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Association between hepatic venous flow and adverse outcomes after cardiac surgery

PhD thesis

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2. List of abbreviations

ACC: Aortic cross-clamp

AKI: Acute kidney injury

ALAT: Alanine aminotransferase

ASAT: Aspartate aminotransferase

AVR: Aortic valve replacement

BUN: Blood urea nitrogen

CABG: Coronary artery bypass graft

COPD: Chronic obstructive pulmonary disease

CPB: Cardiopulmonary bypass

CRP: C-reactive protein

CVP: Central venous pressure

EF: Ejection fraction

EuroSCORE: European System of Cardiac Operative Risk Evaluation

FIO2: Fraction of inhaled oxygen

GFR: Glomerular filtration rate

GGT: Gamma-glutamyl transferase

IABP: Intracortical balloon pump

ICU: Intensive Care Unit

INR: Internationally normalized ratio

IQR: Interquartile range

IVC: Inferior vena cava

KDIGO: Kidney Disease: Improving Global Outcomes

LA: Left atrium

LV: Left ventricle

LVEDD: Left ventricle end-diastolic diameter

LVESD: Left-ventricle end-systolic diameter

MELD: Model for End-stage Liver Disease

MVR: Mitral valve replacement

NO: Nitric oxide

NYHA: New York Heart Association System

OPCAB: Off-pump coronary artery bypass

PEEP: Positive end-expiratory pressure

POCUS: Point-of-care ultrasound

POP: Postoperative period

RA: Right atrium

RASA: Right atrium systolic area

RBC: Red blood cell

RCT: Randomized controlled trial

ROC: Receiver operating characteristic

ROS: Reactive oxygen species

RR: Respiratory rate

RV: Right ventricle

STROBE: Strengthening the Reporting of Observational studies in Epidemiology

TAPSE: Tricuspid Annular Plane Systolic Excursion

TEE: Transesophageal echocardiography

TTE: Transthoracic echocardiography

TV: Tidal volume

VExUS: Venous excess ultrasound

VIS: Vasoactive-inotropic score

VTI: Velocity-time integral

v max: Maximal velocity

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3. Introduction

1. Fluid balance and fluid overload in critically ill patients

The accurate estimate of hemodynamic conditions is crucial in guiding the clinical management of the surgical patient in the postoperative period or during the long-term intensive care unit stay. (1) New protocols and guidelines put more emphasis on bolus and restrictive continuous fluid administration. This approach is ideal for critically ill patients as well, in whom increased endothelial permeability makes this approach more relevant. Malbrain uses the "R.O.S.E. conceptual model (Resuscitation, Optimization, Stabilization, Evacuation)", which summarizes a dynamic approach to fluid therapy, maximizing benefits and minimizing harms. (2)

Progressing heart failure comes with endothelial dysfunction. According to recent studies, it may result from increased oxidative stress and activation of the adrenergic and the renin-angiotensin systems and from the production of inflammatory cytokines, which contribute to reduced bioavailability of nitric oxide (NO). Oxidative stress, determined by excess production of reactive oxygen species and impairment in the antioxidant defense, is responsible for both the decline of diffusible NO and the decrease in the concentration of essential co-factors of NO synthases. This leads to the compromitted NO bioavailability and reduced vasodilatation. This leads to endothelial dysfunction. (3) (4)

Personalized fluid management is particularly important in cardiac surgery patients, especially those with heart failure, prolonged operative and aortic cross-clamp (ACC) time, or renal, pulmonary, or hepatic insufficiency.
A large amount of data in the international literature indicates that postoperative fluid overload in postoperative cardiac intensive care is associated with prolonged mechanical ventilation, higher vasoactive, inotropic support, and mortality. (5) (6) (7)

Fluid overload recognition and assessment require an accurate documentation of intakes and outputs; yet there is a wide difference in how it is evaluated. (8) There are several methods to estimate fluid status; however, most of the tests currently used are inaccurate. Heart failure is one of the main cardiac diseases leading to intensive care unit (ICU) admission (18.6%). (9) Organ congestion is a classical feature of heart failure that is caused by abnormal fluid redistribution into the extravascular space. In addition, during and after cardiac surgery the infusion of considerable amounts of intravenous fluids may be necessary due to cardiopulmonary bypass (CPB) induced inflammation, blood loss, myocardial depression, rhythm disturbances, and impaired vascular tone. Therefore, additional iatrogenic fluid overload is more common at ICU admission of these patients. Furthermore, patients with heart failure often suffer from extravascular over-hydration due to fluid re-distribution during intravascular fluid underload. This may lead to the administration of more fluid for resuscitation purposes, and this leads to more severe organ dysfunction (heart, lung, and kidneys), leading to a vicious circle of organ failure. Among calculating fluid balance (input and output) and checking hemodynamic markers (blood pressure, central venous pressure) protocols using ultrasound examinations are gaining more attention.

Inferior vena cava (IVC) measurements are commonly used by intensive care and emergency practitioners at point-of-care ultrasound (POCUS) examinations to predict fluid status. (10) (11-15) Using IVC measurements only can lead to inaccurate results, as they do not reflect the preload status of the patient's left ventricle accurately. The IVC can also be dilated in conditions such as tricuspid or mitral regurgitation, increased intrathoracic pressure with mechanical ventilation, increased right atrial pressure in pulmonary embolism or pulmonary hypertension, and in increased intra-abdominal pressure. Also, it shows a wide range of individual differences, especially in athletes. (16) Several recent protocols, such as the venous excess ultrasound examination (VExUS), use hepatic, portal, and renal measurements for Doppler ultrasound analysis. (17) The renal venous Doppler pattern is seen as a continuous monophasic flow. As venous congestion increases, there is a decrease of the systolic component of the wave with progression to a biphasic pattern and later a complete absence of systolic flow can be seen. The portal venous flow is normally monophasic with little variation. As venous

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congestion increases, increasing amounts of pulsatility can be detected in the pattern. (18-20)

Several data in the literature suggest that abnormal hepatic, renal, and portal flows are good indicators of abnormal fluid shifts. Bhardwaj et al. evaluated their modified VExUS protocol in predicting AKI in patients with cardiorenal syndrome. They found a strong correlation between grades of VExUS and the stages of AKI. (11, 21)

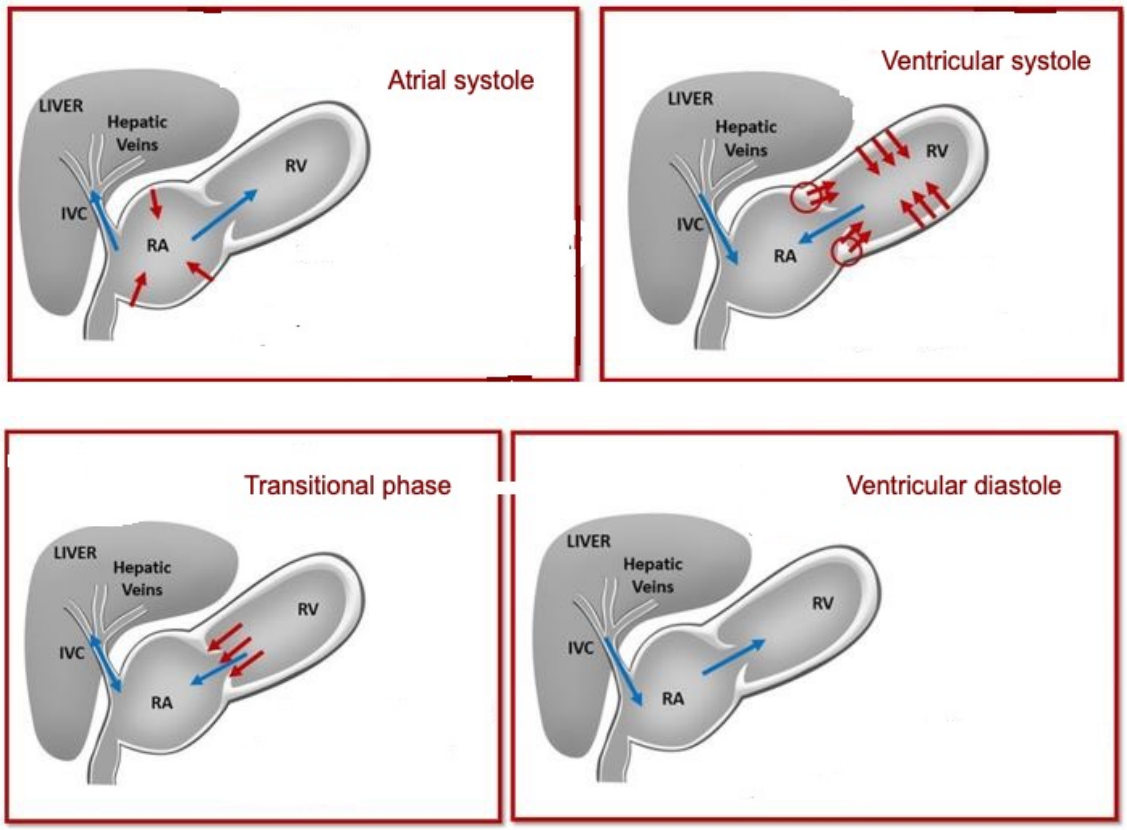

Figure 1 A and B: Connection between the right ventricle, atrium, and the liver in case of right heart failure (own recording and figure) (5, 22)

2. Hepatic venous flow and abdominal congestion

Abdominal complications are well-known phenomena among cardiac surgery patients. Dong et al. observed over 2000 cardiac surgery cases, out of which 33 (1.4%) developed abdominal complications postoperatively, including cases of paralytic ileus, gastrointestinal hemorrhage, gastroduodenal ulcer perforation, acute calculus cholecystitis, hepatic dysfunction, and ischemic bowel diseases. (23)

The latest approaches are focusing on abdominal congestion postoperatively. Abnormal flow patterns in abdominal organs are correlated with elevated right-atrial pressure, thus providing additive information about end-organ congestion. In brief, congestion indicates poor outcomes in heart failure patients; therefore, a comprehensive assessment of venous congestion has prognostic significance**.** (24)

The relationship between the worse outcomes of cardiac diseases and liver dysfunction has been a well-recognized and described phenomenon for several decades. (25, 26) "Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)" showed in 2679 heart patients that abnormal total bilirubin, direct bilirubin, alkaline phosphatase, and albumin levels were predictive factors of the NYHA class (New York According to the Heart Association), the reduction of the ejection fraction, and the development of diabetes mellitus. (27)

The severity of liver congestion alone affects mortality in heart patients. Destruction of the zona pellucida caused by stasis leads to a fistula between the choledochal ducts and the sinusoids. Clinical symptoms can be poor, and in advanced liver failure we observe reduced coagulation factor and albumin synthesis. (28) (29)

In perioperative situations, many factors can influence hypoperfusion, hypoxia, or stagnation in the liver. The most important of these are the length of cardiopulmonary bypass, post-bypass low stroke volume, as well as the use of vasoactive, inotropic, immunosuppressive drugs, and blood products. Influencing factors that cannot be ruled out are mechanical circulatory support devices and the degree of resistance of the right ventricle and pulmonary vessels. It is also a known phenomenon that liver cirrhosis affects the hemodynamic parameters and leads to arterial vasodilatation. In addition, it also changes the fluid and electrolyte balance, which has a negative effect on the physiological regulation of circulation. (30)

We examined the hepatic venous Doppler ultrasound profile closely. There are three main hepatic veins—left, middle, and right—that separate the liver along craniocaudal planes. In 50% of cases, a well-defied right inferior hepatic vein accompanies the right hepatic vein. In about 70% of people, the left and middle hepatic veins merge to form a single vein before entering the IVC. We examined this common vein, right prior to its inflow into the IVC. The normal hepatic vein waveform has four components: a retrograde A

wave, an antegrade S wave, a transient V wave (which can be antegrade, retrograde, or neutral, but mainly retrograde), and an antegrade D wave.

The A wave corresponds to atrial contraction. With the tricuspid valve open, blood is pushed in two directions: antegrade toward the right ventricle and retrograde toward the IVC and into the hepatic veins. This results in a retrograde wave measured over the hepatic veins. As ventricular systole commences, the tricuspid valve closes and the retrograde velocity toward the hepatic veins begins to decrease and approach the baseline. During ventricular systole, not only the ventricular walls contract to push blood into the outflow tract, but there is also a movement of the tricuspid valve annulus toward the cardiac apex. These actions create a relative negative pressure in the atrium, causing antegrade blood flow out of the liver and into the heart during the S wave. In the normal heart, the largest amount of antegrade blood flow is during this phase. The V wave corresponds to atrial overfilling. As the ventricular contraction becomes less intense and the closed tricuspid valve begins to return to its original position, the atrium fills and blood flow velocity toward the heart decreases. The D wave begins as the tricuspid valve opens. During cardiac diastole, the right atrium and ventricle fill passively, with the antegrade flow of blood from the liver into the heart. In the normal patient, the velocity of this passive flow is almost always lower in magnitude than the velocity during the S wave.

There are a few standard differential diagnostic questions we must ask to analyze hepatic venous flow. We used the method applied by Scheinfeld et al. (31)

The first question we need to examine on the flow profile is whether we see any flow at all, and if so, whether it is in the right direction. If there is no flow or only retrograde flow can be seen, hepatic vein obstruction, such as Budd-Chiari syndrome, can be clearly concluded. Turbulent flow can be seen if the obstruction is not complete. If the flow is correct, its regularity must be checked. In the case of monophasic waves or a completely suppressed pattern, we should think primarily of liver tissue damage. This could be fatty liver, cirrhosis, or malignity. If healthy phaticity is observed, the last step is to compare the magnitude of the D and S waves.

Normally, the S wave is greater than or equal to the D. This is because the strong systolic movement of the tricuspid annulus toward the apex of the heart causes a large anterograde flow toward the heart. We can see a deviation from this in cardiac pathologies when the

right side of the heart does not function properly, such as in tricuspid regurgitation, and in this case the diastolic anterograde flow will be greater than the systolic one.
If we take a closer look at the pathophysiology of these conditions, we can see that during atrial systole, the atrium contracts and simultaneously pumps blood into the ventricle and back toward the liver, and this can be seen as a small retrograde A wave on the Doppler ultrasound image of the hepatic veins. During ventricular systole, the ventricle contracts and the tricuspid annulus moves towards the apex of the heart, as has been mentioned above. However, because tricuspid regurgitation exists, blood flows retrograde into the atrium, vena cava, and liver following the flow path. This causes a decrease in the S wave or can even turn it retrograde in the liver. When the ventricles relax and the annulus returns to its original position, blood flows from the atrium again in a retrograde direction towards the liver, and this results in a retrograde V wave. Finally, during diastole, when the myocardium is relaxed and the tricuspid valve is open, blood passively flows from the liver into the right atrium, and this appears as a large, only anterograde D wave. (32)
The picture of right heart failure is similar to tricuspid regurgitation. A slightly enlarged A wave may appear because of the increased backflow, since the abnormal right ventricle cannot adapt to the full atrial anterograde flow. These abnormalities have been observed since the 1980s. (33) (34)

We can divide the waves into retrograde (A and V) and anterograde (S and D) subgroups. If we observe these waves regarding the fluid balance, we can see in the normal hepatic venous blood flow waveform that the amplitude of the systolic component is higher than that of the diastolic component. For mild venous congestion, the amplitude of the systolic component is lower than that of the diastolic component. In severe congestion, there is a retrograde systolic component (opposite to the diastolic component). (35) (36, 37)

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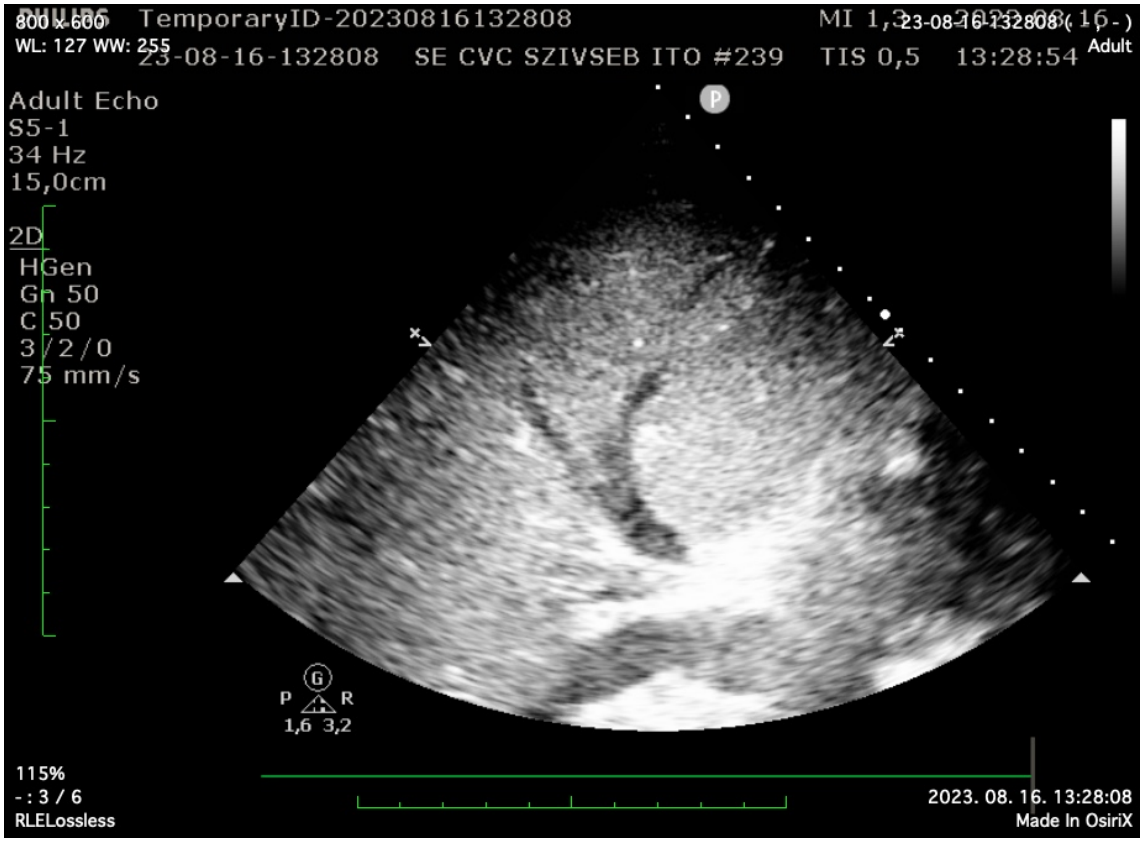

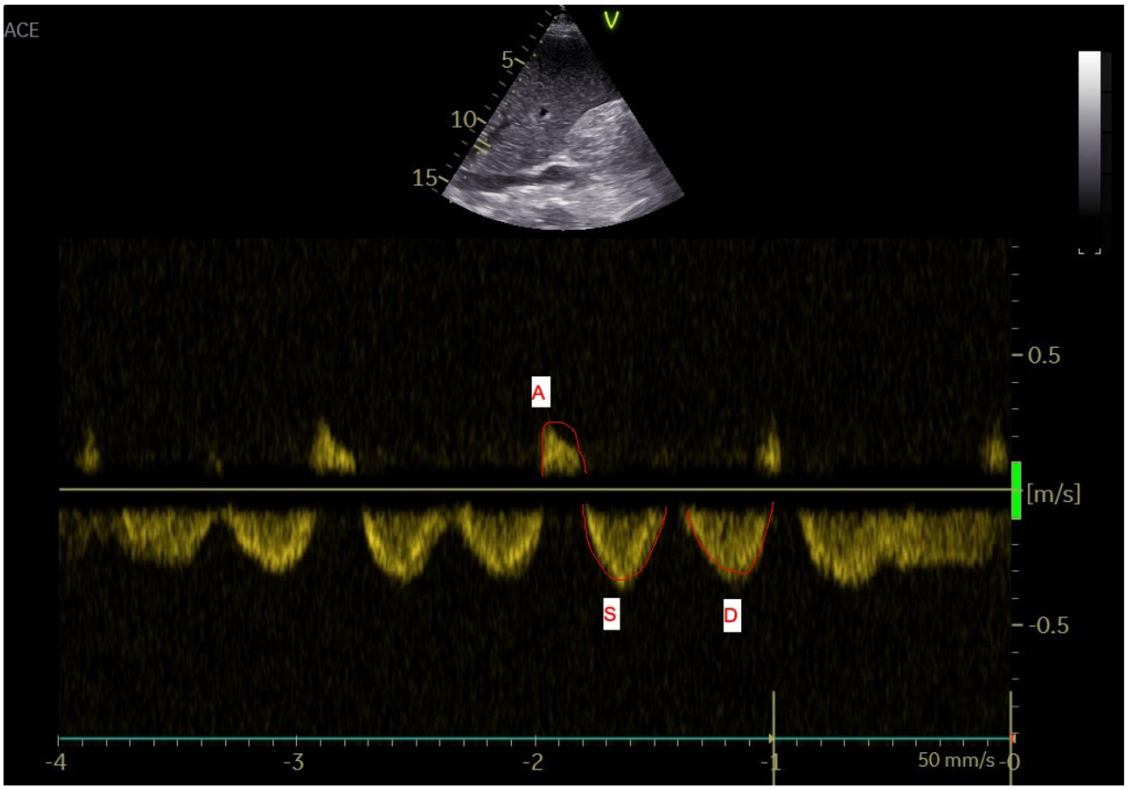

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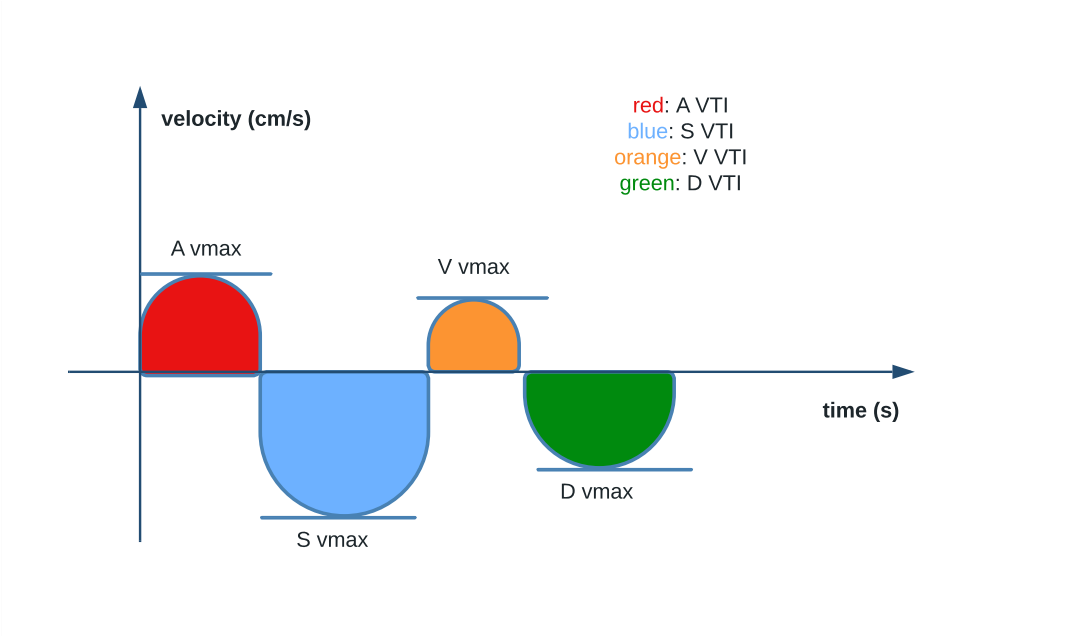

Figure 2 A and B: Hepatic venous flow (own recording and figure) (5, 22)

3. Postoperative right ventricle dysfunction, congestion, and acute kidney injury after cardiac surgery

Assessment of right ventricular (RV) function is crucial since RV failure with a reduced cardiac output (CO) is associated with compromised outcome in cardiac surgery. (38) Right Ventricular (RV) output mostly derives from longitudinal shortening in normal hearts. However, following even uncomplicated cardiac surgery with preserved RV function, a significant and sustained decrease in longitudinal contraction has been observed. (39) RV dysfunction leads to systemic congestion.

Recent studies have recognized that increased renal backpressure caused by venous congestion is the major pathophysiological mechanism of renal dysfunction in postoperative cardiorenal syndrome. The systemic congestion generates increased renal venous pressure and reduces the arteriovenous gradient over renal circulation and thereby impairing renal blood flow. Moreover, independent from renal blood flow, increased renal venous pressure leads to renal parenchymal congestion, resulting in increased

interstitial pressure, which may compress all capillary and renal tubules, thereby reducing GFR in a physical way. (40) Acute kidney injury is a clinical syndrome manifested by rapid decline in kidney function and subsequent dysregulation of body electrolytes and volume, as well as abnormal retention of nitrogenous waste. The widely accepted Kidney Disease: Improving Global Outcome (KDIGO) definition of AKI is based on the change of serum creatinine and urine output: (41)

By the definition using creatinine stage 1 AKI means 1.5-1.9 times the baseline value or more than 0.3 mg/dL creatinine increment, stage 2 AKI 2-2.9 times, stage 3 AKI is more than 3 times increment or more than 4 mg/dL value. By urine output stage 1 means less than 0.5 ml/kg/h for 6-12 hours, over 12 hours is stage 2, and stage 3 means less than 0.3 ml/kg/h over 24 hours or 12 h anuria. (42)

Perioperative AKI is common and is associated with serious morbidity and mortality after cardiac surgery. The pathophysiology behind it is multifactorial. These include genetic predisposition, nephrotoxins, cardiopulmonary bypass (CPB) induced hemolysis, ischemic-reperfusion injury, complexity of cardiac surgery, oxidative stress, and inflammation. (43)

Examining the preoperative factors, advancing age is associated with decrease in renal function and estimated GFR, compromising normal renal physiology and increasing inclination to postoperative AKI. Furthermore, studies have found that women are more prone to develop AKI than men. (44)

Patients with comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, congestive heart failure, and chronic kidney disease (CKD) are prone to develop kidney injury following cardiac surgery. This may be due to impaired renal perfusion, damage to the endothelium, and reduced renal reserve. Moreover, these patients with these comorbidities are often given a variety of nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), which make these situations more severe.

In the intraoperative period, another potential nephrotoxin is free hemoglobin from CPB-induced hemolysis. CPB hemolyzes red blood cells and leads to the production of intravascular free hemoglobin, which depletes circulating haptoglobin and directly damages the renal endothelium. (45) During cardiac surgery, low cardiac output, potential hypothermia, possible bleeding complications, and the non-pulsatile flow of the CPB all cause reduced renal perfusion and can lead to AKI. The other fundamental cause of low renal perfusion is vasoconstriction. The endogenous way is the activation of the sympathetic nervous system and the renin-angiotensin system. The iatrogenic way is the use of vasopressin and catecholamines. Postoperatively, predominant factors influencing the development of AKI include hemodynamic instability, nephrotoxic, inotropic, and vasoconstrictor drugs, as well as systemic inflammation. Conventional on-pump CABG induces a systemic inflammatory response and is associated with elevated postoperative plasma concentrations of proinflammatory cytokines. A systematic review by Cheungpasitporn et al. (46), which included 33 randomized controlled trials (RCTs) showed a protective effect of OPCAB in reducing the risk of AKI, but the finding was challenged by the largest multicenter RCT by Lamy at al., (47) which found no significant difference between the OPCAB and on-pump CABG subgroups. In a prospective study, Bruins et al. reported a biphasic complement activation in cardiac surgery patients, which was activated not only during CPB but also during the first five days thereafter, which increased C-reactive protein levels, contributing to the second activation. (48) Other stimuli, such as endotoxemia, tissue injury, surgical trauma, and even left ventricular dysfunction, may play a role in the activation of the immune system. Inflammatory cytokines are formed, leading to renal tubular injury, which is getting worse by the activation of neutrophils and macrophages and the migration of lymphocytes into the renal parenchyma. Ischemia-reperfusion injury occurs and induces the production of reactive oxygen species (ROS). ROS activates the upregulation of pro-inflammatory transcription factors. (49)

AKI has been associated with an increased risk of sepsis, anemia, coagulopathy, and thus prolonged mechanical ventilation, ICU and hospital stay. (50) (51) The meta-analysis by Yu et al. concludes that the incidence of AKI after cardiac surgery is as high as 40%, and approximately 3% of patients require at least temporary renal replacement therapy. Patients with severe AKI are confronted with a three- to eightfold higher perioperative

mortality. (52) Messmer et al. showed in a meta-analysis that fluid overload and cumulative fluid balance were both associated with pooled mortality in a general postoperative population with AKI and non-AKI subgroups after surgery. (53) Malbrain analyzed 19,902 critically ill patients, and the cumulative fluid balance after one week of ICU stay was 4.4 L more positive in non-survivors compared to survivors. A restrictive fluid management strategy resulted in a less positive cumulative fluid balance of 5.6 L compared to controls after one week of ICU stay. (54) A restrictive fluid management was associated with a lower mortality compared to patients treated with a more liberal fluid management strategy. (2) (55) (56)

Pettey showed an association between the development of AKI and a decrease in hepatic flow ratios on postoperative day 1, driven by low S-wave and high D-wave velocities. The presence of venous congestion was reflected by significantly elevated CVP values, which were independently associated with AKI on day 1. (57)

However, the influence of postoperative interventions, such as fluid therapy and the amount of the vasoactive drugs used has not been analyzed in relation to venous return. Additionally, there is no available data which calculates the retrograde and anterograde flow in the hepatic veins.

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4. Objectives

The aim of our studies was to investigate the perioperative factors that may be associated with increased hepatic venous congestion in the preoperative and postoperative periods in patients undergoing cardiac surgery.

The first objective was to investigate relationships between preoperative Doppler hepatic waveforms and echocardiographic parameters, ventilator settings, vasoactive medications, as well as laboratory parameters of renal and liver functions, especially focusing on renal parameters and AKI.

The second objective was to analyze the anterograde and retrograde flow of the hepatic vein. Our hypothesis was that the retrograde/anterograde ratio before and after cardiac surgery could both be helpful markers in the prediction of postoperative morbidity such as fluid overload, elevated vasoactive and inotrope need, worse left and right ventricle function, and more invasive ventilator settings.

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5. Methods

1. Structure of the studies

All our studies were reported according to the STROBE statement. Both our main studies had approval from the Institutional Review Board of Semmelweis University (IRB 141/2018) and are registered with the ClinicalTrials.gov number NCT02893657. In the first prospective, observational study (study A), we enrolled 98 patients who underwent cardiac surgery between January 2018 and December 2019 in the Városmajor Heart and Vascular Center. In the second study (study B) 41 patients undergoing cardiac surgery between January 2021 and March 2021 were enrolled from the same tertiary heart center. Patients who had preoperative chronic kidney disease (defined as GFR under 30 mL/min/1.73 m^2), hepatic cirrhosis, or portal vein thrombosis were excluded. Each patient who agreed to the participation signed the informed consent before the first echocardiographic investigation, which was usually 24 to 72 hours before the planned surgery.

Demographic data, perioperative echocardiographic parameters (preoperative and postoperative first day), and intraoperative variables (procedure type, cardiopulmonary bypass time) were collected. Postoperative factors (fluid balance, vasoactive requirement, ventilation time and parameters—respiratory rate (RR), tidal volume (TV), positive end-expiratory pressure (PEEP), fraction of inhaled oxygen (FIO2), and perioperative laboratory parameters (liver function, kidney function, albumin) were also used in the analysis. Laboratory results were collected during the preoperative period and on the first, second, and third postoperative days. We collected information on the predictors of the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) and the Model for End-stage Liver Disease (MELD) scores, and the vasoactive-inotrope score (VIS). EuroSCORE II is a widely used risk stratification system for the cardiac surgical population using patient (clinical preoperative state, mobility), operation (urgency, operation on the thoracic aorta), and cardiac risk factors (LV function, recent myocardial infarction, pulmonary hypertension). (58) (59) VIS is calculated using vasopressor

(norepinephrine, epinephrine, vasopressin) and inotropic (dobutamine, dopamine, levosimendan, milrinone) medication doses. VIS was calculated using the highest doses of vasoactive and inotropic medications administered during the first 72 hours post-surgery. The MELD score has been used in transplant surgery since 2003 to estimate the need and urgency of liver transplants, which contains INR, creatinine, and bilirubin levels. The modified MELD-score (modMELD) differs from the standard MELD-score in that it considers the albumin level instead of the INR component, prioritizing the synthetic activity of the liver. Among cardiac and circulatory patients, many are under oral anticoagulation therapy, which greatly affects the INR and distorts the result, so there is an INR-excluding MELD-score too. An alternative MELD scoring system, MELD-Na may improve prognostic efficacy by incorporating low sodium levels, a commonly cited marker of increased mortality in patients with heart failure. (60, 61) We have calculated the AKI score by Thakar et al. – also containing risk factors in terms of patient (age, gender, diabetes, chronic obstructive pulmonary disease) and operation (procedure type, urgency) and preoperative creatinine level. (62) Subsequently, these scores were estimated and adjusted in our multivariable analyses.

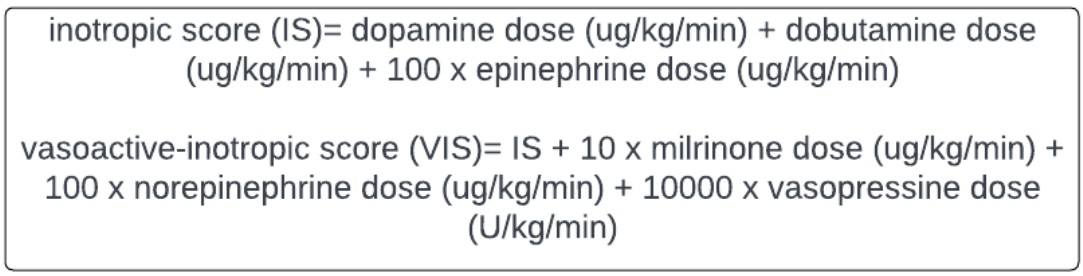

Figure 3: Calculation of the VIS score.

MELD= 10 x (1.12*ln INR + 0.378*ln T. bili + 0.957*ln Creat. + 0.643)
modMELD= 10 x (1.12 * ln (1 + (4.1 -albumin)) + 0.378 * ln T. bili + 0.957 * ln Creat. + 0.643)
MELD Na = MELD − Na − (0.025 × MELD × (140 − Na)) + 140
MELD XINR= 5.1 * ln T. bili + 11.76 *ln Creat. + 9.44

Figure 4: Calculation of MELD-scores

Risk factor	Points
Female gender	1
Congestive heart failure	1
Ejection fraction less than 35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only	1
CABG+valve	2
Other cardiac surgery	2
Preoperative creatinine 1.2 to 2.1 mg/dl	2
Preoperative creatinine more than 2.1 mg/dl	5

Figure 5: AKI score by Thakar (62)

2. Ultrasound examinations

We recorded the maximum velocity of the four waves (A, S, V, D) and velocity-time integral (VTI). The ratio of maximum to retrograde compared to anterograde velocity and the ratio of retrograde VTI compared to anterograde VTIs were calculated. All recordings were made at the influx point of the hepatic veins into the inferior caval vein, and under the patients' inspiration.

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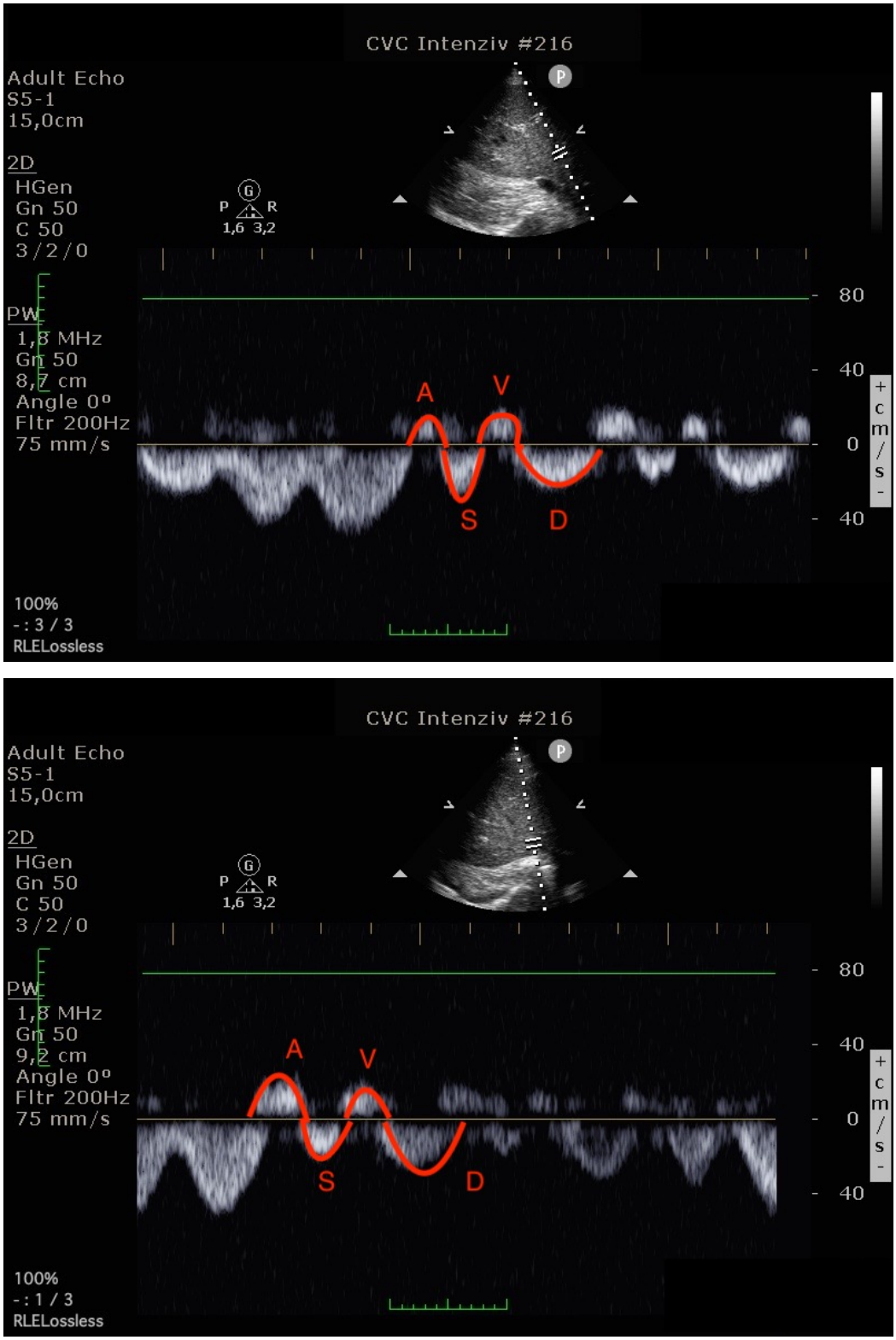

Figures 6 A and B: Postoperative retrograde flow increment (own recording) (5, 22)

The echocardiographic investigations were performed by two cardiologists board-certified in echocardiography and were recorded on the same machine and analyzed by the same person. (Phillips CX50 – SG61102002). Standard 2D parameters were ejection fraction, tricuspid annular plane systolic excursion (TAPSE), the diameters of the atria and ventricles, and the occurrence of valve insufficiency.
The physicians in the postoperative period were blinded to the results of the hepatic flow measurements.

3. Main goals

In "study A" (Connection between preoperative hepatic venous profile and postoperative acute kidney injury) our primary outcome measured was postoperative AKI, as defined by the KDIGO criteria. In case of low population of AKI cases, we have focused on postoperative creatinine elevation (even in cases that did not reach the KDIGO criteria). We calculated the percentage change of the highest postoperative serum creatinine from the baseline preoperative concentration (%ΔCr) on the first three postoperative days. Baseline creatinine was defined as the preoperative creatinine level measured after the indexed hospital admission but before the surgery (usually 24 hours before the surgery).
In "study B" (Connection between hepatic venous congestion and morbidity) our goal was to determine which factors are associated with the increased congestion of the liver as measured by Doppler ultrasound in patients undergoing cardiac surgery. Hepatic venous congestion was based on the changes of the ratios of the retrograde hepatic venous flow between the preoperative and the postoperative period, congestion meant elevated retrograde ratio.

4. Statistical analysis

Normality was tested with the Kolmogorov–Smirnov test. Skewed distributions are described as medians and interquartile ranges (interquartile range 25–75) and were compared using the Mann–Whitney U test. Continuous variables were first expanded with restricted cubic splines and were only used in linear form if the deviation from linearity was not significant, as indicated by the global F test ($p > 0.05$). Multivariable models

were tested for multicollinearity. When we used binary classifier system (for example, VTI-growth and non-VTI growth subgroups) we tested the diagnostic ability with receiver operating characteristic curves. The effect of hepatic waves on the peak creatinine fractional change (%ΔCr) was evaluated using multivariable linear regression analysis and adjusted for patient- and surgery-related characteristics that included adjustment for significant perioperative variables. The variables selection was based on a set of previously published studies with a focus on kidney injury after cardiac surgery. The multivariable models were tested for multicollinearity (by volume inflation factors) between these clinical variables. The adjusted changes in R^2 were reported after each step of the regression model to determine the contribution of each variable that was added to the model. (5, 22) Our power analysis indicated that with eight potential predictors of acute kidney injury, we needed to perform a prediction model with a minimum of 90 patients to avoid overfitting. In the second study our power analysis suggested 50 patients would be ideal.

Statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software, Version 27.0 (IBM, Armonk, NY, USA).

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6. Results

1. Connection between preoperative hepatic venous profile and postoperative acute kidney injury (study A)

1. Descriptive statistics

Of the 98 patients, 66 (67%) were males, 32 (33%) were females. The median age of the patients was 69.8 years (interquartile range [IQR 25–75] 13 years). The most common type of cardiac surgery was coronary artery bypass grafting (CABG) surgery (40%) followed by aortic valve repair (AVR – 29%). Seventeen patients (17.3%) developed AKI according to the KDIGO criteria.

The average change in postoperative creatinine levels compared to baseline was an 8.7% increase from 83.2 µmol/L (IQR 25–75: 7.8) to 91.9 µmol (IQR 25–75: 12.8). Among these patents with AKI, there was a 72.1% increase from 78.4 µmol/L (IQR 25–75: 8.7) to 137.0 µmol/L (IQR 25–75: 32.7), and the ratio of postoperative/preoperative creatinine was 1.65 (1.51–1.81). We can see a significant difference between the AKI and non-AKI subgroups with Mann-Whitney U test (p=0.001). There was a significant difference between the two subgroups in the age of the patients (p=0.015).

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Table 1: Basic demographic and preoperative clinical parameters

	All patients (N=98)	**AKI (n=17)**	**non-AKI (n=81)**	***p***
Male	66 (67%)	11 (62%)	55 (70%)	0.43
Female (Nr)	32 (33%)	6 (38%)	26 (30%)	0.16
Age (years)	68.8 (11.2)	69.1 (7.4)	63.5 (13.9)	0.015
Diabetes	20 (20%)	5 (25%)	15 (19%)	0.09
NYHA III/IV	41 (41%)	10 (58.8%)	31 (39%)	0.12
EuroSCORE	1.6 (0.9)	1.6 (1.0)	1.5 (0.7)	0.09
Weight (kg)	74.6 (8.1)	72.6 (7.1)	75.1 (9.12)	0.43
Operation time (min)	182.4 (39.1)	178.1 (41.1)	188. 8 (39.1)	0.88
Aorta cross clamp time (min)	47.8 (7.1)	40.8 (9.1)	48.1 (7.6)	0.73
Type of surgery				
AVR	28 (29%)	6 (35%)	22 (26%)	0.11
CABG	39 (40%)	7 (41%)	32 (39%)	0.06
MVR	20 (20%)	3 (17%)	17 (20%)	0.09
Combined	12 (12%)	1 (7%)	11 (15%)	0.12
Hemoglobin (g/l)	137.1 (18.5)	135.3 (19.7)	138.4 (18.7)	0.61
Albumin (g/l)	41.4 (8.6)	38.8 (8.1)	43.7 (7.9)	0.83
Platelets (1000/l)	217.5 (62.2)	218.6 (64.9)	211.4 (58.7)	0.75
CRP (mg/l)	4.3 (3.3)	4.2 (3.9)	4.5 (3.3)	0.53
INR	1.9 (10.5)	1.9 (0.3)	1.1 (0.2)	0.34
ASAT (U/l)	20.9 (10.4)	18.8 (6.3)	21.2 (13.2)	0.34
ALAT (U/l)	31.4 (21.3)	34.2 (18.9)	30.4 (27.3)	0.56
Creatinine (µmol/l)	87.8 (20.1)	109.8 (25.1)	78.4 (17.7)	0.001

Urea Nitrogen (mmol/l)	6.4 (2.1)	7.3 (1.8)	5.4 (3.2)	0.18
GFR (ml/min/1.73m2)	79.7 (15.4)	70.2 (15.6)	76.0 (16.6)	0.004
Bilirubin (µmol/l)	17.8 (43.3)	21.4 (7.4)	11.8 (6.5)	0.31
MELD	7.1 (19.0)	7.50 (4.6)	5.3 (1.2)	0.50
NYHA	2.1 (0.5)	2.1 (0.4)	2.2 (0.5)	0.10
EuroSCORE	1.6 (0.9)	1.6 (0.9)	1.5 (1.0)	0.09

AKI: Acute kidney injury, AVR: Aortic valve repair, MVR: Mitral valve repair, CABG: Coronary artery bypass grafting, CRP: C-reactive protein, EuroSCORE: European System for Cardiac Operative Risk Evaluation INR: Internationally normalized ratio, ASAT: Aspartate aminotransferase, ALAT: Alanine aminotransferase, GFR: Glomerular filtration rate, MELD: Model for end-stage liver disease NYHA: New York Heart Association

There was no difference between the AKI and non-AKI patients in their standard echocardiographic parameters before and after surgery.

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Table 2: Echocardiographic parameters

		All patients (N=98)	AKI (n=17)	non-AKI (n=81)	*p*
EF	**preoperative**	54.9 (10.6)	54.0 (11.6)	55.8 (12.3)	0.49
	postoperative	57.3 (8.1)	55.6 (8.9)	58.4 (7.1)	0.77
TAPSE (mm)	**preoperative**	23.6 (8.0)	22.8 (8.8)	24.1 (8.9)	0.4
	postoperative	13.4 (8.1)	13.4 (7.6)	14.6 (8.6)	0.27
LVEDD (mm)	**preoperative**	50.3 (6.1)	50.5 (6.2)	49.6 (5.5)	0.73
	postoperative	46.0 (8.3)	44.6 (9.1)	46.3 (7.1)	0.97
LVESD (mm)	**preoperative**	35.8 (5.1)	36.1 (4.3)	34.3 (5.3)	0.38
	postoperative	34.8 (7.8)	36.1 (7.4)	33.0 (6.4)	0.92
RV (mm)	**preoperative**	30.8 (8.1)	29.2 (8.8)	32.7 (6.5)	0.14
	postoperative	33.2 (9.0)	32.3 (9.0)	33.7 (9.1)	0.96
LA (mm)	**preoperative**	43.1 (8.3)	41.8 (8.5)	43.4 (7.0)	0.44
	postoperative	43.3 (6.3)	43.7 (8.6)	43.2 (3.7)	0.31
RA (mm)	**preoperative**	40.5 (7.6)	38.0 (7.2)	41.9 (8.7)	0.66
	postoperative	43.2 (6.2)	44.1 (7.0)	43.2 (6.7)	0.54

EF: ejection fraction, TAPSE: tricuspid annular plane systolic excursion LVEDD: left ventricle end-diastolic diameter, LVESD: left ventricle end-systolic diameter, RV: right ventricle, LA: left atrium, RA: right atrium

2. Univariable and multivariable regression

We have observed a tendency between the severity of KDIGO stages and the VTI ratio (p=0.045) on ROC analysis. Maximum velocity (vmax) and velocity-time-integral (VTI) of A, S, V, and D waves were analyzed regarding creatinine change in univariable and multivariable regression models. We also calculated the sum of retrograde (retro VTI and retro vmax), the sum of anterograde flow (antero VTI and antero vmax) and the ratio of retrograde and anterograde waves.

The variables were adjusted for age, EuroSCORE (European System for Cardiac Operative Risk Evaluation), AKI (acute kidney injury by Thakar et al) score, operation time, fluid balance, and vasoactive inotropic score (VIS). With univariable linear regression, we calculated the correlation between the preoperative parameters and the changes in postoperative creatinine levels compared to baseline. In the multivariable regression model, VTI and Vmax of the A wave correlated independently with the increase in the creatinine level. The VTI of the retrograde waves (A + D) and the VTI of the retrograde/anterograde waves ratio were independently associated with the increase in creatinine levels.

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Table 3: Correlation between hepatic waves and changes in creatinine levels

	Univariable linear regression				Multivariable regression			
	B	**95% CI**		***p***	**B**	**95% CI**		***p***
A vmax (m/s)	0.640	0.332	0.948	<0.001	0.714	0.437	0.991	<0.001
A VTI (cm)	0.035	0.021	0.050	<0.001	0.038	0.025	0.051	<0.001
S vmax (m/s)	0.049	-0.153	0.251	0.631				
S VTI (cm)	-0.002	-0.011	0.007	0.691				
V vmax (m/s)	0.075	-0.127	0.277	0.462				
V VTI (cm)	0.011	-0.003	0.025	0.127				
D vmax (m/s)	0.151	-0.163	0.466	0.342				
D VTI (cm)	0.010	-0.005	0.024	0.177				
Antero vmax (m/s)	0.062	-0.080	0.204	0.388				
Retro vmax (m/s)	0.168	-0.009	0.345	0.062				
Ratio vmax	0.091	-0.124	0.307	0.402				
Antero VTI (cm)	0.001	-0.006	0.009	0.690				
Retro VTI (cm)	0.017	0.006	0.027	0.002	0.018	0.008	0.027	<0.001
Ratio VTI	0.218	0.086	0.351	0.002	0.233	0.111	0.356	<0.001

Among the postoperative variables characterizing the complications, the amount of transfusion in red-blood cell units and need for furosemide in the first 72 h were associated with changes in postoperative creatinine levels (ΔCr).

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Table 4: Postoperative parameters and correlations with changes in creatinine levels

	All patients (N=98)	**AKI (n=17)**	**non-AKI (n=81)**	***p***	**B**	**95% CI**		***p***
Mechanical ventilation (hours)	46.1 (9.5)	47.1 (9.2)	46.9 (10.1)	0.076	0.026	-0.002	0.054	0.066
Need for vasopressor/ inotrope	29 (32%)	11 (64%)	18 (23%)	0.234	0.282	-0.271	0.836	0.314
VIS	4.2 (8.2)	4.9 (8.1)	3.6 (8.2)	0.122	0.008	0.000	0.017	0.057
Need for dialysis	3 (3.7%)	2 (2.4%)	1 (1.3%)	0.09	0.021	-0.012	0.022	0.065
ICU days	2.2 (0.9)	2.3 (1.0)	2.2 (0.9)	0.123	0.277	-0.223	0.766	0.344
Hospital days	12.8 (5.6)	14 (6.5)	12 (8.7)	0.245	0.123	-0.156	0.544	0.231
Transfusion RBC (U)	0 (0-2)	2.2 (3.1)	0.9 (1.9)	0.002	0.043	0.008	0.078	0.016
CVP (max) (Hgmm)	9.0 (2.5)	11.0 (2.0)	8.0 (1.2)	0.322	0.009	-0.005	0.023	0.197
Fluid balance (ml/kg)	34.8 (29.1)	50.1 (40.1)	19.6 (3.4)	0.098	0.001	-0.005	0.023	0.068
Furosemide (mg)	25.0 (10.0)	40.0 (10.0)	20.0 (10.0)	0.001	0.004	0.003	0.006	0.001

RBC: Red blood cell, ICU: intensive care unit, CVP: central venous pressure

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2. Connection between hepatic venous congestion and morbidity (study B)

1. Descriptive statistics

Of the 41 patients, 20 (48.7%) were male. The median age of the patients was 65.9 years (IQR: 59.8–69.9 years). The average increase in the retrograde/anterograde wave VTI ratio was 0.04 (from preoperative 15.5/20.8 = 0.77 to postoperative 19.7/24.4 = 0.81). After examining the waves, we found that most of the population had an increased retrograde VTI growth (24 - 59%), compared to the baseline preoperative values. In the retrograde VTI growth subgroup, delta D decreased, and there was a tendency toward an increase in delta A and delta V waves. There was no significant difference between the two subgroups among the basic demographic and clinical parameters.

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Table 5: Demographic and basic clinical parameters

	All patients (N=41)	**No retrograde VTI growth (n=17)**	**Retrograde VTI growth (n=24)**	***p***
Age (years)	65.9 (10.8)	63.7 (11.3)	67.1 (10.4)	0.272
Weight (kg)	72.0 (10.2)	73.4 (11.1)	71.1 (10.3)	0.845
Diabetes	19 (46.3%)	9 (53%)	10 (41.6%)	0.53
Sex female	21 (51.2%)	9 (53%)	12 (50%)	0.466
EUROSCORE II	4.7 (1.3)	4.9 (0.9)	4.5 (1.0)	0.197
NYHA III/IV	24 (58.5%)	10 (58.8%)	14 (58.3%)	0.456
Operation time (min)	182.4 (39.1)	178.1 (41.1)	188. 8 (39.1)	0.88
Aorta cross-clamp time (min)	47.8 (7.1)	40.8 (9.1)	48.1 (7.6)	0.73
Operation type				
MVR	9 (22%)	3 (17.6%)	6 (25%)	0.234
AVR	14 (34.1%)	6 (35.2%)	8 (33.3%)	0.199
CABG	15 (36.6%)	7 (41.1%)	8 (33.3%)	0.342
Combined	3 (7.3%)	1 (5.9%)	2 (8.4%)	0.544

NYHA: New York Heart Association, MVR: Mitral valve repair, AVR: Aortic valve repair, CABG: Coronary artery bypass graft, EUROSCORE II: European System for Cardiac Operative Risk Evaluation II

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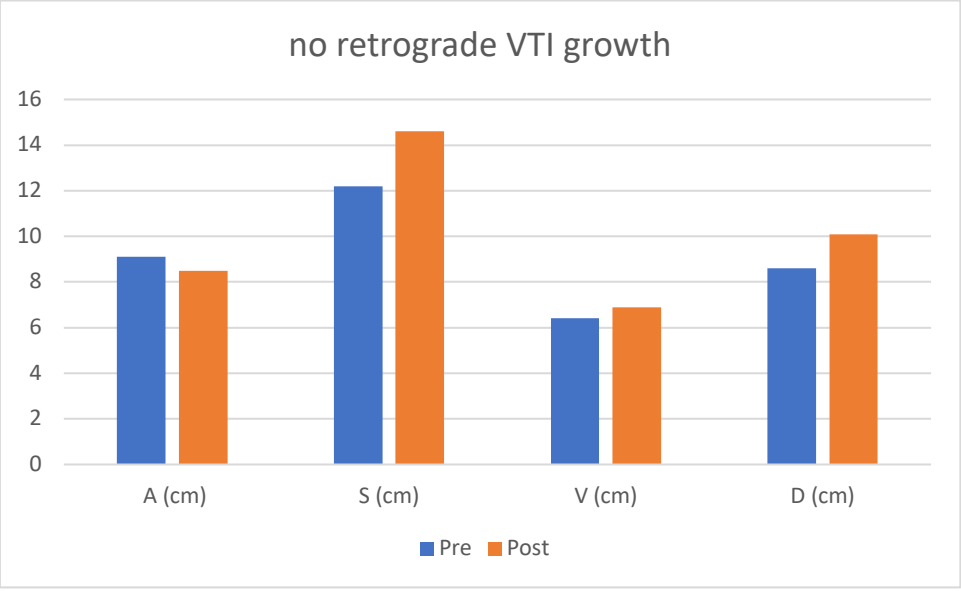
Table 6: Changes in hepatic waves

	non-VTI growth (n=17)	VTI growth (n=24)	*p*
Pre A (cm)	9.1 (7.7)	8.8 (5.3)	0.434
Pre S (cm)	12.2 (9.9)	13.9 (9.9)	0.275
Pre V (cm)	6.4 (4.3)	5.3 (4.5)	0.209
Pre D (cm)	8.6 (4.2)	13.3 (6.7)	0.026
Pre VTI ratio	1.01 (0.02)	0.59 (0.01)	0.098
Post A (cm)	8.5 (5.7)	9.8 (5.6)	0.239
Post S (cm)	14.6 (9.0)	12.4 (8.1)	0.22
Post V (cm)	6.9 (4.1)	7.5 (6.6)	0.375
Post D (cm)	10.1 (7.3)	10.1 (6.9)	0.425
Post VTI ratio	0.65 (0.03)	0.91 (0.03)	0.087
Delta A (cm)	-0.64 (0.01)	0.99 (0.05)	0.08
Delta S (cm)	2.5 (1.1)	-1.4 (0.02)	0.08
Delta V (cm)	-0.01 (0.01)	2.28 (1.2)	0.117
Delta D (cm)	1.3 (0.2)	-2.2 (1.2)	0.007
Delta VTI ratio	-0.35 (0.01)	0.31 (0.02)	0.002



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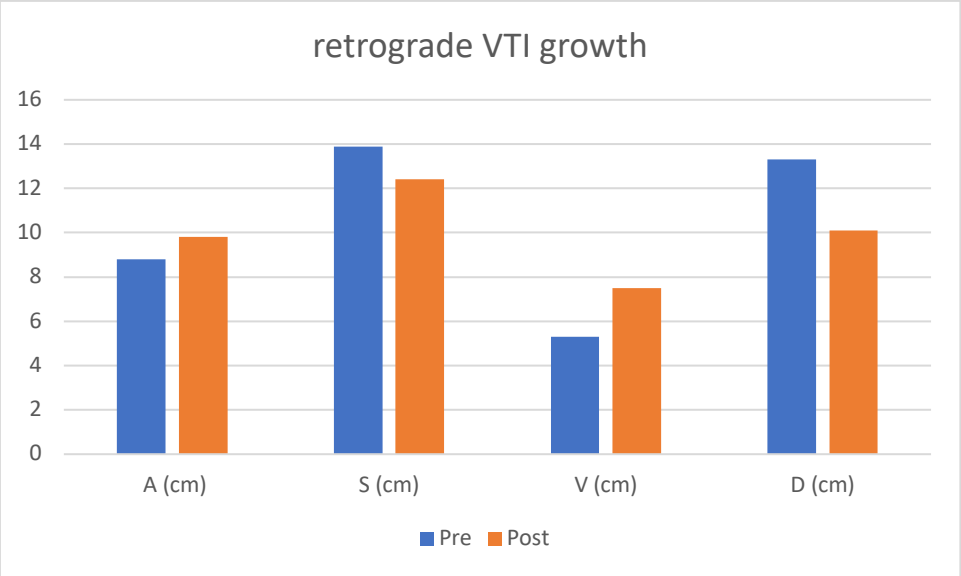

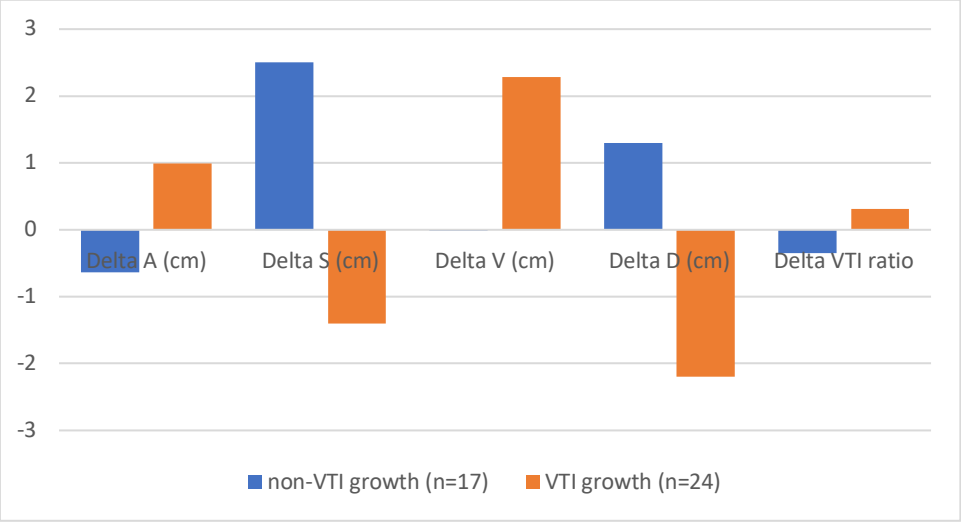

Figures 7 A, B and C: Changes between the waves in the preoperative and postoperative periods

Examining the laboratory parameters, the retrograde VTI ratio (elevated congestion) subgroup had significantly higher blood urea nitrogen and creatine levels.

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Table 7: Laboratory parameters at preoperative and postoperative period's 24h.

	non-VTI growth (n=17)	**VTI growth (n=24)**	***p***	**non-VTI growth (n=17)**	**VTI growth (n=24)**	***p***
	Preoperative			**Postoperative**		
Creatinine (mmol/l)	83.2 (13.3)	85.5 (9.8)	0.381	78.1 (21.2)	93.5 (38.7)	0.07
BUN (umol/l)	5.9 (1.9)	6.3 (4.3)	0.235	4.75 (3.2)	6.4 (2.3)	0.02
AST (U/l)	22.1 (4.3)	34.1 (10.1)	0.135	55.6 (19.8)	47.5 (19.9)	0.297
ALT (U/l)	20.3 (11.1)	22.8 (4.9)	0.303	24.1 (10.1)	18.5 (8.9)	0.103
Bilirubin (umol/l)	11.04 (6.1)	11.07 (7.1)	0.462	11.3 (6.2)	11.1 (5.9)	0.368
GGT (U/l)	35.5 (11.1)	32.9 (13.2)	0.103	43.4 (9.1)	22.8 (8.9)	0.301
GFR (ml/min/1.73 m2)	71.2 (13.4)	65.3 (23.3)	0.112	74.4 (14.3)	55.1 (19.8)	0.001

After comparing the echocardiographic parameters between the two subgroups, the postoperative right ventricular and atrial diameters were significantly greater in the "retrograde VTI growth" group. The postoperative ejection fraction and the decrease in ejection fraction were significantly different between the two groups. (p = 0.001 and 0.009).

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Table 8: Changes in echocardiographic parameters

	non-VTI growth (n=17)	**VTI growth (n=24)**	***p***	**non-VTI growth (n=17)**	**VTI growth (n=24)**	***p***
	Preoperative			Postoperative		
EF	53.7 (10.5)	51.5 (12.4)	0.277	59.4 (11.2)	48.5 (10.7)	0.001
TAPSE (mm)	24.6 (5.1)	22.6 (5.9)	0.127	14.3 (4.2)	15.2 (5.4)	0.251
LVEDD (mm)	51.1 (9.2)	53.1 (10.4)	0.255	44.6 (4.1)	47.4 (6.8)	0.08
LVESD (mm)	39.9 (14.1)	38 (10.1)	0.431	28.4 (9.1)	33.3 (8.7)	0.022
RV (mm)	32.7 (4.4)	32.9 (3.9)	0.457	32.5 (5.1)	35.1 (4.9)	0.01
LA1 (mm)	44 (8.5)	46.6 (8.0)	0.168	43.1 (8.7)	45.2 (8.8)	0.06
LA2 (mm)	49 (10.2)	52.1 (10.1)	0.166	54.1 (8.7)	53.9 (9.1)	0.09
RA1 (mm)	42.7 (6.3)	42.4 (7.1)	0.451	39.5 (6.7)	43.9 (5.9)	0.01
RA2 (mm)	49.3 (9.1)	47.3 (7.9)	0.254	53.5 (6.9)	55.1 (7.1)	0.144
RASA (mm2)	2131.1 (644.1)	1916.2 (577.6)	0.134	2314.2 (498.2)	2278.5 (514.3)	0.646
Delta EF	2.8 (19.4)	-12.1 (3.2)	0.009			

2. Regressions

After analyzing the respiratory parameters and ventilation times, we found that the VTI growth subgroup had longer ventilation duration (the median value was over 24 h) and needed higher positive end-expiratory pressures ($p = 0.003$)

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Table 9: Ventilation parameters

	non-VTI growth (n=17))	**VTI growth (n=24)**	***p***
Mechanical ventilation over than 24 hours	7 (41.1%)	13 (54.1%)	0.091
Resp. time (hours)	20.9 (2.1)	25 (3.2)	0.081
Tidal volume (ml)	470.5 (43.5)	490.5 (44.0)	0.079
RR (/min)	13.4 (2.0)	12.9 (1.9)	0.122
PEEP (cmH2O)	6.5 (1.3)	7.7 (1.9)	0.003
FIo2 (%)	38.5 (4.5)	39 (4.8)	0.051

In the univariable linear regression model, the postoperative/preoperative (baseline) delta VTI ratio of the hepatic venous ultrasound correlated with fluid balance, maximum central venous pressure, and delta ejection fraction.

Table 10: Regressions with postoperative/preoperative VTI ratio

	B	**95% CI**		***p***
Delta EF	-0.365	-0.022	-0.002	0.022
Fluid balance/body weight at POP 24 h (ml/kg)	0.341	0.001	0.021	0.022
CVP POP 24 h (mmHg)	0.546	0.052	0.213	0.002

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7. Discussion

1. Perioperative fluid overload

We found that in the first postoperative 24 hours, increased hepatic venous retrograde flow was associated with worse ejection fraction, higher positive fluid balance, increased right atrial and ventricular diameter, and higher central venous preload pressure.

In the postoperative period, preload optimization can lead to fluid overload, particularly in low cardiac output states, preexisting or newly developed right-sided heart failure, and pulmonary hypertension. In the last decade, this connection between congestive heart failure, right ventricular failure, and liver dysfunction has been examined closer. Right ventricular failure can lead to liver dysfunction ranging from mild enzyme elevations to severe liver fibrosis. Congestion can impair renal function and cause gastrointestinal ischemia due to high backing pressure and a lower effective organ pressure gradient. Progressive increase in venous volume eventually causes the venous walls stretching to the maximum. At this point, the pressure transmission will be significantly increased, leading to peripheral venous congestion. (63) Increased right atrial pressure can be transmitted backwards across the venous tree and lead to congestive organ dysfunction. (64) This can manifest as congestive hepatopathy, delirium from congestive encephalopathy, and acute kidney injury from intracapsular oedema. (65) (66) (67)

Over the last 15 years, several dynamic tests have been developed to predict fluid status and fluid responsiveness in critically ill patients. These tests are based on the principle of inducing short-term changes in cardiac preload, using heart-lung interactions, the passive leg raise or by the infusion of small volumes of fluid, and to observe the resulting effect on cardiac output. Pulse pressure and stroke volume variations were first developed, but they are reliable only under strict conditions. (68-70) The variations in vena caval diameters share many limitations. The passive leg-raising test is now supported by solid evidence and is more frequently used. (71) (72, 73) More recently, the end-expiratory occlusion test was proposed, which can easily be performed in ventilated patients. Unlike the traditional fluid challenge, these dynamic tests do not lead to fluid overload. (74) (75)

Changes in renal venous flow patterns were associated with one-year mortality in patients with advanced heart failure independent from right atrial pressure. (67) The flow of the portal and hepatic veins was also examined. Among heart failure patients, those with reversed V waves had higher right atrial pressure and were at higher risk of adverse prognosis. Reversed V wave was also found to be an independent predictor of cardiac events. (76) Examining the portal vein pulsatility over 50% was an independent negative predictive value of worse outcomes among acute heart failure patients. (20)

These are new diagnostic concepts for practice in the early detection of fluid overload. It may be separate and not accompanying right-sided heart failure. In our study, we measured VTIs instead of the maximum velocity (v max) of the waveforms, which may be more useful for volume estimation. Using ratios to express retrograde and anterograde flows has the advantage of removing the effects of vessel shape and diameter and reducing potential errors.

Our results suggest that an increase in retrograde flow was associated with the severity of fluid overload. It is not clear whether fluid overload leads to increased retrograde flow, or it is caused by pre-existing venous insufficiency (we can see this at lower extremity varicosities), or both.

2. Mechanical ventilation

Fast track management after cardiac surgery can be beneficial, as early return of spontaneous breathing and extubation promotes negative thoracic pressure, increasing the venous return, the preload of the heart, and helps maintaining cardiac output. (5) Negative pressure can also help reduce hepatic afterload, whereas fluid overload, prolonged ventilation, and edema formation worsen venous congestion. A special proof for this physiological phenomenon is patients with univentricular physiology (Fontane circulation), where early weaning from mechanical ventilation and return to spontaneous breathing is key to maintain cardiac output.

Early extubation is associated with lower cardiovascular morbidity, such as myocardial ischemia and lower post-surgical vasopressor requirement. (77) Prolonged positive pressure ventilation is associated with a decreased preload, reduction, and redistribution

of cardiac output, decreased splanchnic blood flow, and reduced blood supply to the liver and kidneys.

Our data suggests the increment of the retrograde hepatic venous flow is associated with longer ventilation duration (the median value was over 24 h) and a strong correlation with higher positive end-expiratory pressures.

3. Echocardiography

Echocardiography is a widely used and accepted technique in the perioperative management of patients undergoing cardiac surgery. In recent protocols echocardiography, with both first and second level parameters, offers the possibility to accurately analyze the right ventricle and optimize patient management. (78) (79) Echocardiography, both transthoracic (TTE) and transesophageal (TEE), may help to identify cardiac tamponade after surgery. (78) A meta-analysis by Heiberg (80) reported that echocardiography is feasible, whether performed by a novice or expert, and frequently resulted in important changes in the diagnosis of cardiac abnormalities and their management. Among the standard echocardiography, several point-of-care ultrasound markers (POCUS) have been identified recently as potential markers to detect venous congestion and fluid overload. (81) In our studies, we have used a combination of these measurements. By comparing the echocardiographic parameters between the venous congestion and non-congestion subgroups, we found significantly dilated right atrium and ventricle and lower ejection fraction in the assumed congestive subgroup.

4. Acute kidney injury

We found a significant correlation between the ratio of retrograde waves compared to anterograde hepatic venous waves, as well as VTI and maximum velocity of the A wave and postoperative AKI. The strong relationship of the retrograde A wave and the retrograde to anterograde ratio with AKI remained statistically significant after adjusting for patient- and procedure-related characteristics. VTI, but not maximum velocity, of the

retrograde and anterograde waves, showed a significant correlation with AKI. This also suggest that VTI is more effective in predicting volume dimensions than velocity. The severity of hepatic venous congestion was found to be a predictor of AKI in a prospective study among cardiac surgery patients. (82) (83)

Postoperative acute kidney injury is a challenge to clinicians at intensive care units. (49) (84) Various studies have measured the maximum velocity of the S and D waves and the severity of venous congestion by the S and D wave ratios preoperatively, during intensive care and after discharge. Based on our results, we found that the magnitude of the retrograde waves in hepatic venous circulation is not solely attributed to the severity of right heart failure. Among these parameters (tricuspid regurgitation, TAPSE, or right ventricular diameters) only the right atrial systolic area showed an association with the retrograde waves of the hepatic vein.

We chose AKI and an increase in creatinine levels as the main outcomes in our study. In the multivariable model, we also adjusted the retrograde waveforms for age, EuroSCORE II, GFR, and operative factors, and venous congestion remained significant. Our results indicate that the severity of venous congestion should be evaluated preoperatively, but it is also advised to follow it up in the postoperative period.

5. Other liver parameters

Severe congestive heart failure is associated with two distinct forms of liver dysfunction: passive congestion and acute hepatocellular necrosis that is caused by inadequate perfusion. Fibrosis may result from prolonged recurrent congestive heart failure. Ischemic hepatitis (shock liver) usually manifests as asymptomatic elevation of the serum aminotransferase (ASAT, ALAT) levels after an episode of hypotension, such as acute viral hepatitis. (85) Calculation of MELD and its modifications has been associated with increased mortality and morbidity in end-stage heat failure and in patients after heart transplantation. (86) (87-89) In our study population, there were no differences between MELD scores in AKI and non-AKI patients, but the association between bilirubin and retrograde A waves draws attention to possible hepatic synthetic dysfunction in cases of fluid overload and supranormal vasoactive drug administration.

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8. Limitations

Our studies have limitations. First, it was a single center study. In the planning of the first study, we did not think about continuing it in the postoperative period. A couple of perioperative factors, such as positive fluid balance, vasopressor use, or positive intrathoracic pressure ventilation, can significantly influence the anterograde/retrograde ratios simultaneously. Therefore, we thought that the retrograde/anterograde ratio measurement would be the least biased choice. Furthermore, ultrasound methodology always has observational bias.

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9. Conclusions

We can conclude that congestion and/or abdominal venous insufficiency in the liver can predict worse postoperative renal function. Abdominal ultrasound is an easily available and, most importantly, noninvasive tool, which is gaining more and more space in emergency and intensive care units. Monitoring the hepatic veins can easily be performed, together with standard preoperative echocardiography it may add more information about the liver and kidney, than laboratory parameters alone. Our new finding was that it is also advised to quantitatively express our measures and not only with flow pattern types.

Moreover, measurement of venous congestion by ultrasound seems to be an important tool in guiding personalized fluid management. Volume and pressure monitoring on the arterial and macrohemodynamic side does not provide sufficient hemodynamic data, and central venous pressure alone provides inadequate information about the venous side of the circulation and all available monitoring methods are extremely invasive or have serious limitations. Monitoring abdominal venous waveforms is an easy and inexpensive noninvasive method that can help to detect fluid overload at an early phase.

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10. Summary

This thesis has set out to determine which factors are associated with the increased congestion of the liver, as measured by Doppler ultrasound in patients undergoing cardiac surgery, and the effect of this abdominal congestion on postoperative morbidity, especially on acute kidney injury.

- In total, we examined 139 patients who underwent an elective cardiac surgery. In study A, of the 98 patients, 66 (67%) were males, 32 (33%) were females. The median age of the patients was 69.8 years (interquartile range [IQR 25–75] 13 years). In study B, of the 41 patients, 20 (48.7%) were male. The median age of the patients was 65.9 years (IQR: 59.8–69.9 years).
- The postoperative/preoperative (baseline) delta VTI ratio of the hepatic venous ultrasound correlated with fluid balance, maximum central venous pressure, and delta ejection fraction.
- The postoperative retrograde/anterograde VTI ratio increment was associated with longer ventilation duration and needed higher positive end-expiratory pressures.
- The postoperative right ventricular and atrial diameters were significantly larger in the subgroup with greater retrograde/anterograde VTI ratio.
- In “study A” (Connection between preoperative hepatic venous profile and postoperative acute kidney injury) our primary outcome measured was postoperative AKI, as defined by the KDIGO criteria. Because of the low number of AKI cases, we have focused on postoperative creatinine elevation (even in cases that did not reach KDIGO criteria).
- VTI and Vmax of the A wave and the VTI of the retrograde waves (A + D), and the VTI of the retrograde/anterograde waves ratio correlated independently with the increase in the creatinine level.

Measurement of venous congestion by ultrasound seems to be an important tool in guiding personalized fluid management. Monitoring abdominal venous waveforms is an

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easy and inexpensive noninvasive method that can help to detect fluid overload at an early phase.

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12. Bibliography of the candidate's publications

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Eke, Csaba ; Szabó, András ; Nagy, Ádám ; Szécsi, Balázs ; Szentgróti, Rita ; Dénes, András ; Kertai, Miklós D. ; Fazekas, Levente ; Kovács, Attila ; Lakatos, Bálint Merkely, Béla ; Székely, Andrea
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