ORIGINAL RESEARCH

Alterations in Portal Vein Flow and Intrarenal Venous Flow Are Associated With Acute Kidney Injury After Cardiac Surgery: A Prospective Observational Cohort Study

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Background—Acute kidney injury (AKI) after cardiac surgery is associated with adverse outcomes. Venous congestion can impair kidney function, but few tools are available to assess its impact at the bedside. The objective of this study was to determine whether portal flow pulsatility and alterations in intrarenal venous flow assessed by Point-Of-Care ultrasound are associated with AKI after cardiac surgery.

Methods and Results—This single-center prospective cohort study recruited patients undergoing cardiac surgery with cardiopulmonary bypass. Hepatic and renal Doppler ultrasound assessments were performed before surgery, at the intensive care unit admission, and daily for 3 days after surgery. The primary statistical analysis was performed using proportional hazards model for time-dependent variables. Among the 145 patients included, 49 patients (33.8%) developed AKI after cardiac surgery. The detection of portal flow pulsatility was associated with an increased risk of AKI (hazard ratio: 2.09, confidence interval, 1.11–3.94, P=0.02), as were severe alterations of intrarenal venous flow (hazard ratio: 2.81, confidence interval, 1.42–5.56, *P*=0.003). These associations remained significant in multivariable models. The addition of these markers to preoperative risk factors and central venous pressure measurement at intensive care unit admission improved the prediction of AKI. (Continuous net reclassification improvement: 0.364, confidence interval, 0.081–0.652 for portal Doppler and net reclassification improvement: 0.343, confidence interval, 0.081–0.628 for intrarenal Doppler)

Conclusions—Portal flow pulsatility and intrarenal flow alterations are markers of venous congestion and are independently associated with AKI after cardiac surgery. These tools might offer valuable information to develop strategies aimed at treating or preventing congestive cardiorenal syndrome after cardiac surgery.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT02831907. **(*J Am Heart Assoc*. 2018;7: e009961. DOI: 10.1161/JAHA.118.009961.)**

Key Words: acute kidney injury • cardiac surgery • congestive heart failure • point-of-care ultrasound

Acute kidney injury (AKI) after cardiac surgery is a frequent complication and is associated with adverse clinical outcomes, including a 50% increase in mortality.[1] While multiple factors can lead to AKI in this setting, the interaction between the heart and the kidneys during the perioperative period is of critical importance.[2] Impairment in kidney function in this setting may be caused by acute cardiorenal syndrome in an unknown proportion of patients. Increased central venous pressure (CVP) is known to be a major factor underlying worsening of kidney function in patients with decompensated heart failure[3] and thus, venous congestion might also be an important cause of AKI after cardiac surgery. In this subgroup of

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Accompanying Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009961

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Received June 26, 2018; accepted July 31, 2018.

Clinical Perspective

What Is New?

- Alterations in portal vein flow and intrarenal venous flow can be detected at the bedside of cardiac surgery patients by Point-Of-Care ultrasound.
- These markers of venous congestion are independently associated with acute kidney injury in the postoperative period.

What Are the Clinical Implications?

- Portal and renal venous Doppler may provide additional tools to assess the adverse hemodynamic impact of venous congestion on end-organs and may offer insights to personalize management in cardiac surgery patients.
- Interventions aimed at normalizing portal and intrarenal venous flow should be investigated in future interventional studies.

patients, alleviating venous congestion may improve renal function.[4] Consequently, identifying a method to detect renal congestion may be useful for the development and assessment of different treatment strategies.

Point-Of-Care ultrasound is enabling clinicians to assess organ-specific blood flow using Doppler assessment. When right heart failure and/or fluid overload result in the distension of the inferior vena cava (IVC), the pressure variations in the right atrium during the cardiac cycle are transmitted through the noncompliant venous system in end-organs. Portal flow pulsatility and discontinuous intrarenal venous flow are echographic signs described in congestive heart failure that may represent clinical markers of the hemodynamic impact of venous congestion.[5–7] In prospective studies among patients with heart failure, portal flow pulsatility has been shown to be the best predictor of elevated serum bilirubin[5] and the detection of portal congestion or abnormal patterns of intrarenal venous flow were associated with an increased risk of death or hospitalization.[6,8]

Whether these echographic features carry prognostic implications in cardiac surgery patients remains unclear. Portal flow pulsatility was associated with AKI in a retrospective cohort[9] and intrarenal venous flow alterations have never been studied in this population. We hypothesized that the presence of these ultrasound features is independently associated with AKI after cardiac surgery. The secondary objectives of this study were to describe the prevalence of these ultrasound markers and the factors associated with their detection before and after cardiac surgery.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

This prospective cohort study (clinicaltrials.org identifier: NCT02831907) recruited patients from a single specialized cardiac surgery center from August 2016 to July 2017. Patients 18 years and older undergoing cardiac surgery with the use of cardiopulmonary bypass were eligible to participate. Patients were excluded if they had severe chronic kidney disease (estimated glomerular filtration rate <15 mL/min per 1.73 m^2 or dialysis) or renal transplantation, critical preoperative state (defined as aborted sudden death, preoperative cardiac massage, preoperative mechanical ventilation, preoperative vasopressor or inotropes support, or intra-aortic counterpulsation balloon pump before surgery), documented AKI or delirium before surgery or any condition interfering with Doppler evaluation of the portal system (including known or suspected cirrhosis or portal vein thrombosis). Screening was performed randomly in patients scheduled for intervention during the following day and the number of patients recruited per day was determined by the availability of the investigators to perform the assessments and time constraints. Patients were followed daily for 3 days, and ultrasound studies were performed after admission to the intensive care unit (ICU) after surgery and daily thereafter. We followed the Strengthening the Reporting of Observational studies in Epidemiology guidelines.[10] The study was approved by the Montreal Heart Institute ethics board. Written informed consent was obtained for all participants.

Data Collection

Demographic and baseline clinical data were collected, including the New York Heart Association functional classification score.[11] The European System Operative Score Risk Evaluation score (EuroSCORE II) was calculated,[12] as well as a validated risk score for the prediction of AKI according to Kidney Disease: Improving Global Outcomes criteria in cardiac surgery patients as based on preoperative characteristics.[13,14] Creatinine measurements were performed before surgery and daily after surgery using an enzymatic assay (IDMS-standardized) and estimated glomerular filtration rate is calculated using the Modified Diet in Renal Disease formula.[15] NT-pro-BNP (N-terminal pro-B-type natriuretic peptide) measurements were performed the day before surgery and on postoperative days 1, 2, and 3. Cumulative fluid balance, duration of cardiopulmonary bypass and aortic cross clamping, and cumulative dose of vasopressors were recorded.

During the postoperative period, cumulative fluid balance including urine output was collected during the ICU stay. The

following information was also gathered at the time of ultrasound assessment: systolic and diastolic arterial pressure, CVP, heart rate, pulmonary artery pressure, ongoing vasopressor/inotropic support, use of mechanical ventilation, presence of arrhythmia during assessment, and use of ventricular pacing. Diastolic perfusion pressure (diastolic arterial pressure–CVP) was also measured from this information.[16]

Clinical Outcomes

The primary outcome was AKI defined by the Kidney Disease: Improving Global Outcomes criteria[17] as an increase of serum creatinine >26 μmol/L within a 48-hour period or 50% from baseline creatinine within a week from cardiac surgery. Severe AKI was defined per an increase of 100% or more in baseline creatinine or to more than ≥354 μmol/L or initiation of renal replacement therapy (Kidney Disease: Improving Global Outcomes stage 2 or 3). The ICU length of stay was recorded. Patients were contacted by phone after 30 days to determine the 30-day mortality.

Ultrasound and Bedside Assessment

Ultrasound studies were performed at the bedside using a Sparq system (Philips Healthcare, Amsterdam, Netherlands) with a phased array transducer (S4-2) or a convex array transducer (C6-2) by 2 investigators trained in hepatic and renal Doppler (W.B.S. and A.B.) under the supervision of a radiologist (P.R). The investigators were blinded to the serum creatinine levels while performing the ultrasound assessments. Patients were positioned in a dorsal decubitus position during the examination with the head of the bed at 0° to 30°. Special attention was made to avoid a Valsalva maneuver during the examination as this could modify the echographic parameters.[18] Concurrent ECG was obtained to precisely identify the phases of the cardiac cycle. The attending physician was unaware of the results of the ultrasound examination.

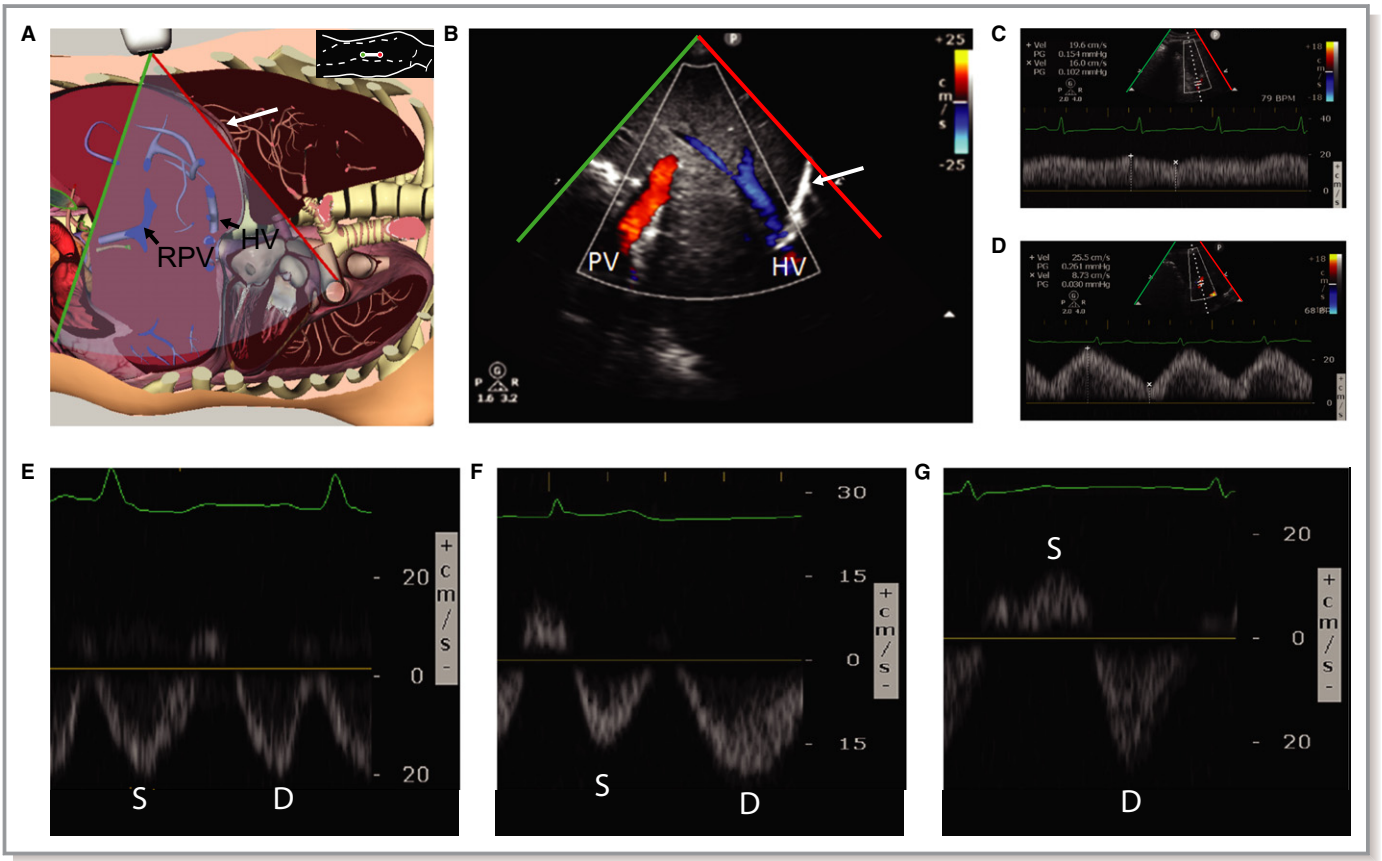

Figure 1. Pulse-wave Doppler assessment of portal vein flow by transthoracic ultrasound. A, Probe position in the mid to posterior axillary position shown using the Vimedix simulator (with permission of CAE Healthcare, St-Laurent, Canada). B, Color Doppler of hepatic vessels showing the position of the hepatic vein (HV) and the portal vein (PV). C, Normal portal flow showing minimal variations of flow velocities during the cardiac cycle (pulsatility fraction: 18.4%). D, Abnormal variations of portal flow velocities during the cardiac cycle (pulsatility fraction: 66%). E, Normal hepatic vein waveform with systolic component (S) equal to or greater than the diastolic component (D). F, Abnormal hepatic venous flow with systolic component (S) less than the diastolic component and, (E), when severe, with reversal of hepatic flow during systole. PG indicates pressure gradient; RPV, right portal vein; Vel, velocities.

Portal vein Doppler assessment has previously been described[19] and is presented in Figure 1. The peak (V_{Max}) and the nadir velocities (V_{Min}) during the cardiac cycle were recorded. The pulsatility fraction (PF) was subsequently calculated as follows:

$$PF(\%) = 100\ [(V_{Max} - V_{Min})/V_{Max}]$$

From the same position, pulsed wave Doppler waveform of the hepatic venous flow was obtained, and the maximal diameter of the IVC was measured in its intrahepatic portion. The pattern of hepatic vein flow was recorded according to the classification described in Figure 1E through 1G.

Intrarenal Doppler assessment is presented in Figure 2. Pulsed wave Doppler waveform at the corticomedullary junction was obtained in all 3 segments during a respiratory pause after the end of expiration to obtain 2 to 3 consecutive cardiac cycles. The peak (V_{Max}) and the nadir arterial velocities (V_{Min}) during the cardiac cycle were recorded. The pattern of intrarenal venous flow was recorded according to a classification described by Iida et al[6] (Figure 2C through 2E). If multiple patterns were present, only the best pattern was recorded based on the magnitude of the velocity and spectral definition (absence of artifacts). The renal arterial resistive index ($RI=(V_{Max}-V_{Min})/V_{Max}$) was measured in the 3 segments of each kidney.[20] The median renal resistive index was obtained in each kidney and a mean of both kidneys was considered.

Reproducibility

Reproducibility was assessed by 3 methods: To validate the technique of ultrasound assessment, both investigators (W.B.S. and A.B.) and a radiologist (P.R.) with extensive experience in renal Doppler assessment performed 10 examinations on patients and healthy volunteers at the Radiology Department. Interobserver agreement was measured for renal RI and venous patterns between the investigators and the radiologist. Secondly, to assess the technique reliability in the context of the study, both investigators (W.B.S. and A.B.) independently performed the assessment in 5 patients at the same time point during the study in a blinded fashion (the other observer left during the examination). Interobserver agreement was measured for renal RI, venous patterns, and PF measurements. Finally, after data acquisition, both investigators (W.B.S.

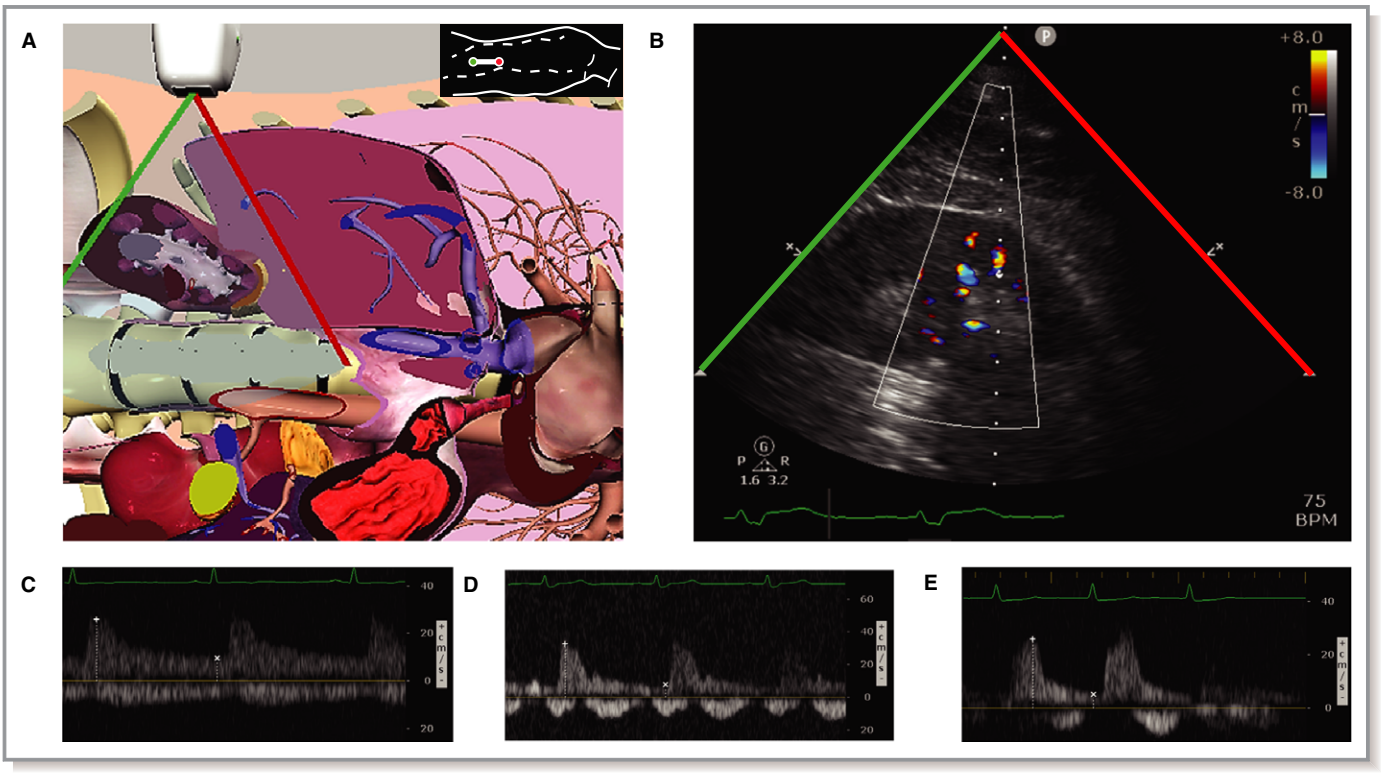

Figure 2. Doppler assessment of renal interlobar arterial and venous flow by transabdominal echography. A, Probe position in the posterior axillary position to obtain a longitudinal view of the right and left kidney shown using the Vimedix simulator (with permission of CAE Healthcare, St-Laurent, Canada). B, Longitudinal view of the right kidney with color Doppler to identify interlobar vessels. The intrarenal venous waveform was classified into 3 patterns. Pattern 1: (C) Normal continuous venous flow during the cardiac cycle or brief interruption of venous flow during atrial contraction. Pattern 2: (D) Discontinuous biphasic venous flow with systolic and diastolic components. Pattern 3: (E) Discontinuous venous flow with flow exclusively detectable during diastole.

and A.B.) and the radiologist (P.R.) analyzed data from 15 examinations independently without knowledge of the other observer's measurements.

Sample Size Estimation and Statistical Analysis

Based on local retrospective data showing an incidence of AKI of 30%, significant portal flow variations in ≈30% of patients, and assuming that patients with pulsatile portal flow are at high risk (odds ratio ≥3.0) to develop AKI based on a previous retrospective cohort study by our group,[9] it was determined that a sample size of 152 patients would have a statistical power of 80% to detect the expected difference in the risk of postsurgical AKI with a significance level of 95%.

For the primary objective, the association between clinical variables including echographic parameters and the risk of new-onset AKI was assessed using a Cox proportional hazards model with the studied echographic parameters considered as segmented time-dependent covariates. Other variables includes preoperative factors (demographic variables, AKI prediction score,[13] baseline echocardiographic features, comorbidities), intraoperative factors (cardiopulmonary bypass time, vasopressor use, fluid balance, hemodynamic variables), and early postoperative factors (vasopressor/inotrope use, hemodynamic variables, blood transfusions). To determine whether the PF and other continuous variables had to be considered as a continuous or categorical variable, the assumption of linearity was verified by using Martingale residuals plot and, in case of nonlinearity, the optimal cut-off was decided based on the appearance of the plot. For the PF, the cut-off used was ≥50% based on previous studies.[9] The proportionality assumption of the Cox model was verified for non-time-dependent variables by confirming that no significant interaction was present between the studied variable and time. Multivariable Cox regression was performed by including variables associated with AKI ($P<0.1$) selected by backward stepwise exclusion by the likelihood ratio method.

The following variables were not included in the primary analysis because they were related to the studied mechanism (venous congestion): right ventricular dysfunction, CVP measurements, tricuspid regurgitation, and NT-pro-BNP. Interactions were tested for variables included in the models. If multiple continuous covariates were included in the models, multicollinearity between those variables was tested. A secondary analysis was performed by including IVC measurements as a time-dependent variable and CVP measurement at ICU admission to determine whether the studied echographic markers were independently associated with AKI.

A post hoc analysis was performed to determine the clinical value of the first assessment upon ICU admission after surgery of the studied echographic markers. Univariate Cox regression was performed, and the survival functions were represented graphically. A multivariate Cox model including the studied echographic markers, preoperative AKI risk score, and the CVP at the time of ultrasound assessment at ICU admission was constructed. CVP was not handled as a time-dependent covariate because missing values were present after postoperative day 0 (removal of central line). Continuous net reclassification improvement (NRI) was calculated.[21,22] The baseline model, including preoperative risk score,[13] intervention on thoracic aorta, and CVP measurements at ICU admission, was compared with a model adding portal flow pulsatility (PF≥50%) or severe alterations in intrarenal venous flow (Pattern 3) detected at ICU admission. Internal validation was performed using bootstrap sample (1000 samples) to produce 95% confidence intervals (CIs). Reclassification plots were produced using the predicted probabilities of AKI.[22,23]

For the secondary objective, a generalized estimating equations analysis was constructed to assess the association between the studied echographic parameters and other variables during the study. This type of analysis accounts for the repeated measures design, implying that the sample was not independent. Using a logistic regression model, the impact of each variable on the studied echographic parameters was assessed. In addition, the time of assessment (4 time points: Day 0 to Day 3) was included as a factor in the analysis and the interaction between the studied variable and the time of ultrasound assessment was tested. In the presence of a significant interaction with time ($P<0.05$), the association was presented for each time point. For continuous covariates, the linearity assumption was verified using the Box-Tidwell test.[24] A robust estimator for the covariance matrix and an autoregressive structure for the working correlation matrix were used.

Results are presented in number (%) for dichotomous variables and in mean±SD or median and interquartile range for continuous variables, where appropriate. Comparisons between 2 groups for continuous variables were done using *t* test or Mann–Whitney *U* test for independent sample where appropriate, and comparison between 2 groups for categorical variables was done using the χ^2 test. Comparison between more than 3 groups was done using ANOVA or Kruskal–Wallis test. Reproducibility was assessed as the mean difference between measurements and the interclass correlation coefficient for continuous variables (RI, PF). For dichotomous variables (renal vein patterns), reproducibility was assessed as a percentage of agreeability and Cohen's kappa statistics. Statistical tests were performed in SPSS version 24 (IBM, Armonk, NY). The NRI was determined using PredictABEL R package and CIs were determined using the nricens R package.[25–27]

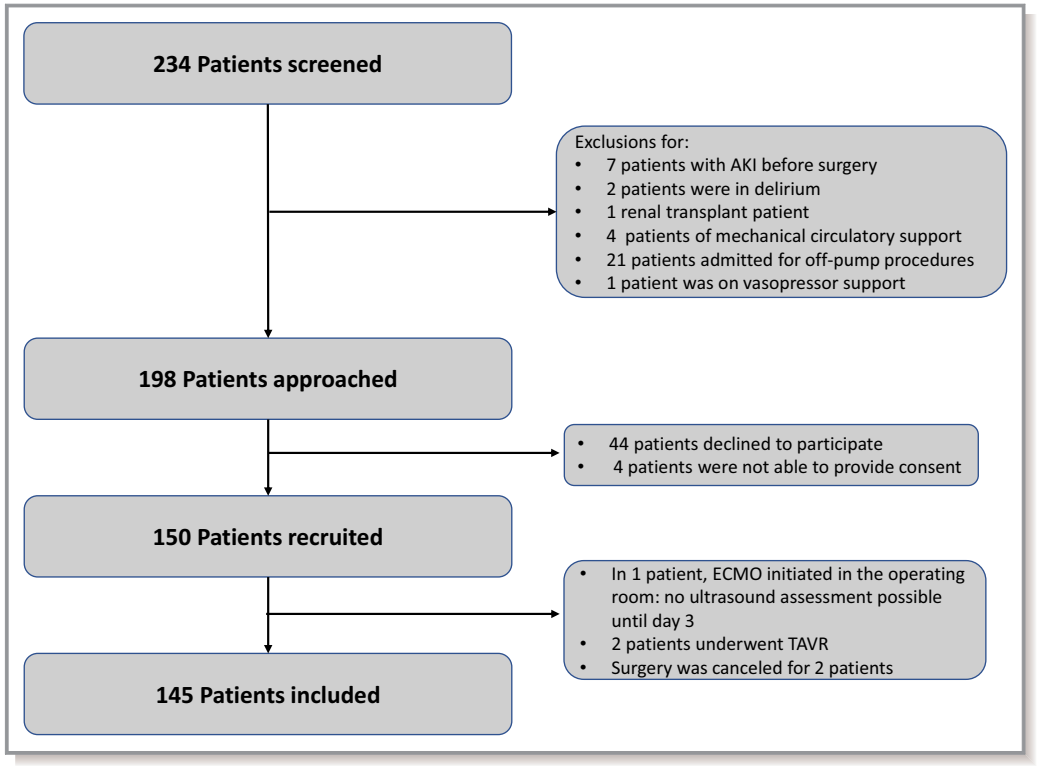

Figure 3. Flowchart of studied patients. AKI indicates acute kidney injury; ECMO, extracorporal membrane oxygenation; TAVR, transcatheter aortic valve replacement.

Results

During the study period, 145 patients were included (Figure 3). Baseline characteristics of patients are presented in Table 1. All patients underwent preoperative ultrasound assessment. After surgery, 1 patient (0.7%) on Day 0, 3 patients (2.1%) on Day 1, 5 patients (3.4%) on Day 2, and 10 patients (6.9%) on Day 3 refused to undergo ultrasound examination. A total of 706 ultrasound assessments were performed. The rate of successful examination was 99.6% for the portal vein, 94.8% for the right kidney, and 85.4% for the left kidney. Adequate interobserver agreement was achieved both in repeated assessment and repeated analysis of the Doppler tracings (Table S1).

The distribution of portal flow pulsatility and intrarenal flow patterns in the perioperative period are presented in Figure 4A and 4B. The distribution of PF was different across patterns of intrarenal venous flow (Figure 4C), with a higher PF being associated with a more severe pattern. Concordant normal and/or abnormal portal and venous flow were present in 77% (Figure 4D). Portal and renal venous flow were discordant in 23% of assessments. During the observation period, portal flow pulsatility was detected at least once in 60 patients (41.4%) but was present at all time points in only 2 patients (1.4%).

During the week following cardiac surgery, 49 patients (33.8%) developed AKI and 10 patients (6.9%) developed severe AKI. No patients required dialysis. The diagnosis of AKI was made on Day 1 for 35 patients, on Day 2 for 9 patients, on Day 3 for 4 patients, and on Day 7 for 1 patient. The detection of portal flow pulsatility and severe alterations in intrarenal venous flow (Pattern 3) were associated with AKI after cardiac surgery (hazard ratio [HR]: 2.09; CI, 1.11–3.94, P=0.02; and HR: 2.81, CI, 1.42–5.56; P=0.003, respectively) (Table 2). Additionally, the difference from baseline renal RI (per 0.01 change) and absolute RI values were also associated with AKI (HR: 1.05, CI, 1.01–1.09; P=0.002 and HR: 1.06, CI, 1.02–1.10; P=0.03, respectively). The detection of portal flow pulsatility was the only variable associated with severe AKI (HR: 5.12, CI, 1.47–17.9; P=0.01).

A higher preoperative AKI risk score (HR: 1.25, CI, 1.09–1.44; P=0.001 per 10% increase in risk), the presence of right ventricular dysfunction at cardiopulmonary bypass separation (HR: 2.61, CI, 1.30–5.25; P=0.007), higher CVP measurements at the end of surgery (HR: 1.04, CI, 1.01–1.08; P=0.02 per 1-mm Hg increase), IVC measurement >2.0 cm (HR: 2.35, CI, 1.14–4.85; P=0.02), and high NT-pro-BNP measurements (HR: 2.06, CI, 1.09–3.91; P=0.03 per 1 log of increase) were associated with AKI (Table S2). In multivariable proportional hazards models, portal flow pulsatility (PF≥50%), severe alterations of intrarenal venous flow (Pattern 3), and change in the renal RI were independently associated with AKI (Table 3). Variables included in the final models were the preoperative AKI risk score and surgery of the thoracic aorta. In addition, previous cardiac surgery was included in the model with renal RI. Only 1 patient (0.7%) died 3 weeks after hospital discharge.

Table 1. Patients' Characteristics

Variables	Total (n=145)	No AKI (n=96)	AKI (n=49)	*P* Value
Age, y	66 ±12.9	65 ±14	68 ±12	0.31
Female sex, n	38 (26.2%)	30 (31.3%)	8 (16.3%)	0.05
Height, cm	168.1 ±9.6	167 ±10	170 ±9	0.15
BMI, kg/m^2	28.9 ±4.7	28.3 ±4.7	30.1 ±4.6	0.025
EuroSCORE II,[12] %	2.96 (1.70; 4.79)	2.74 (1.64; 4.07)	3.70 (1.86; 7.60)	0.01
Preoperative AKI risk score,[13] %	22.9 (14.1; 35.3)	20.6 (11.6; 31.0)	28.2 (19.9; 48.6)	<0.001
eGFR, mL/kg per 1.73 m^2	75.9 ±20.3 Range: (28–132)	76.3 ±19.6	74.2 ±21.8	0.47
HTN, n	122 (84.7%)	80 (83.3%)	42 (85.7%)	0.48
Diabetes mellitus, n	50 (34.7%)	30 (31.3%)	20 (33.9%)	0.25
Peripheral vascular disease, n	17 (11.8%)	9 (9.4%)	8 (16.3%)	0.22
Active tobacco use, n	25 (17.4%)	18 (18.8%)	7 (14.3%)	0.50
COPD, n	22 (15.3%)	11 (11.5%)	11 (22.4%)	0.08
Recent myocardial infarction (<90 d), n	18 (12.5%)	14 (14.6%)	4 (8.2%)	0.27
LVEF, %	55 (45; 60)	55 (45; 60)	55 (42; 60)	0.70
ACEi or ARB use before surgery, n	66 (45.5%)	43 (44.8%)	23 (46.9%)	0.81
Diuretic use before surgery, n	49 (33.8%)	28 (29.2%)	21 (42.9%)	0.10
Active endocarditis, n	3 (2.1%)	1 (1.0%)	2 (4.1%)	0.22
Previous cardiac surgery, n	21 (14.5%)	10 (10.4%)	11 (22.4%)	0.05
Type of surgery, n				
Isolated CABG	42 (29.0%)	34 (35.4%)	8 (16.3%)	0.08
One procedure other than CABG	38 (26.2%)	27 (28.1%)	12 (24.5%)	
2 procedures	50 (34.5%)	28 (29.2%)	22 (44.9%)	
≥3 procedures	11 (7.6%)	6 (6.3%)	6 (12.2%)	
Cardiac transplantation	2 (1.4%)	1 (1.0%)	1 (2.0%)	
Surgery on thoracic aorta	10 (6.9%)	4 (4.2%)	6 (12.2%)	0.07
Context of surgery, n				
Elective	97 (66.2%)	67 (69.1%)	31 (63.3%)	0.72
Urgent*	48 (33.1%)	30 (30.9%)	18 (36.7%)	
NT-pro-BNP before surgery	475 (155; 1588) (Range: 15; 3534)	390 (146; 1532)	690 (172; 1922)	0.16

ACEi indicates angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic pulmonary obstructive disorder; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation[15]; EuroSCORE II, European System Operative Score Risk Evaluation score; HTN, chronic hypertension; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.
*Patients who have not been electively admitted for operation but who require intervention or surgery on the current admission for medical reasons. These patients cannot be sent home without a definitive procedure.

The risk of AKI according to the results of the first ultrasound assessment at ICU admission is illustrated in Figure 5. Both portal flow pulsatility and severe alteration in intrarenal venous flow remained associated with AKI after adjustment with CVP measurement at ICU admission and IVC measurements throughout the study in multivariable models (Tables S3 and S4). From a baseline prediction model including preoperative risk factors and CVP measurements at ICU admission, the addition of portal flow pulsatility and severe alteration in intrarenal venous flow detected at ICU admission resulted in an improvement in the prediction of AKI. (Portal Doppler: NRI: 0.364, CI, 0.081–0.652. Intrarenal venous Doppler: NRI: 0.343, CI, 0.081–0.628). Reclassification plots are presented in Figure 6.

After cardiac surgery, portal flow pulsatility and abnormal intrarenal venous patterns were associated with lower diastolic perfusion pressure, lower heart rate, use of positive

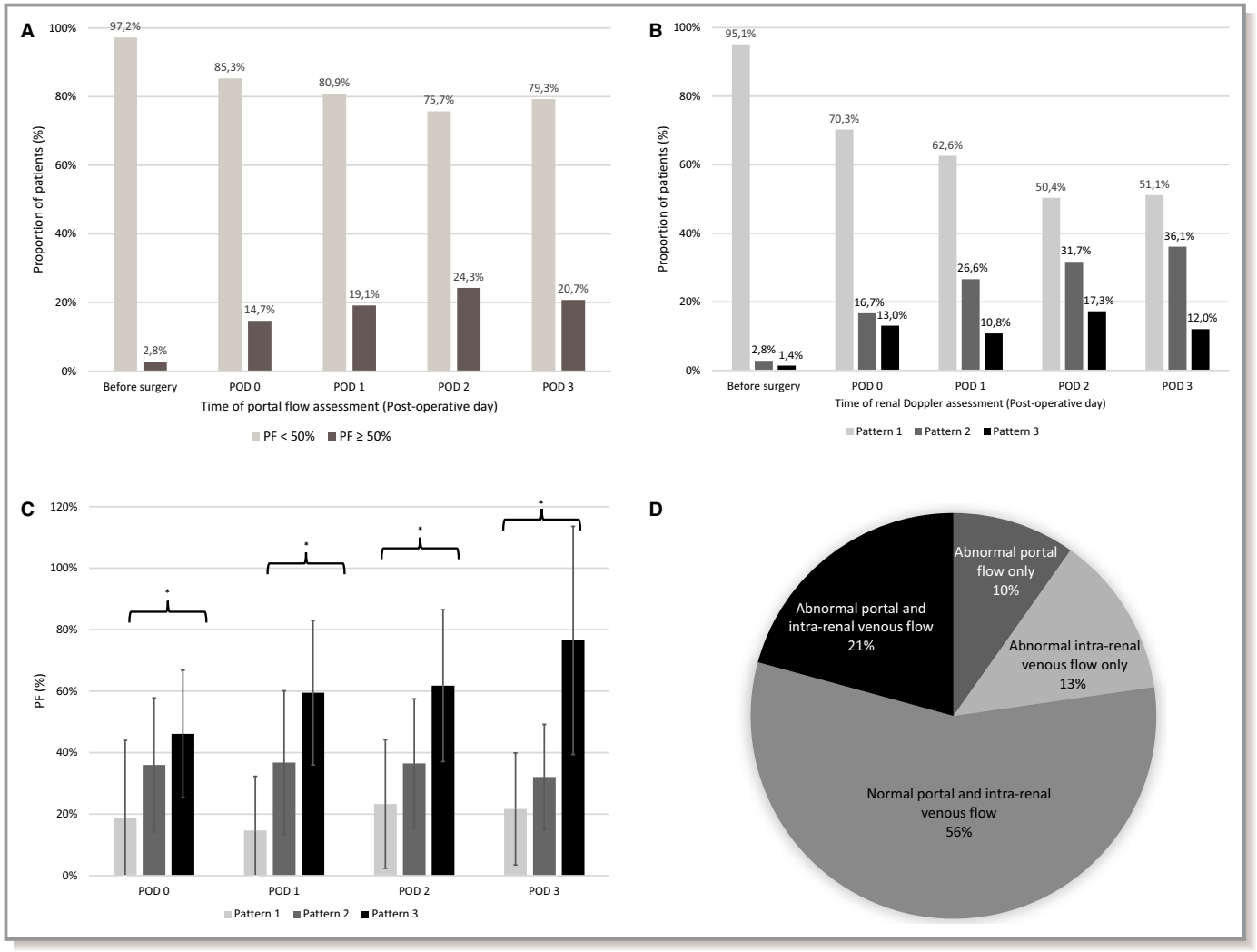

Figure 4. Portal and intrarenal venous flow during the perioperative period. A, Portal flow pulsatility (PF≥50%). B, Intrarenal venous flow patterns. C, Measured portal pulsatility fraction (PF) according to intrarenal flow patterns. D, Proportion of assessments showing concordance or discordance between abnormal portal flow (PF≥50%) or abnormal intrarenal venous patterns (Pattern >1) *Significant difference $P<0.05$. POD indicates postoperative day.

pressure ventilation, use of ventricular pacing, higher NT-pro-BNP measurements, higher measurements of IVC diameter, abnormal hepatic vein waveform (S<D), and higher renal RI (Table 4). Portal flow pulsatility was also associated with higher systolic pulmonary artery pressure, higher cumulative fluid balance, and lower diastolic arterial pressure. Additional information about portal and intrarenal Doppler performed before surgery in relationship with baseline characteristics are presented in Table S5.

Discussion

The aim of this study was to determine whether specific Doppler patterns found in the portal vein and in the interlobar veins of the kidney are associated with AKI, a frequent complication in cardiac surgery for which venous congestion could be a potential reversible causative factor. We observed an independent association with pulsatile portal flow and with severe alterations in intrarenal venous flow after accounting for the baseline risk of AKI. In addition, the introduction of these markers resulted in significant improvement in risk prediction compared with a model including preoperative risk factors and CVP measurements at ICU admission.

Considering that CVP measurements are currently the most common clinical tool used to evaluate venous congestion at the bedside, the present data suggest that adding portal and intrarenal venous flow Doppler lead to a better assessment of the impact of venous congestion on renal function. CVP measurements are commonly performed in the ICU setting but are subject to numerous technical caveats,[28–30] and important interobserver variability even among trained users.[31] Additionally, CVP measurements require a central venous catheter. While this procedure is done routinely in cardiac surgery patients, the central line is usually removed promptly to

Table 2. Echographic Parameters and AKI After Cardiac Surgery

	Any AKI (n=49)			Severe AKI (n=10		
	HR	CI	*P* Value	HR	CI	*P* Value
Pulsatile portal flow (PF ≥50%)	2.09	1.11–3.94	0.02	5.12	1.47–17.9	0.01
Alterations in intrarenal venous flow						
Pattern 1	1.00 (Ref)			1.00 (Ref)		
Pattern 2	1.29	0.62–2.68	0.50	3.34	0.82–13.61	0.09
Pattern 3	2.81	1.42–5.56	0.003	2.55	0.46–14.02	0.28
Renal resistive index						
Absolute value (per 0.01 elevation)	1.06	1.02–1.10	0.002	1.02	0.95–1.11	0.58
Change from baseline (per 0.01 change from baseline)	1.05	1.01–1.09	0.03	1.08	0.98–1.18	0.11

Univariable Cox proportional hazards models for the risk of acute kidney injury (AKI) were developed with the studied echographic parameters coded as segmented time-dependent covariates. CI indicates confidence interval; HR, hazard ratio; PF, pulsatility fraction.

minimize the risk of infection. As such, a noninvasive assessment of venous congestion using ultrasound has the added benefit of being possible without the need for invasive monitoring.

We found an association between portal flow pulsatility and alterations of intrarenal venous flow as previously proposed by Tang et al in patients with congestive heart failure.[7] While severe intrarenal flow alterations were more strongly associated with AKI than portal flow pulsatility, the success rate was lower for intrarenal venous flow despite adequate training because of the technical difficulty of the assessment. This suggests that portal flow assessment might be more realistically integrated into patients' care. However, it must be noted that in 10% of assessments, portal flow pulsatility was not associated with alterations in intrarenal venous flow. Other unknown factors may influence portal and intrarenal Doppler waveforms such as body habitus and intrathoracic pressure during positive pressure ventilation.[18,32] Consequently, portal flow pulsatility does not act as a perfect surrogate for severe alterations of intrarenal venous flow. Nevertheless, both markers were associated with higher NT-pro-BNP measurements, with higher IVC diameter and lower diastolic perfusion pressure.[16]

Renal congestion currently has no universally accepted definition. An increase in pressure in the renal vein leads to an acute reduction in the glomerular filtration rate and hypoxia of the renal cortex.[33–35] This hemodynamic phenomenon is likely to be exacerbated in the context of a variable degree of cardiac dysfunction in the perioperative period. In this setting, the organ perfusion gradient is hampered by both a reduction of cardiac output and an elevation of CVP from fluid overload and/or right ventricular dysfunction.[16,36] While these dynamic hemodynamic changes occurring rapidly may result in renal dysfunction, venous congestion can also refer to interstitial edema within the renal parenchyma.[37] According to the revised Starling equilibrium, interstitial edema is promoted by an increased hydrostatic capillary pressure in conjunction with an alteration of the endothelial glycocalyx.[38,39] The latter

Table 3. Multivariable Proportional Hazards Models for the Risk of AKI After Cardiac Surgery

	Portal Flow Pattern (PF≥50%)	Intrarenal Venous Flow Pattern	Change in Renal Resistive Index From Baseline* (HR for Each Increase of 0.01)
Echographic marker	2.00 (1.04–3.85) *P*=0.04	Pattern 1: 1.0 (reference) Pattern 2: 1.23 (0.58–2.60) *P*=0.59 Pattern 3: 2.62 (1.24–5.56) *P*=0.01	1.05 (1.01–1.09) *P*=0.03
AKI preoperative risk score[13]	1.25 (1.08–1.44) *P*=0.002	1.22 (1.05–1.42) *P*=0.009	1.27 (1.10–1.46) *P*=0.001
Surgery on thoracic aorta	2.76 (1.15–6.62) *P*=0.02	3.12 (1.27–7.59) *P*=0.01	2.52 (1.06–6.00) *P*=0.04
Previous cardiac surgery			1.92 (0.97–3.82) *P*=0.06

Multivariable Cox proportional hazards models for the risk of AKI were developed with the studied echographic parameters coded as segmented time-dependent covariates. Other known preoperative risk factors associated with AKI were selected by backward stepwise exclusion by the likelihood ratio method. AKI indicates acute kidney injury; HR, hazard ratio; PF, pulsatility fraction.

*Results for absolute values of renal resistive index are not presented because a significant interaction with AKI risk score was present ($P<0.05$).

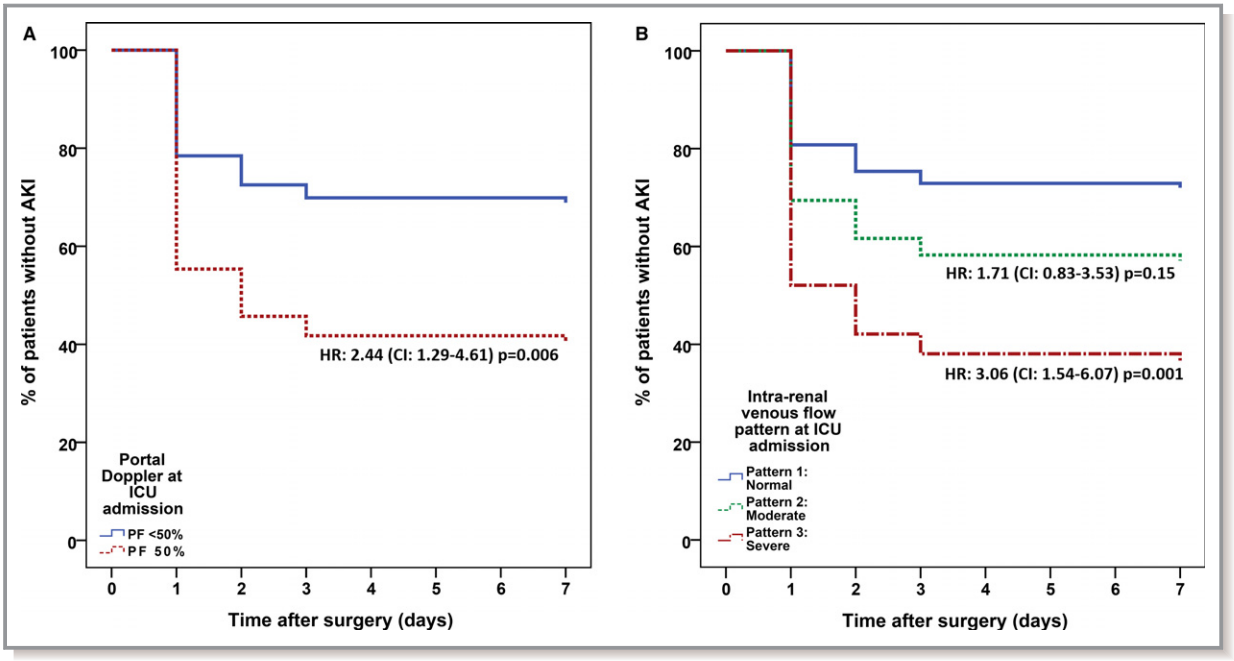

Figure 5. Acute kidney injury (AKI)–free survival according to (A) portal Doppler patterns and (B) intrarenal venous flow patterns at the intensive care unit (ICU) admission after cardiac surgery. The association between each ultrasound finding and AKI was determined by univariate Cox regression and the results are presented adjacent to the survival curves as hazard ratio (HR) with 95% confidence intervals (CI). PF indicates pulsatility fraction of the portal vein.

is a structure composed of glycated proteins and lipids creating a local oncotic barrier to fluid transfer.[38] The endothelial glycocalyx is altered in the setting of cardiac surgery, leading to increased vascular permeability.[40–42] Because the kidney is an encapsulated organ, the interstitial pressure might rise rapidly if interstitial edema develops.[43,44] An increase in interstitial pressure leads to a reduction of the glomerular filtration gradient.[45] Avoiding high capillary

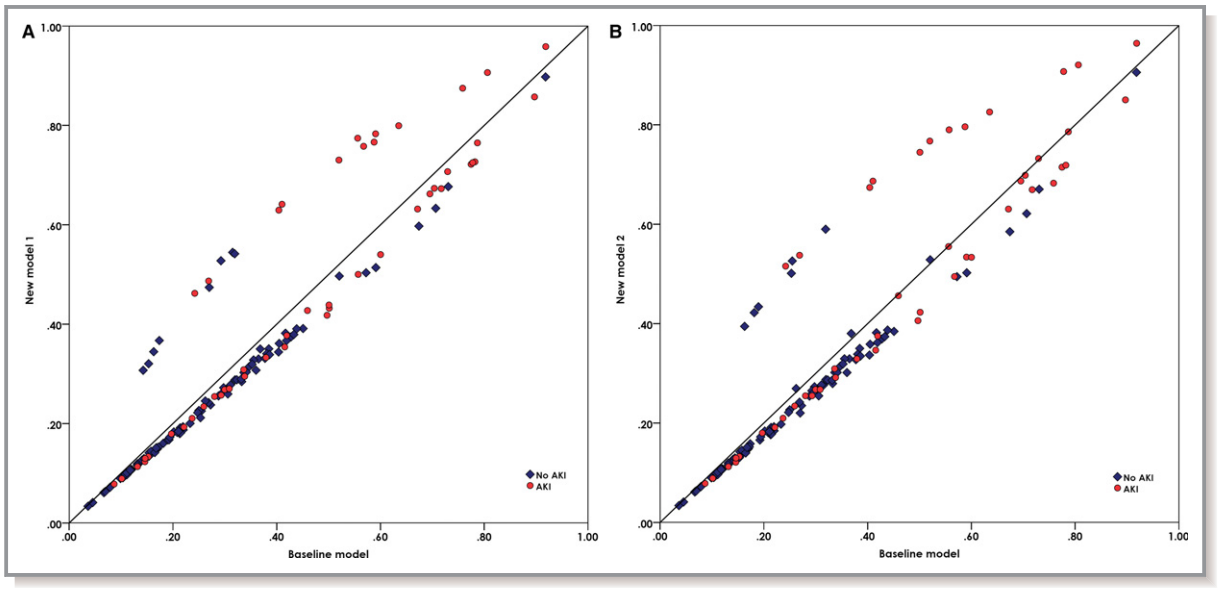

Figure 6. Reclassification plots illustrating the added value of the studied ultrasound markers compared with a baseline risk prediction model of acute kidney injury (AKI). A, New model with the addition of portal flow pulsatility at ICU admission. B, New model with the addition of severe intrarenal venous flow alteration at ICU admission. AKI cases above the reference line and non-AKI cases below the reference are appropriately reclassified in the new model. For both analyses, the baseline model was composed of preoperative risk factors (AKI risk score[13] and intervention on thoracic aorta) and central venous pressure measurement at ICU admission. ICU indicates intensive care unit.

Table 4. Association Between the Studied Echographic Markers of Venous Congestion and Clinical Parameters at the Time of Assessment

	Portal Flow PF ≥50% (560 Assessments in 145 Patients)			Discontinuous Intrarenal Venous Flow (Pattern 2 or 3) (550 Assessments in 145 Patients)			Absence of Systolic Intrarenal Venous Flow (Pattern 3) (550 Assessments in 145 Patients)		
	OR	CI	*P* Value	OR	CI	*P* Value	OR	CI	*P* Value
Hemodynamic and clinical parameters									
CVP (per 10 mm Hg increase)	2.08	(0.96–4.53)	0.06	1.82	(0.98–3.39)	0.06	2.27	(0.76–6.82)	0.14
Systolic PAP (per 10 mm Hg increase)	2.23	(1.45–3.42)	<0.001	Day 0: 2.62 Day 1: 0.92 Day 2: 5.32	(1.52–4.53) (0.49–1.74) (0.31–65.40)	0.001 0.80 0.27	1.36	(0.76–2.41)	0.30
Diastolic PAP (per 10 mm Hg increase)	1.52	(0.80–1.12)	0.20	Day 0: 2.02 Day 1: 0.53 Day 2: 0.17	(0.99–4.12) (0.15–1.74) (0.01–1.88)	0.05 0.29 0.15	0.91	(0.18–4.53)	0.91
Systolic arterial pressure (per 10 mm Hg increase)	0.94	(0.80–1.12)	0.49	0.96	(0.84–1.08)	0.50	0.90	(0.73–1.11)	0.34
Diastolic arterial pressure (per 10 mm Hg increase)	0.68	(0.50–0.91)	0.01	0.76	(0.60–0.96)	0.02	0.69	(0.47–1.01)	0.06
Diastolic perfusion pressure (per 10 mm Hg increase)	0.59	(0.39–0.90)	0.01	0.70	(0.53–0.95)	0.02	0.92*	(0.52–4.41)	0.01
Heart rate (per 10 bpm increase)	0.78	(0.65–0.94)	0.009	0.81	(0.70–0.92)	0.001	0.71	(0.57–0.90)	0.003
Cardiac index (per 1 L/min per m^2 increase)	0.63	(0.22–1.78)	0.38	0.52	(0.24–1.10)	0.09	2.14*	(0.74–6.20)	0.16
Cumulative fluid balance (per L of increase)	1.27	(1.07–1.50)	0.007	1.07	(0.93–1.23)	0.34	1.09	(0.92–1.29)	0.34
Positive pressure ventilation	6.72	(1.89–23.95)	0.003	4.02	(1.96–8.26)	<0.001	2.66	(0.96–7.40)	0.06
Ventricular pacing	3.71	(1.66–8.27)	0.001	Day 0: 5.32 Day 1: 5.47 Day 2: 1.71 Day 3: 1.28	(1.92–14.78) (1.82–16.42) (0.53–5.50) (0.37–4.42)	0.001 0.002 0.37 0.70	2.84	(0.99–8.17)	0.05
Echographic parameters									
IVC diameter (per 1-cm increase)	1.76	(1.08–2.87)	0.02	2.09	(1.38–3.18)	0.001	2.09	(1.38–3.18)	0.001
Abnormal hepatic vein waveform (S<D)	17.36	(7.15–42.18)	<0.001	3.85	(2.48–5.95)	<0.001	13.45	(6.54–27.69)	<0.001
Renal resistive index (per 0.1 increase)	1.76	(1.18–2.63)	0.005	1.54	(1.17–2.02)	0.002	1.50	(0.97–2.32)	0.07
Laboratory parameters									
Log NT-pro-BNP (per 1 of increase)	10.7	(4.16–27.4)	<0.001	6.92	(2.81–17.05)	<0.001	10.36	(3.86–27.85)	<0.001

Generalized estimating equations analysis was performed using a logistic link function. The odds ratio (OR) presented for each variable is adjusted for the time of assessment, which was included as a factor in the models. bpm indicates beats per minute; CI, confidence interval; NT-pro-BNP, N-terminal-pro-B-type natriuretic peptide
*Linearity assumption could not be demonstrated, OR is presented for perfusion pressure ≥40 mm Hg and for cardiac index <2.2 L/min per m^2.

pressure from venous hypertension may minimize the development of renal interstitial edema in the perioperative period.

Our group previously described cases where the use of inhaled drugs to induce pulmonary vasodilatation in patients with right ventricular dysfunction resulted in a reduction of the portal flow variations in the postoperative period[46] and the normalization of intrarenal venous flow during off-pump cardiac surgery.[47] Additionally, Nijst et al demonstrated that fluid loading in patients with congestive heart failure resulted in the appearance of a discontinuous pattern of intrarenal venous flow and reduced diuretic response.[48] In order to prevent or treat congestive AKI in the setting of a critically ill cardiac patient, a strategy based on the normalization of portal vein flow and intrarenal venous flow might be considered for future trials. This approach might involve combining inhaled pulmonary vasodilators, in the setting of right ventricular dysfunction, and the induction of a negative fluid balance using diuretics in patients with fluid overload.

This study has some limitations. This is a single-center study that was performed only in cardiac surgery patients. Its results should not be generalized to other critically ill patients. Echocardiographic assessment of LVEF and right ventricular function was not performed at the time of assessment. However, this issue is being explored in another study by our group (NCT02658006). While multivariable analysis was performed, residual confounding is possible, and the number of variables included in the models were limited by the number of events. In addition, no validation sample was available to confirm the improvement of the risk prediction of AKI. Finally, a cause–effect relationship cannot be inferred by the available data because both the consistency and the coherence of this association will need to be further explored in subsequent studies.

Conclusion

In summary, we have shown using time-dependent models that both portal flow pulsatility and severe intrarenal flow alteration are independently associated with subsequent AKI in cardiac surgery patients. In comparison with other clinical tools to evaluate venous congestion, these Doppler features are available at minimal cost, are noninvasive, are rapidly assessed at a good success rate, and can be easily repeated at the bedside. Whether a personalized treatment strategy aimed at preventing or reversing portal and intrarenal flow alterations based on the clinical context could prevent AKI and other complications in cardiac surgery patients should be investigated.

Acknowledgments

We sincerely thank Anne-Marie Claveau (Medicine Student) for her help in data collection, Denis Babin (Research Assistant) for his help in manuscript preparation, and Anna Nozza (Biostatistician) for the sample size estimation.

Sources of Funding

Beaubien-Souligny has received salary support from Fonds de Recherche du Québec en Santé (FRQS). The costs for laboratory measurements were covered by the SQIC-Alliance BMS-Pfizer grant on heart failure and renal failure from Société Québécoise de l'Insuffisance Cardiaque (SQIC). Denault is supported by the Montreal Heart Institute Foundation and the Richard Kaufman Endowment Fund in Anesthesiology and Critical Care.

Disclosures

Denault is on the Speaker bureau for CAE Healthcare and Masimo. The remaining authors have no disclosures to report.

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Supplemental Material

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Table S1. Inter-observer agreement and variability for the studied echographic parameters. Observer 1 performed ultrasound assessments during the study and interpreted the Doppler tracings after the study, Observer 2 performed ultrasound assessments during the study, Observer 3 is a clinical radiologist with extensive experience in renal Doppler.

		Observer 1 / Observer 3				Observer 2 / Observer 3				Observer 1 / Observer 2			
		Mean difference (±SD) / % of agreement	ICC (CI) / κ	p-value	n	Mean difference (±SD) / % of agreement	ICC (CI) / κ	p-value	n	Mean difference (±SD) / % of agreement	ICC (CI) / κ	p-value	n
Healthy volunteers / outpatients	Renal RI	0.033 (±0.029)	0.931 (0.887-0.958)	<0.001	51	0.045 (±0.035)	0.777 (0.561-0.886)	<0.001	48				
	Renal venous flow patterns	All patterns were continuous											
Repeated assessment during the study	Portal PF									0.011 (0.010)	0.954 (0.902-0.979)	<0.001	5
	Renal RI									0.030 (±0.023)	0.994 (0.946-0.999)	<0.001	28
	Renal venous patterns									100%	*		25
Repeated analysis of the Doppler tracing after the study	Portal PF	0.062 ± 0.081	0.953 (0.818-0.986)	<0.001	14	0.099 ± 0.080	0.911 (0.587-0.974)	<0.001	14	0.061 ± 0.062	0.951 (0.858-0.983)	<0.001	15
	Renal RI	0.018 ± 0.025	0.956 (0.930 – 0.972)	<0.001	75	0.025 ± 0.023	0.943 (0.910-0.964)	<0.001	75	0.026 ±0.022	0.960 (0.937-0.974)	<0.001	82
	Renal venous patterns	93.8%	Kappa = 0.868	<0.001	65	87.1%	Kappa = 0.738	<0.001	70	91.3%	Kappa = 0.826	<0.001	69

RI: resistive index, PF: pulsatility fraction, ICC: interclass correlation coefficient, κ: cohen's kappa statistic, CI: confidence interval, SD: standard deviation

Table S2. Associations between clinical parameters and the risk of AKI after cardiac surgery.

N=145	HR (CI)	p
Pre-operative risk factors		
Female sex	0.52 (0.24-1.11)	0.09
Age (for every year above 60)	1.01 (0.97-1.04)	0.74
Pre-operative risk prediction score[1] (for a 10% increase in risk)	1.25 (1.09-1.44)	0.001
Hypertension	1.32 (0.56-3.09)	0.53
Diabetes	1.34 (0.76-2.37)	0.31
Chronic obstructive pulmonary disease	1.61 (0.82-3.16)	0.16
Left ventricular ejection fraction ≤40%	1.19 (0.62-2.28)	0.62
Mitral regurgitation (>1 grade) before surgery	0.81 (0.42-1.55)	0.52
Tricuspid regurgitation (Grade >1) before surgery	1.77 (0.94-3.35)	0.08
Pulmonary hypertension (mPAP ≥ 25) before surgery	1.04 (0.52-2.08)	0.92
Peripheral vascular disease	1.54 (0.72-3.27)	0.27
Coronary disease	1.21 (0.62-2.36)	0.60
Previous cardiac surgery	1.91 (0.97-3.74)	0.06
Recent infarct (90 days)	0.59 (0.21-1.63)	0.31
Use of ACEi or ARB before surgery	1.09 (0.55-2.18)	0.81
Use of loop diuretics before surgery	1.82 (0.89-3.73)	0.10
Contrast exposure < 7 days before surgery	1.58 (0.38-6.49)	0.53
eGFR before surgery <60 mL/min	1.30 (0.71-2.39)	0.40
Intra-operative and post-operative risk factors		
Valvular procedure	1.61 (0.82-3.15)	0.20
Multiple procedures	1.37 (0.78-2.40)	0.27
Surgery on thoracic aorta	2.20 (0.93-5.19)	0.07
CPB length (per h)	1.30 (0.94-1.80)	0.11
Hourly dose of norepinephrine during surgery (per mg/h)	1.02 (0.98-1.06)	0.42
Blood transfusions during surgery	1.09 (0.39-3.04)	0.86
Right ventricular dysfunction at the end of surgery	2.61 (1.30-5.25)	0.007
CVP at the end of surgery	1.04 (1.01-1.08)	0.02
Diastolic PAP at the end of surgery	1.03 (0.98-1.08)	0.28
Systolic PAP at the end of surgery	1.01 (0.98-1.04)	0.67
mPAP/MAP ratio at the end of surgery	2.73 (0.20-37.21)	0.45
Perfusion pressure (MAP-CVP) at the end of surgery	1.00 (0.76-1.28)	0.93
Vasopressor support at ICU admission		
- No vasopressor support	1.0 (ref)	
- 1 agent	1.01 (0.51-2.0)	0.99
- 2 agents	1.92 (0.90-4.11)	0.09
- 3 agents	2.09 (0.70-6.20)	0.19
Other time dependant variables (multiple measurements)		
IVC diameter > 2.0 cm	2.35 (1.14-4.85)	0.02
NT-pro-BNP (per 1 log increase	2.06 (1.09-3.91)	0.03

Univariable Cox proportional regression models for the risk of acute kidney injury (AKI). Legend: CVP: central venous pressure, eGFR: estimated glomerular filtration rate, MAP: mean arterial pressure, PAP: pulmonary artery pressure

Table S3. Multivariable Cox model for the risk of acute kidney injury after cardiac surgery according of pre-operative risk and assessment at ICU admission.

	Portal Doppler			Intra-renal venous Doppler		
	HR	**CI**	**p**	**HR**	**CI**	**p**
Echographic marker at ICU admission	2.03	1.02-4.06	0.04	Pattern 1: 0 (Reference) Pattern 2: 1.42 Pattern 3: 2.44	0.63-3.20 1.12-5.29	0.40 0.02
Pre-operative AKI risk score*	1.02	1.002-1.03	0.03	1.01	0.998-1.03	0.08
CVP at ICU admission	1.10	1.01-1.19	0.04	1.10	1.01-1.20	0.03

*Pre-operative AKI risk score by Birnie et al.[1]

Table S4. Multivariable Cox model for the risk of acute kidney injury after cardiac surgery according to inferior vena cava (IVC) diameter, portal Doppler and intra-renal venous Doppler ultrasound as time-dependant variables.

	HR	CI	p
Portal vein Doppler			
Portal flow pulsatility	1.98	1.06-3.70	0.032
IVC >2cm	2.18	1.05-4.51	0.036
Intra-renal venous flow patterns			
Pattern 1	0 (reference		
Pattern 2	1.13	0.54-2.37	0.75
Pattern 3	2.44	1.21-4.90	0.013
IVC >2 cm	2.02	0.96-4.25	0.07

Table S5. Association between portal flow pulsatility fraction (PF) and clinical, hemodynamic and echographic parameters before surgery.

			Portal vein flow		Intra-renal venous flow	
		n	Median PF (IQR)	p-value	% Discontinuous renal flow	p-value
LVEF	≥50%	101	13.3 (0.0; 20.6)	0.924	7 (6.9%)	0.614
	<50%	43	14.2 (0.0; 21.9)		2 (4.7%)	
Mitral insufficiency	Grade 0 or 1	98	12.2 (0.0; 19.6)	0.095	5 (5.1%)	0.266
	Grade >1	40	15.3 (0.0; 28.2)		3 (10.0%)	
Tricuspid insufficiency	Grade 0 or 1	109	12.1 (0.0; 19.4)	<0.001	6 (5.5%)	0.214
	Grade >1	26	25.7 (0.0; 39.3)		3 (11.5%)	
eGFR	≥60 mL/min	107	10.4 (0.0; 20.5)	0.026	3 (2.8%)	0.003
	<60 mL/min	37	16.2 (0.0; 30.9)		6 (16.2%)	
	<30 mmHg	64	15.1 (0.0; 23.7)		6 (9.4%)	
NYHA functional classification	1	27	0 (0.0; 22.8)	0.112	0 (0%)	0.460
	2	48	0 (0.0; 17.0)		3 (6.3%)	
	3	55	17.0 (0.0; 23.1)		5 (9.1%)	
	4	13	15.9 (0.0; 31.50		1 (7.7%)	

LVEF: left ventricular ejection fraction, eGFR: estimated glomerular filtration rate, NYHA: New York Heart Association, RV: right ventricular.

Supplemental Reference:

1. Birnie K, Verheyden V, Pagano D, Bhabra M, Tilling K, Sterne JA, Murphy GJ. Predictive models for kidney disease: Improving global outcomes (kdigo) defined acute kidney injury in uk cardiac surgery. *Critical care*. 2014;18:606