on the brain through the development of interstitial edema and increased intracranial pressure, venous congestion of other organs might contribute to cognitive dysfunction (Figure 1, *A*). The development of elevated intra-abdominal pressure is a well-known consequence of congestive heart failure, as well as fluid overload in critically ill patients, and may contribute to elevated intracranial pressure as previously presented.[23] Furthermore, intestinal edema may be an important contributor to the general inflammatory reaction seen in cardiac surgery patients through the dysfunction of the intestinal barrier function leading to endotoxin translocation. This phenomenon, colloquially known as cardiointestinal syndrome, (Table E1) has been described in congestive heart failure patients but may also occur in acute settings. Whereas the link between unabated inflammation process and cognitive dysfunction after cardiac surgery is well documented, the contribution of endogenous endotoxemia is not documented. Finally, in extreme cases, congestive liver and kidney function impairment may contribute through hepatic and uremic encephalopathy. Portal vein flow pulsatility may be a practical marker of relative cardiogenic portal hypertension able to identify patients at risk for developing these phenomena.[24]

A NEW MODALITY

Assessing the influence of venous congestion directly in end organs by a noninvasive method might be an important adjunct to correctly identify a congestive phenotype. Distension modifies the properties of the systemic venous system, which changes from a highly compliant structure to a more rigid network. Pressure variations in the right atrium are usually poorly transmitted distally due to high damping. However, they are readily transmitted in a distended, stiff system. Point-of-care ultrasonography enables clinicians to assess venous blood velocity directly into end organs using Doppler imaging.[25] Using this modality, it is possible to detect characteristic distal pulsatile venous waveforms suggesting decreased systemic venous compliance. Portal vein flow is perhaps the most reliable window to assess the compliance of the venous system. Portal flow pulsatility is defined as a difference greater than 30% to 50% between the maximum and minimum Doppler flow velocities measured in the main portal vein during the cardiac cycle (Figure 1, *B*).[26] Originally described in congestive heart failure patients with right heart failure and/or tricuspid regurgitation, it has been shown to be the best sonographic predictor of a cholestatic liver profile in this population.[27] Notably, it was superior to other complex echocardiography measurements of right ventricular function and pressure.[27] This suggest that, in addition to being less technically complex, assessing the hemodynamic influence on portal blood flow might be a better congestion marker than traditional echocardiographic assessment of right ventricular function. More recently, we have shown that portal pulsatility is detected in an important proportion ($\approx$20%-25%) of the cardiac surgery population, including during surgery[28] and in the days following cardiac surgery,[29] with a peak on postoperative day 2 after surgery. The magnitude of pulsatility is correlated with right ventricular diastolic pressure during surgery[28] and natriuretic peptide after surgery[29] strengthening its potential role as a congestion biomarker in cardiac surgery populations. In a first prospective cohort study (n = 115), the detection of portal flow pulsatility by transesophageal echocardiography at the end of surgery was independently associated with major complications (odds ratio [OR], 5.13; 95% confidence interval [CI], 1.58-16.67; $P = .007$). In a second prospective cohort study (n = 145), portal flow pulsatility detected during the first 3 days after cardiac surgery was independently associated with acute kidney injury and renal venous flow alterations. The success rate of portal flow assessment



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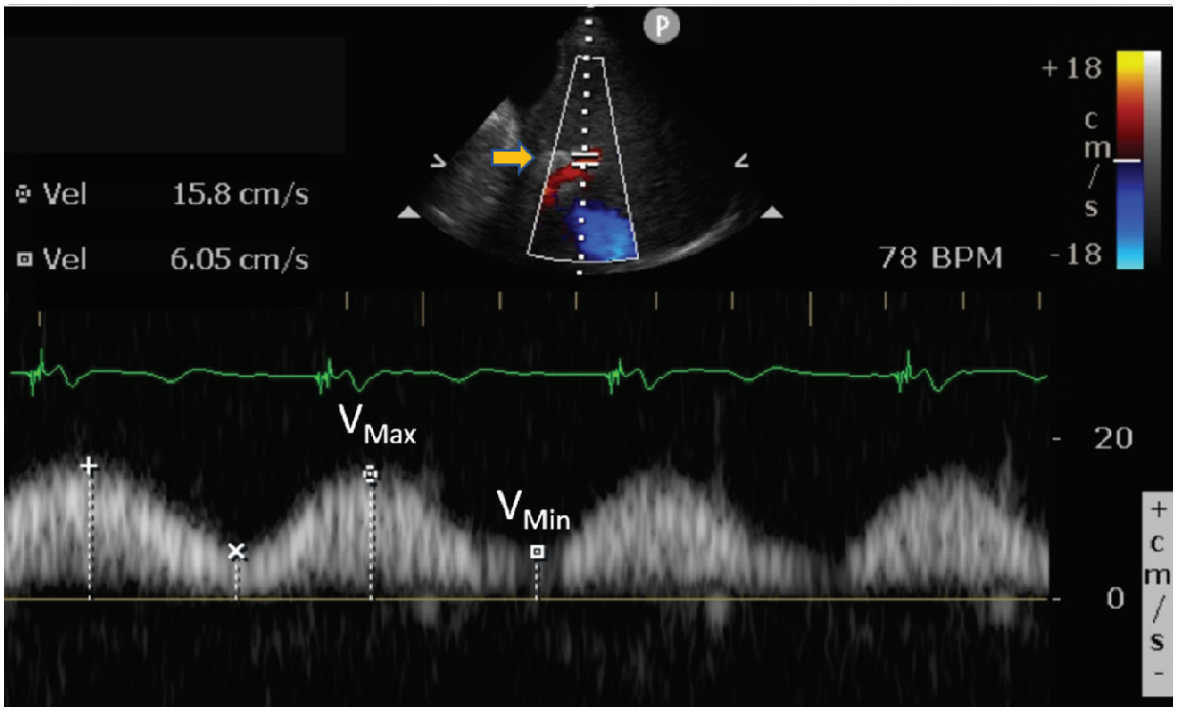

B

FIGURE 1. A, Potential mechanisms linking systemic venous congestion to postoperative delirium. B, Portal flow pulsatility in a patient aged 79 years detected 3 days after mitral valve replacement. Variations in blood velocity within the portal vein are optimally assessed at end expiration at the hepatic ilium where the vessel enters the liver (*orange arrow*) using a cardiac probe (phased-array transducer) or an abdominal probe (curved array transducer) using pulsed wave Doppler. The concurrent echocardiogram tracing enables the identification of the minimal (V_{Min}) and maximal (V_{Max}) velocity during the cardiac cycle. Portal pulsatility fraction (PF) can be quantified as following: $[V_{Max} - V_{Min}]/V_{Max}$ (PF, 62% is shown). PF of 30% up to 50% is considered mild pulsatility, whereas PF >50% is considered severe pulsatility. At the time of assessment, the patient was disoriented and presented asterixis. He had a weight gain of 2.6 kg compared with preoperative baseline, a N-terminal-pro beta-natriuretic peptide measurement of 3474 pg/mL (preoperative level, 1060 pg/mL) and a brain oxygen saturation of 52% representing a 21% relative decrease from preoperative baseline. *Vel*, Velocity.

was 94% to 95% by transesophageal echocardiography[28] and 98% to 99% by transthoracic echocardiography[28,29] with a good interobserver agreement (mean absolute percentage difference, 6.1% ± 6.2%) and a very good intraclass correlation coefficient (0.95; $P < .001$).[29]

In a prespecified substudy, the detection of portal flow pulsatility was associated with cognitive dysfunction (OR, 2.10; 95% CI, 1.25-3.53; $P = .005$) and asterixis (OR, 2.23; 95% CI, 1.13-4.41; $P = .02$) assessed by the investigators as well as POD detected by the nursing staff during regular screening (hazard ratio, 2.63; 95% CI, 1.13-6.11; $P = .025$).[30] Of note, patients with portal flow pulsatility were more likely to present significantly lower cerebral tissue oximetry at the time of assessment compared with preoperative baseline (OR, 2.23; 95% CI, 1.12-4.71; $P = .02$). Whether this finding was related to the greater proportion of venous blood in the cerebral circulation or to a reduction of cerebral perfusion due to elevated intracranial pressure is not known. These observations are the first to report the association between an echocardiography marker of congestion and cognitive dysfunction in a cohort of patients undergoing cardiac surgery.

A WAY FORWARD

These novel findings should be interpreted with caution. A multicenter cohort study is currently ongoing to confirm the association found between portal flow pulsatility and postoperative complications, including delirium (ClinicalTrials.gov identifier: NCT03656263). Nevertheless, validating this finding is only the first step in determining whether interventions targeted at restoring normal venous compliance in response to the detection of portal flow pulsatility may contribute to prevent POD or treat a subgroup of patients with congestive POD. An overview of the critical time points where portal flow assessment may be warranted is presented in Figure 2. Preventive strategies to avoid congestive POD could be first related to achieving an optimal fluid balance status before surgery in patients with pre-existing congestive heart failure who present with a pulsatile portal vein flow during the preoperative consultation. Secondly, detecting a pulsatile portal flow by transesophageal echocardiography at the end of surgery or at intensive care unit admission might represent a second opportunity to prevent congestive organ injury. Interventions that may accomplish that goal may include the induction of a negative fluid balance, the pre-emptive use of renal replacement therapy when significant renal dysfunction is present, or the use of inhaled or intravenous inotropes to improve heart function and right ventricular afterload. The best strategy may vary according to patient status at the time of assessment. Finally, portal vein flow assessment may be performed in patients presenting POD to determine if venous congestion might contribute to cognitive dysfunction, which may respond to the aforementioned decongestion strategies.

Each of these clinical questions represents an indication to perform a different clinical trial to determine whether an ultrasound-based approach integrating portal vein Doppler would contribute to improve the care of patients undergoing cardiac surgery. Numerous challenges are foreseen when considering such types of interventional studies. These include defining the nature of the proposed intervention and whether it will be appropriate in most patients given the highly variable and rapidly evolving nature of postcardiac surgery care. Notably, it will be important to determine the potential situations in which portal vein Doppler may be misleading; to validate the optimal cutoff suggesting a pathologic process; and to determine how

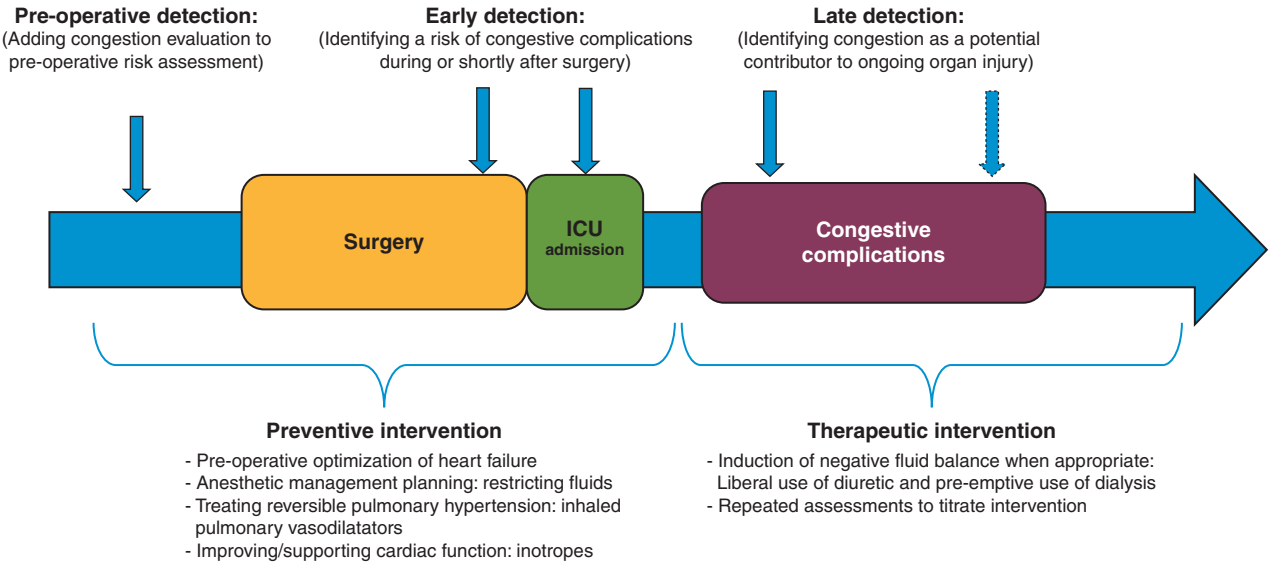

FIGURE 2. Potential preventive and therapeutic applications of assessing venous congestion in the perioperative period. *ICU*, Intensive care unit.

combining it to other echocardiography, clinical, and laboratory variables might improve interpretation. Ultrasound-guided interventions also necessitate a critical mass of trained ultrasound operators to perform the assessments. Fortunately, portal vein Doppler is a reliable technique that may be rapidly learned by operators with intermediate ultrasound skills. It is likely that this level of competency will be considered standard in the future given the current growth of enthusiasm for point-of-care ultrasound within the acute cardiac care community, opening opportunities to study the influence of ultrasound-guided strategies.

Preliminary data suggest that portal flow Doppler could be a simple noninvasive tool to detect clinically significant venous congestion at the bedside of cardiac surgery patients. Whether or not portal flow Doppler is confirmed to be the optimal clinical tool, clinicians should be aware that venous congestion could be a major contributor to the high incidence of POD after cardiac surgery. Unraveling congestive brain injury may enable clinicians to treat the cause of POD in selected patients rather than merely controlling the symptoms.

Conflict of Interest Statement

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The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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