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# The Role of Venous Congestion in Multiple Organ Dysfunction

*Renal, Hepatic, and Intestinal Dysfunction*

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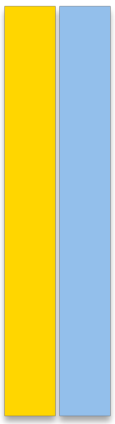

**The Role of Venous Congestion in Multiple Organ Dysfunction**

Renal, Hepatic, and Intestinal Dysfunction

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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*À minha mãe*

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**Abstract**

**Introduction:** Multiple organ dysfunction is prevalent in critical care. During the last decades, venous congestion (VC) has resurfaced both as an indicator of worse outcomes and as a factor contributing to the deterioration of renal, hepatic, and intestinal function. It correlates with hypoxia, ischemia, inflammation, and edema due to elevated venous pressure. Point-of-care ultrasound (POCUS) is a promising way to easily assess VC at the bedside and some advances, such as Venous Excess Ultrasound Scoring may have the potential to guide therapy to decrease organ injury.

**Objectives:** To review some basic physiology of the venous system, the impact of VC on renal, hepatic, and intestinal injury as well as review methods to assess organ congestion.

**Data Sources:** A PubMed database search using the keywords “venous congestion” “venous return”, “multiple organ failure”, “right-sided heart failure”, “positive fluid balance”, "central venous pressure", “hepatic failure", “acute kidney injury” and “intestinal dysfunction”, and combinations of these, was done to identify possibly eligible papers through title and abstract, from January 1980 to May 2022. Full text versions were analyzed and important references from these articles that were not identified in the initial search were added. Most reviews and case reports were excluded.

**Summary:** The venous system accommodates most of one’s blood volume. It can be subdivided into peripheral and splanchnic circulation, the latter being more compliant and acting as a blood reservoir that the circulation depends on in moments of stress. VC is a determinant of worsening renal function, increasing interstitial pressure, activating sympathetic pathways and the renin-angiotensin-aldosterone system, and decreasing glomerular filtration rate. It also seems to be a source of inflammation and oxidative stress, observed in hepatic and intestinal dysfunction due to VC. Hepatic congestion, due to heart failure or other conditions causing increased venous pressures, is associated with hypoxia, ischemia, and structural changes. Furthermore, portal hypertension and intestinal edema can induce changes in the intestinal tract, and may cause impairment of mucosal function, malabsorption, and gastrointestinal symptoms. There are several ways of assessing congestion, of which POCUS is emerging as a tool with some advantages. Other than being easily accessible, it allows measurements of vein diameters and flow pattern analysis through Doppler ultrasound. New scoring systems for the prediction of organ failure and volume status assessment such as Venous Excess Ultrasound Score can change hemodynamic management to decrease organ dysfunction.

**Conclusion:** VC is associated with renal, hepatic, and intestinal dysfunction. POCUS may be the future of congestion assessment and further validation of scoring systems needs to be done. Future

studies should be performed to better understand the pathophysiology, assessment, and potential therapies to decrease organ dysfunction due to VC.

**Keywords:** "*Venous congestion", "Right-sided cardiac failure", "Liver failure", "Acute kidney injury", "Intestinal failure"*

**Abbreviations**

aBWT: Average Bowel Wall Thickness
ACS: Abdominal Compartment Syndrome
ACLF: Acute-On-Chronic Liver Failure
AKI: Acute Kidney Injury
ADHF: Acute Decompensated Heart Failure
BUN: Blood Urea Nitrogen
CI: Cardiac Index
CO: Cardiac Output
CRP: C-Reactive Protein
CSA: Cross-Sectional Area
CVP: Central Venous Pressure
DAP: Diastolic Arterial Pressure
DPP: Diastolic Perfusion Pressure
eGFR: Estimated Glomerular Filtration Rate
FB: Fluid Balance
GI: Gastrointestinal
GFR: Glomerular Filtration Rate
GGT: Gama-Glutamyl Transferase
HABR: Hepatic Artery Buffer Response
HF: Heart Failure
HVPG: Hepatic Vein Pressure Gradient
IAP: Intra-abdominal Pressure
IAH: Intra-abdominal Hypertension
ICU: Intensive Care Unit
IL-6: Interleukin-6
IVC: Inferior Vena Cava
IVCc: Inferior Vena Cava Collapsibility
IVCcons: Constricted Inferior Vena Cava
IVCd: Inferior Vena Cava Diameter
JVP: Jugular Venous Pressure
LFT: Liver Function Tests
LPS: Lipopolysaccharides
LS: Liver Stiffness
LV: Left Ventricle
LVF: Left Ventricular Failure
LVEF: Left Ventricular Ejection Fraction
MAP: Mean Arterial Pressure
MCFP: Mean Circulatory Filling Pressure
MFI: Microcirculatory Flow Index
MPP: Mean Perfusion Pressure
MOD: Multiple Organ Dysfunction
MSFP: Mean Systemic Filling Pressure
NHE3: Sodium-Hydrogen Exchanger 3
PAC: Pulmonary Artery Catheter
PASP: Pulmonary Artery Systolic Pressure
PF: Portal Venous Flow Pulsatility
PI: Pulsatility Index
PPF: Portal Vein Pulsatility Fraction
PV: Portal Vein
PVCI: Portal Vein Congestion Index

PVPI: Portal Vein Pulsatility Index
POCUS: Point-Of-Care Ultrasound
RAAS: Renin-Angiotensin-Aldosterone System
RAP: Right Atrial Pressure
RI: Renal Arterial Resistive Index
RRT: Renal Replacement Therapy
RPP: Renal Perfusion Pressure
RVF: Right Ventricular Failure
RVP: Renal Venous Pressure
SA-AKI: Sepsis Acquired Acute Kidney Injury
SAPS II: Simplified Acute Physiology Score II
SBP: Systolic Blood Pressure
SCr: Serum Creatinine
SMA: Superior Mesenteric Artery
SIRS: Systemic Inflammatory Response Syndrome
SOFA: Sequential Organ Failure Assessment
STAT3: Signal Transducer and Activator of Transcription 3 Transcription Factor
SVR: Systemic Vascular Resistance
TAPSE: Tricuspid Annular Plane Systolic Excursion
TNF-α: Tumor Necrosis Factor α
US: Ultrasound
VC: Venous Congestion
VExUS: Venous Excess Ultrasound
VH: Venous Hypertension
VR: Venous Return
Vs: Stressed Volume
Vu: Unstressed Volume
WRF: Worsening Renal Function

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## Introduction

Multiple organ dysfunction (MOD) refers to an evolving clinical syndrome characterized by the development of otherwise unexplained abnormalities of organ function in critically ill patients.[1] MOD is associated with longer stays in the intensive care unit (ICU) and higher mortality rates.[1-3] It is considered a consequence of systemic inflammatory response, especially in trauma, sepsis, and surgical patients[1, 2, 4-7] where respiratory, cardiac, or renal dysfunction, and particularly mechanical ventilation and fluid resuscitation for acute circulatory failure may lead to venous congestion that in itself seems to have an impact on organ dysfunction.

Increased heart filling pressures are a sign of disease even when the primary cause lies outside the heart, as occurs in chronic or acute arterial or pulmonary hypertension, or in conditions affecting the semilunar valves or the left or right outflow tract. In heart failure (HF), worsening of cardiac systolic function causes a downshift in the Starling curve, meaning that cardiac output (CO) is maintained at the cost of a higher pressure than in the normal heart. In HF with preserved ejection fraction, impaired ventricular filling due to abnormal relaxation, increased stiffness or increased ventricular volume results in an upward and often rightward displacement of the diastolic pressure-volume relationship with increased end-diastolic, atrial, and venous pressures. This increase in venous pressure leads to symptoms of congestion, pulmonary when the affected ventricle is the left and systemic when the affected ventricle is the right. The cause of venous obstruction may lie before the ventricle, as happens with venous thrombosis or tumor both in the pulmonary or central venous circulation, congenital or acquired disease in the atria, or in the atrio-ventricular valves or by external compression of the heart by tumor or pericardial fluid.

Since congestive HF provides a model for the study of congestive states, most of the knowledge that exists so far regarding this topic focuses on HF patients. It was once thought that “forward failure” of the heart was the major cause of secondary organ lesions in patients with HF. However, research in the last decades has shown otherwise, demonstrating that venous congestion (VC), also referred to as “backward failure”, appears to be the primary hemodynamic cause of organ injury in these patients.[8-12]

Acute kidney injury (AKI) is widely prevalent in the ICU.[13] Renal dysfunction is associated with hypoperfusion but also VC. Indeed, elevated central venous pressure (CVP) is associated with greater mortality in critical ill patients with acute kidney injury[9, 10], although cardiac index (CI) has been shown not to be the main factor behind AKI in HF patients.[11] In patients with acute decompensated HF (ADHF), studies suggest VC is the main hemodynamic factor triggering AKI in patients.[12] In other conditions, such as septic AKI, not only does high CVP seem to be associated

with the development and progression of AKI[14], but also low CVP may have a protective effect on the kidney.[15]

Although earlier studies stated that possibly the cause for hepatic dysfunction in chronic HF was thrombotic occlusion of sinusoidal vessels leading to hepatic fibrosis[16], recent studies have shown more and more a relationship between elevated venous pressures and hepatic dysfunction related to biliary ductular compression under pressure inside non-distensible hepatic lobules. [8, 17-22]

Regarding intestinal injury, right ventricular failure (RVF) causes elevated venous pressure than can be transmitted to the portal circulation, causing intestinal edema[23], hypoxia, ischemia, and inflammation. It has been reported that RVF correlates with absorption deficiency and intestinal microbiome changes, which are also associated with cardiac cachexia.[24-29]

There are various methods for assessing organ congestion. However, there is an increase in interest in point-of-care ultrasound (POCUS) because of its accessibility at the bedside and non-invasiveness. [30, 31] Measurements of inferior venous cava (IVC) diameter, decreased respiratory IVC diameter variability, congestion index[32], portal vein pulsatility index (PI)[33, 34], portal hypertension[35], hepatic venous pressure gradient (HVPG)[36], liver stiffness(LS)[37], bowel wall thickness[23], all correlate with organ congestion and will be explored in this review. Recently, a new scoring system based on the Doppler assessment of portal and hepatic veins and ultrasound (US) IVC evaluation for prediction of AKI – Venous Excess Ultrasound Score (VExUS) [38-40] - has shown promising results and is in the process of validation for guiding decongestion in certain patient populations.[31, 41, 42]

Recognizing the importance of VC can shed a light on fluid management of various clinical conditions, such as congestive HF, shock/resuscitation, and acute kidney injury amongst others. In fact, in any condition where fluid therapy can be a possible therapeutic approach, one must monitor VC.[42]

In an ICU setting, when organ dysfunction is present, the main goal is to maintain organ perfusion pressure, but it may come at the risk of congestion[43], which is often neglected. [44] However, considering that congestion has deleterious effects on organ function, searching for better ways to assess volume status and organ congestion may have an impact on the management of fluid therapy, diuretics usage, and renal replacement therapy (RRT), both in acute and acute on chronic disease.

Therefore, this work aims to review the literature on the impact of VC on renal, hepatic, and intestinal injury, as well as methods to assess organ congestion in the ICU. Some basic physiological aspects will also be discussed since they are crucial for the understanding of the importance of VC.

## Methods

An initial search in the PubMed database using the keywords “venous congestion” “venous return”, “multiple organ failure”, “right-sided heart failure”, “positive fluid balance”, "central venous pressure", “hepatic failure", “acute kidney injury” and “intestinal dysfunction”, and combinations of these, was done to identify possibly eligible papers, from January 1980 to May 2022. Only articles in Portuguese, English, or Spanish and with available free text on PubMed, SpringerLink, Science Direct or ResearchGate were included.

The articles were analyzed regarding their title and abstract. If eligible for the purpose of this review, i.e., if the content made a possible connection between venous congestion, positive fluid balance or increased central venous pressure and organ dysfunction, the full text was acquired.

Full text papers were then analyzed, and relevant references from these articles that had not been identified in the initial search were included.

Most reviews and editorials were excluded unless they provided clues for future research. Case reports were also excluded, unless they provided findings important for the understanding of venous congestion.

(Figure 1)

## Multiple Organ Dysfunction

Multiple organ dysfunction (MOD) refers to an evolving clinical syndrome characterized by the development of otherwise unexplained abnormalities of organ function in critically ill patients. [1] It occurs when two or more organs or systems are in acute but potentially reversible dysfunction. It can be triggered by various conditions, such as trauma, sepsis, or shock. [1, 2, 4] It is common in the critical care patient and accounts for high mortality, up to 50% in adults, in the ICU. [1, 3]

Systemic VC is associated with worse outcomes [6, 45] and seems to be a major factor for organ failure, such as AKI [12, 46-48], hepatic [8, 19, 49], and gut dysfunction [24, 26-28]. A multicenter study revealed that for each 1 mmHg increase in central venous pressure (CVP), there was an 12% increased risk of death in noncardiac surgery patients in the ICU. [6]

MOD is associated with the systemic inflammatory response syndrome (SIRS) in most patients. [1, 2] VC may induce a pro-inflammatory response. In a cohort of 24 healthy subjects, peripheral VC was achieved by inflating a tourniquet cuff around the dominant arm and the expression of pro-inflammatory molecules such as interleukin-6, endothelin-1, angiotensin II, vascular cell adhesion molecule-1, and chemokine ligand 2 were shown to increase with peripheral VC. [50] These molecules are usually expressed in acute heart failure and renal failure, where inflammation, neurohormonal activation, and endothelial cell activation are often associated with venous congestion.

MOD in itself has no treatment. It relies on the urgent treatment of the underlying cause. Meanwhile, organ support is required to gain time for the body to recover.

Further research needs to be done on the effect of systemic congestion on MOD, since it could be important for the establishment of new hemodynamic targets.

## The Venous System and Venous Congestion

Before discussing the effect of VC on organ dysfunction, some physiology basics regarding circulation should be noted.

The main function of the venous system is to return blood from the periphery to the heart and the veins accommodate approximately 70% of all blood in one's circulatory system.[51, 52] The arterial side of the circulatory system is governed mostly by pressure differences and resistance, but this is not the case with venous circulation. Since veins are capacitance vessels[52, 53], a key mechanical factor in their hemodynamics is flow, but backward pressure is still important. We must think of VC, instead of venous flow.[51, 54]

VC refers to the increased pressure of fluid in the venous system. Various signs in the physical exam indicate VC, including elevated jugular venous pressure (JVP), hepatic enlargement, effusions, or edema. [45, 55]

Mean circulatory filling pressure (MCFP) is the elastic recoil in the vasculature caused by the stressed volume (Vs), the volume that is in the systemic circulation and stretches the vasculature and creates intravascular pressure in a steady-state.[51, 56] It is equal to the sum of the stressed volume divided by the total compliance of the system. In no flow conditions, it is equal to mean systemic filling pressure (MSFP). MCFP and MSFP are usually very similar since systemic vein compliance is dominant.

The unstressed volume (Vu) is the volume of blood in the systemic vasculature that isn't distending veins causing pressure; it accounts for 70-75% of circulation at rest. If one imagines the venous system as water filled bathtub with the drain on the side of the tub rather than the bottom, Vu is the water under the level of the drain. In stress situations, venoconstriction acts as a lowering the drain level of the bathtup, and more water (blood) can drain, shifting to Vs. [57] MSFP reflects Vs and is a determinant of the driving pressure of venous return. In case of need, there is an increase in MSFP, which increases venous return and, therefore, augments CO if the heart is operating in the ascend part of Starling's curve. [51, 58]. When the plateau of Starling's curve is reached, increasing blood volume or MSFP won't increase CO unless there is a reduction in CVP to maintain VR. [59]

Guyton et al., circa 1950, created a model that states that in a steady-state, the gradient between the MSFP and the pressure in the right atria (RAP) is the driving force for venous return (VR). This means that CO will decrease with the increase of RAP - this is known as Guyton's venous return curve [51, 52]. RAP is increased in positive pressure ventilation, cardiac tamponade, tension pneumothorax, among other situations, and this increase limits venous return. Therefore, in these situations, MSFP must increase to maintain CO. [52, 58] This model has since been criticized as some investigators believe that the cardiac pump is the key to pressure in the vasculature and that this view of venous return as the main component for circulation is an oversimplification. [60]

More and more research suggest that Guyton's curves are essential for a better understanding of hemodynamics and critical care management. Previously, animal models showed that by obtaining a set of steady-state CO and RAP values, it is possible to predict hemodynamic responses from changes in stressed volume. [61] Therefore, if we were able to get to steady-state conditions in patients, we could understand the determinants of circulation and use these measurements to achieve a better understanding of pathological circulatory states and how to manage them. Using inspiratory-hold maneuvers to achieve something proximal to a steady-state with VR equal to CO alongside contour-derived CO, VR curves can be generated and MSFP estimated at the bedside [62, 63] Arm stop-flow procedures also allow estimation of MSFP, as well as Vs. [64] Cardiac function and venous return curves can be created and predict fluid responsiveness. Guyton's model has also been applied to fluid challenges in postsurgical cardiac and critical ill patients, using an algorithm, Navigator CDSS, in conjunction with RAP to describe VR, and was shown to be accurate assessing CO response to volume expansion. [59, 65] Navigator CDSS uses a mathematical model to overcome limitations of using this model in clinical practice, such as the need for a steady-state. [59] However, these methods can trigger vascular reflexes and adaptative responses and not be 100% applicable in clinical practice. [56]

When volume is added to the veins when there is no more capacity for it, it's like adding water to something that's already filled-up - it will spill; it causes fluid extravasation, particularly if there is increased permeability. [51] In capsulated organs, this can cause parenchymal edema and hypoxia.

The Krogh model states that we have two sets of vascular beds – the splanchnic circulation, more compliant and which holds more volume, and the peripheral circulation, which is less compliant. Splanchnic circulation accommodates approximately 20% of total blood volume. It is a very compliant system that regulates volume shifts in stress situations in response to sympathetic nervous system signals. [52] Veins act in response to baroreceptors, chemoreceptors, and cardiac receptors, shifting unstressed to stressed volume in response to greater cardiac needs. [53] This two-model perspective makes sense from an evolutionary point of view as in states of hypovolemia, vital organs can be better protected from hypoxia and ischemia. [51] There's a shift of volume from the splanchnic circulation to the systemic circulation without an increase in venous resistance, which would decrease VR and CO. [52]

Estimation of MSFP, given that it reflects Vs, could be helpful to assess intravascular volume status in critical ill patients and provide therapeutic guidance. [64] For instance, we can add more volume through fluid infusions to increase MSFP or use venoconstrictors to decrease venous capacity and shift Vu to Vs. [52]

Regarding VC in the abdominal compartment, we should consider splanchnic venous resistance, the main sources of which are the hepatic veins and the liver itself. Great increases in this resistance can cause upstream congestion. Furthermore, persistent elevations of intra-abdominal (IAP) pressure can have different effects on VR, either leading to greater VR due to an increase in Vs in the splanchnic circulation or decreasing VR due to increased venous resistance.[52]

**Central Venous Pressure**

CVP is determined by the cardiac function, represented by the Starling curve, and its interaction with the return function, represented by the Guyton curve. This explains the need to measure CO coupled with CVP for the determination of fluid responsiveness. CVP has been used until recently to estimate cardiac preload and volume status.[52, 66]

In the absence of tricuspid stenosis, CVP is equal to right ventricular end-diastolic pressure. CVP may be increased due to volume overload, tricuspid regurgitation, right-sided heart failure, increased thoracic pressure, cardiac tamponade, and elevated IAP.[10, 52, 53] An increased CVP is an independent determinant of all-cause mortality in patients with cardiovascular disease or AKI and critically ill patients.[10, 48] A retrospective study in shock patients showed lower CVP was associated with higher CO and improved 28-day mortality rates. [67] In patients undergoing cardiac surgery, patients with CVP >11 mmHg post-ICU admission showed worse outcomes, suggesting that dividing patients in low and high CVP groups could be used for risk stratification for cardiac patients perioperatively in the future.[68] CVP was also associated with prolonged mechanical ventilation, ICU stays and mortality in patients undergoing lung transplantation.[69]. Mortality related to CVP was also higher in patients undergoing coronary artery bypass graft and associated with increased renal dysfunction.[70]

CVP has the disadvantage that its direct measurement requires an invasive procedure, the central venous catheter, such as several potential complications such as patient discomfort and catheter associated infection [53]. Also, accurate measurement is fraught with multiple causes of error. [66] Considering that normal CVP ranges are low, a 10 mm transducer placement error can have an impact on the interpretation and consequently hemodynamic management and can be associated with errors greater than CVP itself. There is also a significant inter-personal variability in its assessment. [71]

From a macrocirculatory perspective, mean perfusion pressure (MPP) is the difference between mean arterial pressure (MAP) and CVP. Maintaining an adequate MPP is used to obtain a normal organ perfusion. The microcirculatory perfusion pressure can be defined by the difference between post-arteriolar pressure and venular pressure. Microcirculation is considered a low-pressure compartment and it can be closer to CVP than MAP [72]. In fact, an observational study in

patients with septic shock showed that increases of MAP with norepinephrine did not correlate with improved severe microcirculatory alterations[73], but a post hoc analysis of a prospective study of microcirculation in septic patients after resuscitation revealed significantly decreased microcirculatory flow index (MFI) and percentage of perfused vessels in the cohort of patients with CVP >12 mmHg (high CVP) when compared to patients with CVP <12 mmHg (low CVP). Furthermore, $SvO_2$ was lower, and lactate was higher in the high CVP group. Curiously, high CVP was the only significant predictor for altered MFI.[72] Even though causality couldn't be assessed, it can be hypothesized that elevated venous pressures may cause microvascular impairment.

**Positive Fluid Balance**

Positive fluid balance (FB) has been associated with organ dysfunction, worse early and late outcomes, increased length of stay in critical care and cardiac surgery patients and is related to greater incidence of postoperative complications[74-85] In a recent retrospective study in a medical ICU, positive FB between the $4^{th}$ and $7^{th}$ day after admission was associated with increased long-term mortality in patients without shock. In patients with shock, positive FB in the first week was associated with increased long-term mortality.[77] In surgical ICU patients, a positive FB during surgery was associated with MOD, especially neurological, cardiovascular, and respiratory dysfunction, as well as more infectious complications.[85] However, in a study with critically ill patients with negative FB, increased fluid intake and urinary output were associated with a decrease in hospital mortality.[86]

In septic shock, initial management requires fluid resuscitation in the first hours, which was associated with decreased mortality. However, positive FB after resuscitation has been associated with worse outcomes and greater lengths of stay.[43, 87-92] In non-critically ill patients with sepsis, the relationship between worse outcomes and positive FB hasn't been shown.[93] The ideal way to hemodynamically manage these patients is still under debate.

A retrospective multicenter study of 778 septic shock patients showed a correlation between positive FB at resuscitation and in the 4 days post-admission. The same study demonstrated only a modest correlation between CVP and FB (FB) (r 0.2 and p<.001). Interestingly, in contradiction with the target CVP 8-12 mmHg recommended at the time, CVP at 12h of <8 mmHg had better survival rates, and survival rates continued to decrease with the elevations of CVP, even though CVP did not correlate with mortality on subsequent days. [43] Another study, with a similar population, revealed that positive FB was associated with greater ICU length of stay and in patients with higher FB, FB tends to increase during the shock period and after recovery. [94]

A multicenter study in ventilated patients with CVP monitoring showed decreased mortality with conservative fluid management in patients with low initial CVP (<8 mmHg), compared to liberal

fluid administration. However, negative FB was not associated with mortality.[95] In another study with surgical ICU patients, a negative FB 1 day after surgery showed decreased risk of infection or inflammatory complications.[83] Whether restrictive fluid management is an appropriate measure to counteract the negative outcomes in these patients is still something to be further studied in prospective randomized trials.

**Venous Congestion and Acute Kidney Injury**

Acute kidney injury (AKI) is a very prevalent condition in intensive care and is associated with worse outcomes, more re-hospitalizations, and greater length of stay affecting more than 50% of patients[10, 13, 96, 97]. It is very common in patients who experienced major blood losses, shock, and drug toxicity.[13, 97]

In a rat model with abdominal VC by constriction of the thoracic inferior vena cava, the group of rats with constricted IVC (IVCcons) had significantly increased spleen weight/tibia ratio which is reportedly an indicator of portal hypertension. Furthermore, SCr levels and cystatin C levels were higher in these animals twelve weeks after the procedure, indicating WRF was caused by abdominal VC. Interestingly, these rats also had albuminuria, suggesting that VC might have had a structural impact on the kidney, although glomerular density was similar between the IVCcons and the control group.[98] The same happens in renal vein thrombosis, where occlusion of the lumen causes upstream congestion. Some of the causes are external compression[99], nephrotic syndrome, infections[100, 101], and malignant renal tumors.[102] These are associated with structural changes such as renal vein dilatation, collateral venous vessels and nephromegaly, which can be assessed through renal ultrasound.[103]

Worsening renal function (WRF) is a consequence of VC in cardiac failure. However, it can be associated with other conditions, such as trauma or sepsis. Overall, in critical ill patients, increased CVP and the presence and severity of peripheral edema were associated with AKI in the first 7 days in the ICU.[104]

When associated with MOD, AKI in-hospital mortality is higher than 50%.[14, 97] In a large cohort of critical care patients, a prospective multicenter study demonstrated that 36% of all critical ill patients admitted for more than 24 hours developed AKI and had 60-day mortality rates of 35,6% and 37,8% for early and late-onset AKI, respectively when compared to overall critical ill patient 60-day mortality (23,3%).[105] This was reaffirmed recently, in a retrospective study including 1986 patients, showing that for each 1 mmHg increase in CVP, there was an increased risk of mortality for AKI as well. This relationship was further confirmed in a cohort of critical ill patients with multiple comorbidities with AKI.[106] Additionally, patients with CVP ≥ 10 mmHg had higher percentages of KDIGO stage 3 AKI, more complications, higher SOFA and SAPS II scores, and higher serum creatinine (SCr) and BUN, indicating that higher CVP might be correlated with severe disease.[9]

Renal perfusion pressure is the difference between renal arterial pressure and renal venous pressure (RVP). CVP must be lower than RVP to ensure adequate renal blood flow (RBF). When CVP approaches RVP, RBF is compromised, causing kidney dysfunction. Even in patients without volume overload, a high CVP could compromise RVP and increase the risk of AKI.[107] Maintaining RPP

through fluid therapy and pressure optimization is the basis of improving renal hemodynamics, however excessive efforts to increase MAP might be deleterious to renal function due to increased CVP, causing renal VC[14], also referred to as increased renal "afterload".[107] Overall, a meta-analysis of studies in critical patients reports that each increase in CVP of 1 mmHg, increases the risk of AKI by 6%. In patients with sepsis this number rises to 23%.[10]

**Positive Fluid Balance and Acute Kidney Injury**

Even though positive FB isn't the same as VC, they are intimately related.[43] Positive FB has been associated with increased mortality in critical[105, 108-110] and non-critical ill patients with AKI[111], and has been linked with decreased renal function[112]. Fluid overload has been associated in retrospective studies as a negative contributor for renal function recovery after RRT.[111]

In critically ill patients, a relationship between positive FB and mortality related to AKI has been observed with a more positive FB in AKI patients relative to non-AKI patients in the first week. Oliguric patients and patients who underwent RRT showed more positive fluid balances than non-oliguric, non-RRT patients. However, patients that started RRT earlier had shorter hospital stays and decreased mortality. At the time, it wasn't possible to establish a causal effect between positive FB and mortality.[105] At diagnosis of AKI, patients with fluid overload were less likely to recovery kidney function, and it was independently associated with mortality, with or without RRT.[108] In a cohort of patients with AKI who underwent RRT, fluid overload was found to be ≥10% higher in patients who did not recover renal function in the long term and a predictor of loss of renal function, indicating that FB could potentially be a marker for timing of initiation of RRT or a marker for AKI severity.[111]

In a prospective multicenter study regarding AKI in critical care patients, fluid overload was associated with an increased risk of mortality. Fluid accumulation increased in the 3 days before and after the diagnosis of AKI, and the speed of fluid accumulation was independently associated with ICU mortality.[109]

Beyond being associated with the development of AKI, positive FB has been also associated with underdiagnosis of AKI[113] and its severity can be underestimated due to hemodilution.[112, 114]

A randomized pilot trial using forced fluid removal versus standard care, was undertaken in 23 critically ill AKI patients. Although there were several limitations to the study, forced fluid removal with furosemide or RRT targeting a negative FB of 1 mL/Kg ideal body weight/hour may be an effective way to target fluid accumulation in AKI patients. However, further studies, with a larger

patient cohort including patients with other conditions causing positive FB should be performed.[115]

**Relationship between Venous Congestion, Heart Failure, and Acute Kidney Injury**

Heart failure causing AKI is called cardiorenal syndrome or worsening renal function. The importance of VC is now well established.[116] In patients with ADHF, WRF occurs in more than 20% of the patients[117, 118], reaching almost 40% in some studies.[119]

Congestion of the parenchyma in the non-distensible renal capsule causes an increase in interstitial renal pressure, which compresses parenchymal vessels causing changes in intra-renal flow[120], culminating in a decrease in glomerular filtration rate (GRF) and hypoxia of the renal parenchyma. Moreover, renal VC is associated with activation of sympathetic pathways and the renin-angiotensin-aldosterone system (RAAS)[121], leading to an intrarenal arterial vasoconstriction and decreased GFR[122]. Also, high renal pressure further decreases GFR due to loss of atrial natriuretic peptide effects.[121] Furthermore, duration, degree, and speed of fluid accumulation in AKI are associated with increased mortality in critical patients.[108, 109]

In HF, it has also been hypothesized that VC might be a source of inflammation, stimulating pro-inflammatory cytokines, oxidative stress, and interstitial macrophage infiltration. However, further investigation confirming a causal relation must be done, since only retrospective studies have been reported.[123]

Even though in patients with AHF it was originally thought that reduced CO leading to hypoperfusion of the kidney was the main reason for WRF, research in the last decades has shown otherwise[11, 121] It has been shown that in patients with cardiac dysfunction, not only decreased renal flow can lead to renal failure, but also VC. Studies in patients with diagnosed pulmonary hypertension with cardiac dysfunction showed that GFR is determined by VC and reduced CO. VC was determined by an increase in right atrial pressure (RAP). SCr levels in patients with increased venous pressure were also significantly higher. Furthermore, this study was particularly important because it showed an independent relationship between GFR and RAP, regardless of the renal blood flow (RBF), proving that, by itself, VC may be a cause for renal dysfunction. It is important to note that states of low RBF and high RAP add the lowest GFR, showing an additive effect. [124] In addition, a single-center study of the impact of CVP on impaired renal function in patients with ADHF revealed that only in patients with lower systolic blood pressure, CVP levels above 15 $cmH_2O$ were significantly associated with WRF, possibly reflecting the multifactorial essence of AKI. However, CVP at admission and discharge did not correlate with estimated Glomerular Filtration Rate (eGFR).[46]

High IAP had already been associated with renal failure in patients with liver transplants[19]. Further research showed that the reduction of IAP by mechanical fluid removal, causing relief in volume overload and therefore VC, could be responsible for renal function improvement in patients with acute decompensated heart failure (ADHF) refractory to intensive medical therapy.[125] This is relevant because it is easy to measure IAP, and it might be a target for the prevention and treatment of renal dysfunction. The ESCAPE trial, a large prospective study in patients with HF, found some correlation between baseline SCr levels and RAP as well as baseline GFR and RAP, but there was no significant correlation between baseline SCr and CI, suggesting, once again, that VC is a determinant of renal dysfunction. [126] More recent research in a similar population showed that baseline RAP did not predict WRF [127] but was a predictor of changes in GFR.

It was also observed that, in patients with ADHF, rather than CI, the presence of VC seems to be the primary hemodynamic factor driving WRF in patients with ADHF, proving that it can be more of a "backward failure" than a "forward failure". Furthermore, restoring CI with intensive medical therapy didn't seem to make a difference on whether WRF was developed or not[12]. Some level of disagreement is seen when it comes to this topic. For instance, this research stated that CVP was an adequate measurement for VC, however, elevated CVP at baseline was not a good predictor of baseline renal function.[47] Contrary to the latter research, a study in patients with ADHF, measuring RAP and other hemodynamic parameters, showed that although congestion was an important determinant of WRF, RAP was not a good surrogate for the magnitude of the congestion and risk of WRF.[127] In trying to preserve the renal function of patients with ADHF, one could consider using levosimendan, an inodilator with arterial and venous dilation properties by activation of potassium channels.[128] Significant improvements in GFR were seen in patients with severe low-output systolic HF receiving Levosimendan when compared with patients receiving dobutamine, even though both increased CO.[129] However, drugs such as this one, which supposedly improve renal perfusion haven't demonstrated improvement in outcomes in patients with HF.[130]

Some signs and symptoms of congestion can be observed on physical examination in patients with HF, such as elevated JVP, effusions, peripheral edema, and orthopnea. It has been shown that these signs and symptoms are associated with decreased renal function and worse prognosis with more signs of congestion associated with worse prognosis.[8] Furthermore, in agreement with previous investigations, the cohort of patients with the best left cardiac function had significant deterioration of renal function if signs and symptoms of VC were present.[131] Management of these patients is always a challenge - on one hand, diuretics can be used to reduce congestion [132], but on the other, they can cause decreased renal blood flow, leading to decreased

GFR[133, 134] and worse outcomes if in high dosages.[55] Interestingly though, a study using the ESCAPE trial database, showed that aggressive decongestion, even at the cost of WRF, may be associated with greater survival rates.[135] It is hypothesized that this may not be the consequence of a cause-effect relationship but may occur because the subjects that are aggressively decongested have healthier kidney function and therefore are more responsive to diuretics.[136] Hence, in patients that have a chronically diseased kidney, either due to WRF or other comorbidities such as diabetic or hypertensive nephropathy or even nephrotoxicity, increasing diuretic usage won't improve renal function or patient outcomes, since the kidney isn't able to respond.[134] In these patients, ultrafiltration might be helpful, since studies indicate that in congestive HF patients, starting ultrafiltration before intravenous diuretics wasn't associated with complications like WRF and resulted in reduced length of stay and decreased re-hospitalizations in the next 3 months.[137] Moreover, a randomized trial showed that patients with HF treated with ultrafiltration had more weight loss and symptomatic relief, and lower HF readmission rates when compared to patients treated with intravenous diuretics. Ultrafiltration was also associated with reduced events when compared to standard diuretic use in this study.[138]

This idea that renal venous hypertension can be a key determinant in renal dysfunction in HF was further accentuated when new research using the ESCAPE trial database revealed no correlation between CI and eGFR in patients with decompensated HF, meaning that hypoperfusion may not be the major marker for developing WRF.[11]

Increased CVP was also associated with impaired renal function in a broad spectrum of cardiovascular patients, and it is also a risk factor for decreased renal function in patients with decreased or preserved cardiac function. It should be noted that increases in CVP up to 6 mmHg were accompanied by a gradual and subtle increase in GFR. However, patients with CVP above 6 mmHg had a significant decrease in GFR, probably because the plateau between VR and CO was achieved.[48]

In patients with chronic HF with renal dysfunction, dilation of peritubular capillaries of the kidney, as well as the presence of fibrosis and tissue nitrosylation, CD-68 cell infiltration in the renal interstitium suggest that VC is associated with renal oxidative stress and inflammation.[123]

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**Relationship between Venous Congestion, Septic Shock, and Acute Kidney Injury**

Septic AKI is associated with a higher burden of illness, changes in blood biochemistry and increased markers of inflammation, nonrenal organ failure, greater hospital length of stay and mortality.[139, 140] Almost 40% of patients with severe sepsis develop AKI. In these patients, AKI is most common if septic shock is present.[139]

The management of sepsis shock is based on achieving optimal hemodynamic balance, with guidelines recommending targeting MAP of at least 65 mmHg at initial resuscitation. [141]

A retrospective observational study in critical ill patients with septic AKI showed significantly higher CVP levels in the AKI group, opposite to other hemodynamic parameters which revealed a weak relationship with the development or progression of AKI. Furthermore, CVP had a practically linear relationship with new or persistent AKI, suggesting a connection between VC and AKI in septic shock. Furthermore, it suggests that optimal renal perfusion is achieved at CVP below 8 mmHg [14], which was the interval target CVP suggested by the Sepsis Survival Campaign guidelines for septic shock and sepsis at that time for non-mechanically ventilated patients. [142] Diastolic perfusion pressure (DPP) is defined as difference between DAP and CVP. DPP, in this study, averaged around 35 mmHg in the AKI group and 42 mmHg in the non-AKI group. Also, DAP was lower between the AKI and non-AKI groups, whereas CO and arterial pressure were not. Since renal vascular resistance is low, DAP might be a target for maintaining organ perfusion in septic AKI. The retrospective aspect of this study doesn't allow a causal relationship to be proven.[14]

In patients with septic shock, it was determined that MAP and mean perfusion pressure (MPP) deficits between premorbid values and those in the ICU after 24 hours were averaging around 15% for MAP, 20% for MPP and there was also 20% CVP excess. Additionally, time-weighted CVP was significantly higher in patients with severe AKI whereas time-weighted MAP and MPP were similar in patients with or without severe AKI. On top of that, higher CVP was associated with worsening AKI in patients with septic shock and undifferentiated shock. Accordingly, it is thought that in septic shock, CVP should impose a limit in management and not a target.[143]

Hemodynamic targets for AKI prevention are still not well established. [144] MAP is usually used as a target for organ perfusion improvement, even though there's little evidence of MAP being accurate for this purpose. In a large multicenter prospective randomized study, targeting MAP of 80-85 mmHg did not improve 28- or 90-day mortality. However, in patients with chronic arterial hypertension, targeting higher MAP reduced the incidence of doubling SCr and rate of RRT.[145]

Even though positive FB has been associated with worse outcomes in septic shock[87-89], a retrospective study in severe sepsis and septic shock patients found that positive FB was neither a risk nor a protective factor for AKI in these patients[146], although, in another prospective study in critical ill patients, mean fluid overload was stated as a risk factor for developing AKI.[109]

**Abdominal Compartment Syndrome and Acute Kidney Injury**

Increased abdominal pressure restricts venous blood flow, causing congestion with organ dysfunction, known as Abdominal Compartment Syndrome (ACS). In the ICU, around 32% of

patients develop intra-abdominal hypertension (IAH) and abdominal compartment syndrome has a prevalence of around 4,2% and is associated with MOD.[147]

ACS is associated with large volume resuscitation and transfusion, open body surgery, coagulopathy, septic shock, and mechanical ventilation.[147, 148] FB and peak airway pressure are predictive of ACS in non-trauma surgical patients. For instance, a patient with a peak airway pressure of 45 mmHg and 12L positive FB has a 41% chance of developing ACS.[149]

Intra-abdominal hypertension (IAH) in a cohort of patients with abdominal trauma had higher incidence and severity of MOD as well as increased mortality compared to patients without IAH. [150] Abdominal compartment syndrome (ACS) secondary to severe shock is associated with very high mortality rates and massive fluid resuscitation appears to be a critical factor for its development. [151, 152] Furthermore, studies have also identified an association between ACS and more ventilator days and MOD.[152]

IAH often causes renal dysfunction in critical and surgical patients. It is associated with hypotension and shock, commonly as a consequence of severe abdominal trauma. [153-155] AKI in trauma is often multifactorial. It can be associated, in an earlier stage, with direct kidney injury, rhabdomyolysis, or hemorrhagic shock and, in a later stage, with abdominal compartment syndrome, reperfusion injury after high volume resuscitation, nephrotoxic drugs or sepsis. Higher volumes of blood transfused were associated with an increased risk of AKI in trauma patients.[156]

Increased IAP is associated with a decrease in SCr and IAP above 15 mmHg causes oliguria due to hypoperfusion and renal compression. In a prospective study in critically ill patients, shock and cumulative FB were independent predictors of IAH. 70% of the patients who developed IAH had diseases associated with high volume fluid resuscitation, inflammation, and increased capillary permeability, like shock, sepsis, or SIRS.[153] Histological examination of rat kidneys has shown that elevations in urea and SCr due to IAH were associated with glomerular congestion, interstitial hemorrhage, pelvicalyceal and ureteral dilation.[157]

In 2020, a case report showed renal VC following traumatic liver injury causing hemorrhagic shock. This was the first reported case of trauma-induced renal VC, where a hematoma compressed the IVC, causing AKI. This suggests that renal VC should be assessed in the presence of unexplained AKI in trauma patients.[158]

**Venous Congestion in Liver Dysfunction**

More than half of the patients in the ICU have abnormal liver function tests (LFT).[159] Liver dysfunction is a determinant of mortality in multiple organ failure.[160] It can express itself in two ways: acute liver failure or, more commonly, decompensation of chronic liver disease, frequently associated with acute on chronic liver failure (ACLF).[161] Passive hepatic congestion due to elevated CVP impairs oxygen and nutrient delivery, generating hypoxia but also structural changes like enlargement of sinusoidal fenestrae.[162, 163] Centrilobular pressure is transmitted to the liver sinusoids, compressing lobule structures like bile ducts.[164] Congestion can manifest as portal hypertension which can be the root cause of complications of liver dysfunction such as spontaneous bacterial peritonitis or ascites, hepatorenal syndrome, or even acute kidney failure.[161]

The term congestive hepatopathy refers to signs and symptoms of chronic passive congestion of the liver in the context of HF, and other conditions that lead to augmented CVP, such as tricuspid regurgitation, restrictive cardiomyopathy, or intrinsic or extrinsic vascular obstruction of the organ. Hepatic artery buffer response (HABR) allows the liver to compensate for up to a 60% increase in portal flow, accounting for the liver resistance to injury.[165] Despite that, HABR can be exhausted, leading to tissue damage.[166] When a hepatic injury in congestive states does occur, it is due to three possible mechanisms: reduced blood flow, reduced arterial oxygen saturation, and/or increased hepatic venous pressure. Hepatic function alterations are expected when CVP rises above 10 mmHg and CI is below 1,5 L/min.m$^2$.[49, 167-169] Tricuspid regurgitation is a cause of elevated CVP, leading to hepatic congestion, and is also associated with liver dysfunction.[170] Another retrospective study showed that CVP rather than CI was the major determinant for gamma-glutamyl transferase (GGT) changes. [8] Increased venous pressures cause sinusoidal congestion and edema, resulting in hypoxia and ischemia and eventually fibrosis [171, 172]. Furthermore, chronically elevated CVP is the major cause of chronic liver disease due to cardiac dysfunction.[167] Other hepatic conditions, such as Fontan liver disease, also suggest that continuously elevated hepatic venous pressures can lead to hepatic injury and ultimately liver cirrhosis. [20, 21] The same is true for congenital heart defects causing right-sided heart failure.[167, 173]

Hypoxic hepatitis has an incidence of approximately 2% in critically ill patients. It is usually accompanied by other organ dysfunction, especially acute renal failure.[49, 174] It is triggered by an acute drop in CO or hypoperfusion associated with increased venous pressure, usually in patients with congestive HF.[49, 168, 172] One study revealed that elevation of hepatic markers in 322 episodes of hypoxic hepatopathy was identified in patients with and without hypotension, indicating that hypoperfusion isn't the only reason behind this illness. [175] Another study, done over a 10 year period in an ICU, showed that all patients with congestive HF who developed hypoxic

hepatitis had signs of right heart failure and elevated CVP. [168] Furthermore, chronically elevated CVP is the major cause of chronic liver disease due to cardiac dysfunction.[167]

In other situations, like liver transplant, VC due to regional venous outflow interruption causes an impact on the clinical course post-transplant. The higher degree of congestion volume of the remnant liver was associated with a delay in the recovery of liver function, poor regeneration, and transient liver dysfunction. [17]

Regarding sepsis, liver congestion itself won't be the cause of it. However, if sepsis is present, the state of constant inflammation provoked by prolonged venous pressure, along with the production of inflammatory cytokines and acute-phase proteins in the liver in response to aggression, can be a risk factor for a worse prognosis.[176]

**Venous congestion in Intestinal Dysfunction**

Intestinal failure is related to the incapability of the intestinal wall to absorb nutrients or water.[177] Dysfunction of the intestine is said to be the main factor for MOD.[178] In critically ill patients, inadequate splanchnic blood flow is a cause of morbidity and mortality in ICU.[179]

The splanchnic system accommodates around 20% of total blood volume. [52] Since, as it was previously stated, the splanchnic circulation is very compliant, it ends up being the greatest venous reservoir. Sympathetic nervous system activation, as it happens in HF and other conditions, decreases splanchnic venous capacitance by venoconstriction, shifting Vu to Vs. Therefore, there's an increased volume of blood circulating that can cause congestion.[172] More than intestinal ischemia, intestinal congestion can cause severe gut damage and prolonged recovery times. Intestinal congestion reperfusion injury is related to several pathologies such as liver transplantation, portal vein occlusion, or mesenteric vein thromboses[180] Ischemia caused by VC creates an acidotic environment that incites mechanisms of FB, such as the sodium-hydrogen exchanger 3 (NHE3), which exchanges $Na^+$ for $H^+$, creating an even greater fluid overload in a vicious cycle. On the other hand, $H^+$ excess on the intestinal tract deregulates the microbiome, increasing LPS levels and causing endothelial damage.[26]

High volume resuscitation with crystalloids and transfusions in situations like hemorrhagic shock, induce rapid increases in hydrostatic pressure – inducing venous hypertension and shifting volume to the interstitium causing intestinal edema.[181] Besides that, hypoproteinemia due to hemodilution in high volume crystalloid infusion is also a contributing factor to edema since it decreases oncotic pressure.[181-183]

A rat model created to obtain mesenteric venous hypertension and gut edema without resuscitation-induced injury and determine the main factor contributing to intestinal dysfunction, revealed that acute mesenteric venous hypertension, and not only crystalloid resuscitation, produce gut edema associated with increased permeability and decreased epithelial resistance. The effects of venous hypertension lasted for more than 12 hours after surgery, but no ischemia, signs of inflammation, or injury were reported, but both mesenteric venous hypertension and crystalloid resuscitation were correlated between impairment intestinal transit and alterations in intestinal permeability. [181] Also in a rat experiment, it was shown that gut edema due to resuscitation is associate with expression of inducible nitric oxide synthase (iNOS) [184] which induces inhibition of intestinal transit. [185] This could correlate with intestinal ileus, which is common after abdominal surgery, patients under mechanical ventilation, or patients with sepsis under vasopressors [182, 183] and correlates with increased morbidity and healthcare costs. Congestion-induced ileus seems to represent a vicious cycle. For once, VC causes ileus but on the other ileus represents impaired peristalsis which impedes lymphatic drainage and increases edema. [183] Also, in rats in

hemorrhagic shock presenting with a 30-60% decreased jejunal wall contractility, increased polymorphonuclear cell (PMN) infiltration was observed, as well as increased interleukin-6 (IL-6) and granulocyte-colony stimulation factor (G-CSF), suggesting a pro-inflammatory state. [186] This implies that, in congestion-induced edema, similar mechanisms might be at work.

Delayed GI transit is due to diminished intestinal contractile activity because of decreased levels of myosin light chain (MLC) phosphorylation and studies in rat models with VH and fluid resuscitation revealed an increase in the signal transducer and activator of transcription 3 (STAT3) transcription factor, even though the same wasn't true for rats with only VH or only fluid resuscitation. Furthermore, AG490 (selective Janus kinase 2 (JAK2) inhibitor) inhibits STAT3 and seems to have a reversal effect on diminished contractility and MLC phosphorylation. [187]

Rat models of hemorrhagic shock demonstrate high levels of neutrophils in the muscularis 4h hours post-resuscitation and increased further after 24h, a correlation between decreased motility and quantity of neutrophiles infiltration was also observed and mucosal lesion in resuscitated animals, suggesting induction of inflammatory response causing intestinal injury during resuscitation. [178]

In chronic HF, elevated RAP causes mesenteric VC leading to injury. Engorging of venous intestinal vessels and capillary leaking causes edema which produces increases in intestinal wall thickness, resulting in dysmotility, malabsorption, gastrointestinal (GI) symptoms as well as appetite loss. Furthermore, increases in intestinal permeability, impairment of mucosal barrier function, providing an entryway for lipopolysaccharides (LPS) or endotoxins produced by bacteria, bacterial translocation, and induction of pro-inflammatory cytokine production are to be expected, such as tumor necrosis factor α (TNF- α). [25, 28, 29, 172, 180, 188, 189] Bowel edema was also associated with C-reactive protein levels and blood leukocytes. [29] Protein-leaking is also related to high venous pressures, being described not only in HF but also in constrictive pericarditis, tricuspid regurgitation, and congenital heart disease [172]. Interestingly, after diuretic administration in CHF patients with edema, a decrease in endotoxin concentrations was observed. [188] In a dog model, elevated CVP causes decreased lymph flow to the thoracic duct. Induced increased IVC pressure, caused elevation of portal and cisterna chily pressure leading to bowel edema and ascites. [190]

Patients with CHF seem to have intestinal edema even if they don't have any signs of peripheral edema or GI symptoms. [29] Cardiac cachexia has a multifactorial nature, but in part can be attributed to malabsorption; it is mostly related to right ventricular (RV) dysfunction [28], hence the thesis that intestinal congestion might be related to cachexia. 20 HF patients with moderate and severe left ventricular dysfunction diagnosed with cardiac cachexia went through abdominal US and echocardiography, against a control group, where bowel wall thickness was measured and

their appetite, GI symptoms, and functional status evaluated. As expected, cachectic patients had higher RV dysfunction and higher RAP. In addition, left ventricular ejection fraction (LVEF) was less accurate at discerning cachexia than the combination of RAP and tricuspid annular plane systolic excursion (TAPSE) [191] - an echocardiographic parameter related to RV function. Higher RAP seems important for the development of cachexia since in patients with RV dysfunction and normal CVP cachexia was less common. Cachectic patients also had thicker bowel walls, and elevated RAP and RV dysfunction were linked to higher to greater average bowel wall thickness (aBWT), which makes sense due to splanchnic venous accumulation. Intestinal edema correlated with C reactive protein, an acute phase reactor, hypothetically due to chronic translocation of LPS, GI symptoms, and overall cachexia. Grossly, intestinal VC seems to be associated with cachexia in HF patients. [27]

In cirrhotic patients, portal hypertension is also associated with intestinal edema and therefore bowel wall dysfunction and motility alterations and correlates with intestinal permeability and bacterial overgrowth in this population. [192-195] These changes corelate with GI symptoms in these patients. [196]

**Abdominal Compartment Syndrome and Intestinal Dysfunction**

Venous obstruction caused by IAH leads to increases of capillary hydrostatic pressure and impacts blood flow. Hence, when the there's high volume resuscitation, the interstitial pressure rises and causes gut edema. [190, 197]

Resuscitation induced gut edema, caused by raised mesenteric venous hypertension, is a contributor for abdominal compartment syndrome and multiple organ failure. It is commonly associated with fluid resuscitation from post-traumatic hemorrhagic shock. [198] Resuscitation with excessive crystalloid fluids was associated with decreased intestinal perfusion, higher incidence of intra-abdominal hypertension, abdominal compartment syndrome, MOD, and mortality. [199]

Tension pneumoperitoneum, which causes IAH, has been shown to decrease intestinal and hepatic microcirculation, causing ischemia.[200-202] When the tension is released, as reperfusion starts, there is an increase in oxygen free radicals. IAH was also linked to bacterial translocation. [200] IAH can also be associated with gastric mucosal acidosis shown by a study that revealed improvement of pH in 6 out of 8 patients with gastric mucosal acidosis and IAH. [150] Moreover, IAH was associated in an animal model with increased cytokine production, such as IL-1β and IL-6, and reperfusion might be associated with increased release of TNF-α. [203]

**Future perspectives**

The question of whether targeting right-sided pressures to alleviate congestion is still under debate, and further studies must be performed. [27] Nonetheless, improvement of RV function with Omecamtiv Mecarbil, a direct myosin activator, or Ranolazine, a $Na^+$ current inhibitor may be an option to explore. On the other hand, NHE3 inhibitors like Tenapanor have the potential to alleviate not only gut congestion but also restore the gut microbiome. Rat model studies suggest improvements in LV hypertrophy, albuminuria, and blood pressure, making it a promising drug for HF. [204]

Regarding management of intestinal congestion, studies suggest that decreasing the amount of fluid given after surgery is a source of better outcomes, not only when it comes to morbidity, incision complications, and cardiopulmonary complications but also in terms of faster GI recovery and shorter hospital stays. [205, 206] In this sense, fluid objectives after surgery could be lowered without compromising the patient and could have the chance to improve outcomes. However, in a study with 3000 patients undergoing major abdominal surgery, restrictive fluid therapy did not improve 1-year outcomes, and patients given liberal fluid therapy had decreased acute kidney injury. [207]

Additionally, targeting molecules such as STAT3, using, for example, AG490 or other JAK2 inhibitors, might be a possibility for treatment of edema-induced intestinal dysfunction or other conditions causing decreased contractile dysfunction due to congestion. [187]

Nuclear factor κB (NF-κB) is a transcription factor associated with inflammation and oxidative stress that resulted in the suppression of colonic contractility in canine models [208] and it could be studied in congestion-induced intestinal dysfunction as it could also be a target for the treatment of the congestion consequences on the gut.

## Assessment of Venous Congestion

### Inferior vena cava measurements: a surrogate for venous congestion?

Point-of-care ultrasound (POCUS) is a useful tool to evaluate VC and guide hemodynamic therapeutic options at the bedside. Echocardiographic IVC diameter and its respiratory changes are used to estimate RAP. [209, 210]. Echocardiography is the initial screening for VC since IVC and RV are the first places wher VC becomes apparent. [38] In patients with and without heart failure, dilated IVC (> 2cm) without respiratory collapse is a predictor of 90-day and 1-year poor outcomes.[210] In the intensive care setting, qualitative assessment of IVCd had a good correlation with quantitative assessment and there was no significant inter-operator variation. Hence, US is an accessible, reproducible and non-invasive way to evaluate the IVC. [211] IVCd correlates with congestion index and congestion symptoms in patients with and without HF.[210] Moreover, it also has been related with renal [48] and hepatic dysfunction. [212]

In hemodynamically stable patients without mechanical ventilation, end-inspiratory IVCd had a good correlation with RAP, and IVC collapsibility (IVCc) had an accuracy of 88% for RAP < 10 mmHg (IVCc <50%) and 81% for RAP <10 mmHg (IVCc ≥50%). [213] IVDd sniff test showed the highest accuracy for determination of RAP in patients undergoing right heart catheterization. [214]

Critically ill patients often aren't stabilized and need mechanical ventilation. In spontaneously breathing patients, when there's increased venous return, IVCd in inspiration compared to IVCd in expiration (IVC collapsibility index) is decreased. The opposite happens in mechanically ventilated patients, and IVC distensibility index is increased since there is positive pressure applied during inspiration. Therefore, it can be a useful tool to assess fluid responsiveness and seems to have the same predictive value as pulse pressure variation [215] in mechanically ventilated patients [199, 215, 216] However, this hasn't been validated in patients with non-invasive ventilation or high PEEP levels. Furthermore, in patients with conditions that limit venous return, such as tricuspid regurgitation, IVCd is dilated at baseline, causing bias in this method for assessing fluid responsiveness. Also, an increase in IAP can cause the IVC to collapse and have decreased diameter. [217, 218]

Pressure flows backwards from the IVC, eventually causing changes in portal vein flow, going from a monophasic pattern to a pulsatile one. [42] A retrospective study in cardiac surgery patients who underwent POCUS transthoracic echography revealed that Doppler evaluation of portal and splenic veins might be an accurate way to assess organ congestion in this population. [35] One of the parameters measured is Doppler US of the portal venous flow pulsatility (PF), which will be further explained since it is related to fluid overload.

**Assessment of Renal Congestion**

Evaluation of VC is essential for hemodynamic management in the critically ill patient. As stated previously, CVP is an independent predictor of mortality and poor prognosis for critical patients with AKI [9].

Regarding renal VC, there is no consensus on the better way to assess it. [38]. Doppler ultrasonography (US) is a great tool for easy assessment of renal venous and arterial blood flow. Elevated CVP can be transmitted backward, resulting in hepatic venous flow and intrarenal venous flow pattern alterations. [219] Inferior vena cava diameter is a determinant of estimated GFR in HF[123] and its dilation was associated with WRF in ADHF. [220]

Normal portal vein flow occurs with minimal variations of flow velocities in Doppler US. Abnormalities in systolic or diastolic flow waves are seen when there is congestion. Portal pulsatility fraction (PF) quantifies portal flow variation using the assessment of maximum and minimum velocities ($V_{max}$ and $V_{min}$) in the following equation: $PF(\%) = 100[\frac{Vmax-Vmin}{Vmax}]$.

Elevated PF is suggestive of cardiogenic portal hypertension, due to pulmonary hypertension, right ventricular failure, or tricuspid regurgitation. [35] Individuals with a pulsatile portal flow are at high risk for the development of AKI. [39]. Assessment of intrarenal vein Doppler waveforms also correlates with changes in CVP, switching from a continuous flow in a normal state to a pulsatile and biphasic flow (with systolic and diastolic waves) in a congestive state or a monophasic diastolic wave if severe congestion is present. [219] [30] Intrarenal venous flow (IRVF) is affected by CVP and renal parenchymal changes. In a study by Ilda et. al, 217 patients with HF underwent renal Doppler US evaluation; monophasic renal vein patterns were correlated with higher RAP levels and BUN and lower eGFR and systolic blood pressure, when compared with the other two patterns mentioned previously. Additionally, mean RAP was higher in patients with biphasic flow patterns, when compared to those with continuous patterns. A significant relation wasn't seen for CI. Discontinuous patterns were associated with worse outcomes. Generally, IRVF can potentially be a good surrogate for assessing renal VC, especially in patients with HF, because it seems to be more accurate to detect potentially dangerous VC than CVP, which makes sense since renal VC has more than one mechanism behind it. Despite this, the development of WRF wasn't significantly associated with any flow pattern, even though its prevalence was greater in the monophasic group. Increased renal arterial resistive index (RI) (≥ 0.70), calculated by the following equation:

$$RI = (VPeakSyst - VMinDiast)/\mathrm{VPeakSyst}$$

where Vpeaksyst is the peak systolic flow velocity of intrarenal arteries and VMinDiast is the minimum diastolic flow. IRVF patterns, rather than RI, depended on RAP, suggesting a correlation

with renal congestion. In this study IRVF patterns strongly correlated with clinical outcomes independent of RAP. [120]

In renal obstruction, markers of VC in Doppler US can be useful. For instance, an obstruction can create a decrease in renal compliance and an increase in renal interstitial pressure, causing a low intrarenal venous impedance index [221]

A prospective observational study showed that portal flow pulsatility and intrarenal flow alterations are accurate markers for VC and are independently associated with WRF after cardiac surgery and can potentially predict the development of AKI. [39] Moreover, US patterns of renal VC have a predictive value in the detection of renal dysfunction and stratification of prognosis in CHF [222]. In this sense, POCUS using Doppler is a useful tool to estimate VC and it has the advantage of being done at the bedside and can be very helpful in an ICU setting. In addition, it has the advantage of permitting assessment of VC without the need for a central venous catheter. [39] It can possibly identify patients at high risk for the development of WRF and guide treatment. [220]

Assessment of intrarenal flow alterations seems to be more difficult and has a lower success rate than evaluation of portal flow and for this reason, portal flow measurements might be more applicable daily. [39] [30] However, basing VC assessment only on PF might lead to errors. [39]. Hence, the Venous ultrasound grading system (VExUS) was created, which is a grading system based on the severity of echocardiographic markers of VC that allows the practitioner to assess systemic congestion. This system combines measurement of the diameter of the IVC and venous Doppler waveforms of the portal, hepatic, and interlobular renal veins. The 3 components of assessment of congestion by VExUS are described in Table 1 according to severity, making up 5 VExUS grades, from A to E, that ultimately translate to 4 grades of systemic VC, described in table 2. If two or more severe alterations of the hepatic vein, portal vein, or intra-renal venous flow with an increased IVC diameter (≥ 2 cm) indicate a greater risk of post-surgery AKI. Curiously, there wasn't a statistically significant correlation between RHF and VExUS score, meaning that VExUS might be more a predictor of fluid overload than cardiac dysfunction. [40]

In a prospective study with 30 ICU patients with cardiorenal syndrome and AKI, 87% of patients with resolving AKI had a decrease in VExUS score, meaning that we can probably correlate the improvement of grade with the improvement of AKI. Accordingly, VExUS might have a prognostic purpose as well. Interestingly, even though elevated CVP correlated with AKI, it didn't normalize with the clinical improvement of the patients, proving that it is not a reliable prognostic tool. This research is especially relevant regarding fluid therapy in the treatment of such conditions, hence why it was proposed that a non-post-renal AKI with VExUS grade 0 should be treated with fluids, but a grade 2 or 3 without cardiac dysfunction might benefit from diuretics only. [38] Some case reports also indicate that VExUS might be useful for therapy guidance in perioperative

settings.[41] Despite all this, randomized trials with bigger cohorts should be done to further validate this assessment approach. [38]

**Assessment of Hepatic Congestion**

For diagnosis of hepatic VC, biochemical profiles lack interest since LFT aren't specific and generally of a small magnitude. However, changes in LFT in HF are strongly associated with elevated CVP. Moreover, in patients with congestive HF, the elevation of cholestatic parameters particularly elevated bilirubin levels in patients with volume overload should raise suspicion on potential hepatic suffering due to elevated CVP. [212, 223, 224] Elevated prothrombin time associated with high serum bilirubin is a usual pattern in passive congestion. [173] A 2014 review suggests that LFT might be useful as another indicator of congestion and may be used in the future to adjust the dose and length of diuretic use in ADHF. [225] It is hypothesized that hepatic congestion can be linked to nonspecific mechanical obstruction of the bile ducts, causing ischemia. [226]

Hepatic Doppler US can provide information on portal vein blood flow [227], since pressure flows backward through the veins, creating flow and structural changes. [223]
The Portal vein pulsatility index (PI) is a percentage of peak-to-peak maximum portal vein velocities. Firstly, it was associated with the prediction of right cardiac failure. [34] Later, it was shown that PI seems to be lower than 40% if RAP is <10 mmHg and >40% if RAP is >10 mmHg, indicating that it might be a way to evaluate right cardiac function. Besides, it is a better indicator of right heart function than the congestion index.[33]

Liver stiffness (LS), which relates to its resistance to deformation, is also directly linked with VC. It is affected by changes in the extracellular matrix – for instance liver fibrosis, pressure around the organ, and pressure inside it, like congestion, which creates resistance within the liver and viscosity. Measurements of LS can be performed via vibration-controlled transient elastography, a non-invasive method that can substitute hepatic biopsy. LS is increased in decompensated HF, and it reverts in response to diuretic therapy; however, constant congestion may increase LS and ultimately induce liver cirrhosis. [37]

Measurements of congestion liver area on CT scan with contrast enhancement are also a possibility, observed as a hyperattenuating of the signal on the arterial phase. [17]

Occlusive hepatic vein catheterization is very invasive and is no longer performed for measuring portal vein pressures. [36] However, transjugular liver biopsy allows the assessment of venous pressures using a catheter through the jugular vein to the hepatic vein. [172] Hepatic venous pressure gradient (HVPG) ($HVPG = Pwedge - Pfree$), the gradient of pressure between the portal and hepatic veins, evaluates the existence and severity of portal hypertension. [36] In patients with ascites, HVPG allows differentiating between cardiac or liver ascites. [172, 173]

**Assessment of Intestinal Congestion**

A prospective single-center investigation studied the impact of hemodynamic HF changes on intestinal function. The abdominal US was performed, measuring cross-sectional area (CSA), maximum velocity, blood flow volume, pulsatility index (PI) ($PI = (Vmax - Vmin)/Vmean$) of the superior mesenteric artery (SMA), inferior mesentery artery, and portal vein (PV) and congestion index at PV (PVCI) ($PVCI = CSA/Vmean$)) [32]; evaluation of aBWT was also performed by the median of ascending, transverse, descending, and sigmoid colon thicknesses. PVCI and aBWT, a reflection of VC and intestinal edema, respectively, were associated with worse outcomes and symptoms in ADHF patients and advanced right ventricular dysfunction. aBWT correlated with PV CSA and PVCI, suggesting a relationship between intestinal edema and VC; and higher levels of CPR and lower serum albumin. Hypothetically, intestinal VC can then be associated with inflammation. [23]

## Conclusion

The venous system and its properties are commonly overlooked in clinical practice, especially when it comes to hemodynamic management; and the role of VC in organ dysfunction is usually underestimated.

Renal, hepatic, and intestinal dysfunction are common in critical care [13], and they can coexist in the same patient with MOD. VC could be one of the links between these entities.

Increased CVP and IAP are associated with AKI [14, 19, 98, 108, 158] and worse outcomes [108]. Congestion of renal parenchyma causes decreased GFR and hypoxia leading to ischemia. It activates sympathetic pathways, RAAS, and is potentially associated with increased release of pro-inflammatory cytokines and oxygen reactive species. [120, 121, 123] In HF, VC seems to be one of the major driving factors for AKI, both in patients with HF and patients with sepsis. In contrast in these two populations, CI seems to have no significant correlation with the development of AKI. [11, 12, 127] This raises the importance of reliveing VC in patients with worsening renal failure in HF, both with drugs or ultrafiltration. [129] [137, 138]

Hepatic congestion also leads to hypoxia, ischemia, parenchymal edema, and increased inflammation, which when persistent, generates structural changes such as fibrosis [172, 176, 223]; it is a determinant of mortality in MOD[160]. The liver has a bigger resistance to hemodynamic injury due to HABR, but when that mechanism exhausts, injury begins[166, 228]. Congestive hepatopathy has a clear association with hypoperfusion and elevated venous pressures[49, 167, 168, 170, 223, 229]; the same seems to be true for hypoxic hepatitis [168, 172, 175].

Intestinal congestion causes engorgement of venous intestinal vessels, increasing the thickness of intestinal wall, rendering it less capable of absorption and prone to inflammation. Also, intestinal congestion is related to dysmotility, impairment of barrier function with disruption of normal bacteria on the GI tract, and is related to GI symptoms [25, 28, 172, 180]. In addition, VC creates an acidotic environment that influences the mechanism of FB and gut microbiome[26]. In CHF, intestinal edema is common [29], related to RVF and RAP, and cardiac cachexia [28, 191].

Regarding the assessment of VC, CVP is not the most adequate surrogate[52, 66]. POCUS is nowadays a great option because of its accessibility and non-invasiveness. Using Doppler US, measurement of IVC, renal, portal and hepatic veins can provide great insight on VC and volume status. In fact, VExUS seems to be a promising tool in the guidance of hemodynamic management and can be a predictor of worse outcomes in AKI [39, 220]. When it comes to hepatic congestion, PI is associated with RVF. [34] Liver stiffness isn't a direct measure of VC, but it's directly linked to it and can be useful in patients with chronic hepatic congestion. [37] HVPG evaluates portal hypertension but it is an invasive procedure [36]. Finally, regarding intestinal congestion, abdominal

US allows measurements of bowel wall thickness, assessing intestinal edema. PVCI can also be associated with intestinal edema. [23, 32]

Further studies must be done on all these dysfunctions to allow better comprehension of the role of VC in organ failure. In patients with VC decreasing RAP seems to be an important hemodynamic target. However, first, investing in a better understanding of the venous system, as well as determining adequate surrogates for its assessment is also a priority, since it can change the hemodynamic approach in critical care and could be associated with better morbidity and mortality outcomes.

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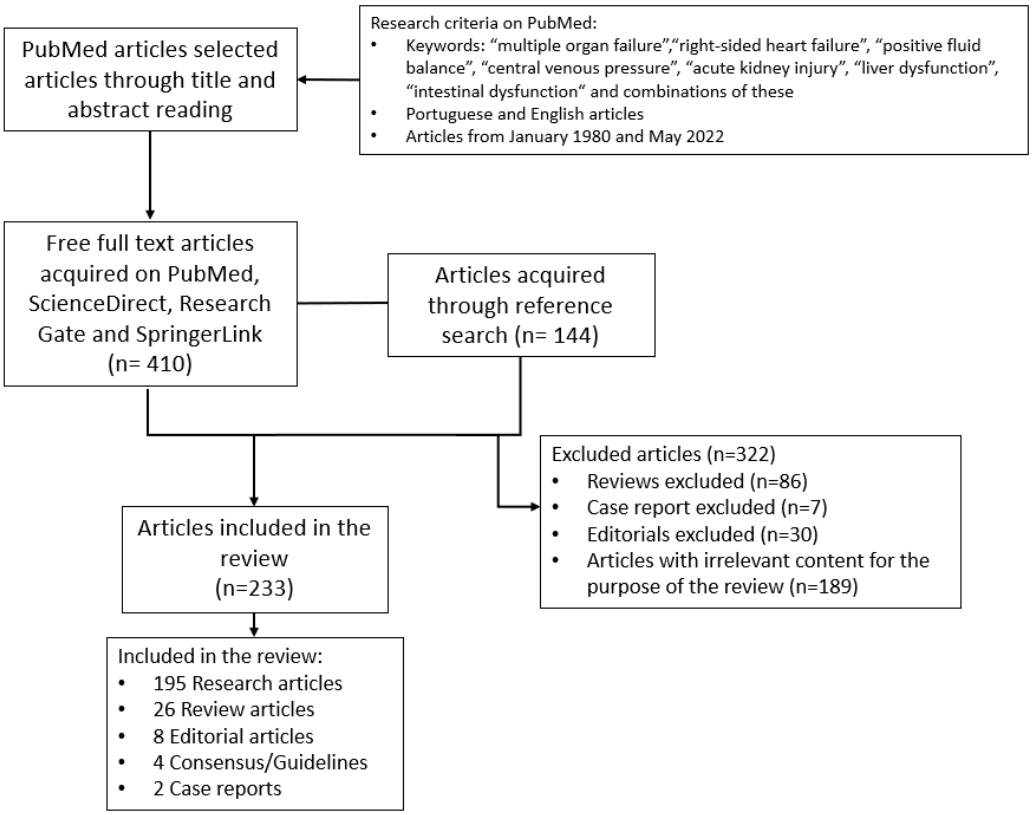
## Appendix I - Figures

**Figure 1.** Methodology for article selection



## Appendix II - Tables

**Table I.** Studies on the impact of central venous pressure on outcomes (AKI: Acute Kidney Injury; ARDS: Acute Respiratory Distress Syndrome; CABG: Coronary Artery Bypass Graft; CI: Cardiac Index; CO: Cardiac Output; CVP: central venous pressure; FB: fluid balance; ICU: intensive care unit; MELD: Model for End-Stage Liver Disease; RRT: Renal Replacement Therapy)

| Author | Year | Study Design | Population | Number | Key Findings |
|---|---|---|---|---|---|
| Pilcher, D.V., et al. **[69]** | 2005 | Single-center retrospective longitudinal | Patients undergoing lung transplantation | 118 | • High CVP is associated with prolonged mechanical ventilation, longer ICU stay and higher early mortality<br>• There is no evidence of decreased long-term mortality in high CVP patients |
| Damman, K. et al. **[48]** | 2009 | Single-center retrospective | Patients with cardiovascular disease who underwent right heart catheterization | 2557 | • Increased CVP is independently associated with all-cause mortality<br>• CVP > 6 mmHg is associated with decreased eGFR in patients with or without decreased CI |
| Boyd, J.H., et al. **[43]** | 2011 | Multicenter randomized controlled retrospective | Patients with septic shock receiving a minimum 5 µg of norepinephrine /min. | 778 | • CVP < 8 mmHg had the lowest mortality rate; CVP > 12 mmHg had the highest |
| William, J.B., et al. **[70]** | 2014 | Multicenter prospective observational | Patients undergoing CABG | 126 | • CVP at 6h post-op. was associated with early mortality and renal failure, independently of CI |
| Semler, M.W., et al. **[95]** | 2016 | Multicenter retrospective observational | Ventilated ARDS patients with CVP monitoring with and without baseline shock | 934 (609 without baseline shock) | • Decreased mortality with conservative fluid management in patients with low initial CVP (<8 mmHg), compared to liberal fluid administration<br>• Net even or negative FB did not associate with mortality |
| Su, et al. | 2019 | Single-center retrospective | Patients with circulatory shock | 134 | • Low CVP is associated with higher CO and may improve renal function<br>• Lower CVP is associated with decreased 28-day mortality rates |
| Huang, A. et al. **[9]** | 2021 | Single -center retrospective | Adult critical patients with AKI with CVP recordings in the 1st 72h | 1986 | • Minimum categorical or continuous CVP levels after ICU admission are a predictor of 90-day all-cause mortality<br>• Higher CVP levels are associated with worst ICU outcomes<br>• Per 1 mmHg CVP increase, chances of mortality increase |
| Schiefenhövel, F., et al. **[68]** | 2021 | Retrospective observational | Cardiac surgery patients | 9802 | • Higher CVP in the 1st 24h after admission had increased in-hospital and ICU mortality and increased length of stay in both<br>• Incidence of RRT, AKI, post-op. MELD, time on mechanical ventilation was higher in the high CVP group |

**Table II**. Studies on the impact of positive fluid balance on outcomes (APACHE: Acute Physiology and Chronic Health Evaluation; CHF: Chronic Heart Failure; CVP: Central Venous Pressure; ECMO: Extracorporeal membrane oxygenation; EGDT: Early Goal Directed Therapy; FB: Fluid Balance; FO: Fluid Overload; ICU: Intensive Care Unit; NE: Norepinephrine; Post-op.: Post-operative)

| Author | Year | Study Design | Population | Number | Key Findings |
|---|---|---|---|---|---|
| McArdle, G.T., et al. **[81]** | 2007 | Retrospective single-center | Open infrarenal abdominal aortic aneurysm repair surgery patients | 100 | • Major complications were seen in patients administered greater fluid volumes in early post-op. period, especially cardiac and respiratory<br>• - The most common complication was acute pulmonary edema |
| Pradeep, A., et al. **[75]** | 2010 | Retrospective multicenter | Cardiac surgery patients | 358 | • Administration of IV fluids greater than the median amount was associated with >3x times increased 90-day mortality |
| Boyd, J.H., et al. **[43]** | 2011 | Multicenter randomized controlled retrospective | Patients with septic shock receiving a minimum 5 μg of NE/min. | 778 | • More positive FB at 12h and 4 days was associated with increased mortality<br>• CVP was correlated with FB at 12h |
| Smith S. H. and Perner, A. **[90]** | 2012 | Prospective observational multicenter | Unselected patients with septic shock | 164 | • Patients receiving higher initial fluid volumes had higher lactate levels but equal 90-day mortality, when compared to patients with lower initial fluid volumes<br>• Patients with shock for ≥3 day had decreased mortality with higher volumes including crystalloids, colloids, and blood products |
| Cordemans, C., et al. **[82]** | 2012 | Observational multicenter | Mechanically ventilated ICU patients | 123 | • Persistent increase in capillary leak index, extravascular lung water index, and FB was associated with organ dysfunction and worse outcomes |
| Silva, J. M., et al **[85]** | 2013 | Prospective observational multicenter | Patients undergoing surgery requiring post-op. ICU | 479 | • Intraoperative positive FB was associated with organ dysfunction, especially neurological, cardiovascular, and respiratory; longer ICU stay; more infectious complications post-op., and increased mortality |
| Micek, S.T., et al. **[87]** | 2013 | Retrospective single-center | Septic shock patients | 325 | • Positive FB at 8 days post-shock were associated with increased mortality<br>• Daily and overall cumulative FB and cardiac function predict outcome |
| Barmparas, G., et al. **[83]** | 2014 | Prospective observational single-center | Patients admitted to the surgical ICU | 144 | • FB was a time-dependently variable predictive of mortality<br>• Patients achieving a negative FB until day 5 post-op. had almost 70% decreased mortality compared to patients with positive FB<br>• Patients with negative FB at day 1 post-op. had decreased risk for infection or inflammatory complications |
| Pipanmekaporn, T. et al. **[76]** | 2014 | Retrospective single-center | Patients undergoing thoracotomy for non-cancer lesions | 720 | • Positive FB was an independent risk factor for post-surgery cardiovascular complications<br>• Excessive fluid administration was one of the reasons for positive FB |
| Shim, H. J., et al. **[84]** | 2014 | Retrospective single-center | Surgical patients in the ICU | 148 | • Positive FB in the 1$^{st}$ 3 days was related to in-hospital mortality<br>• In patients with APACHE II ≥ 20, positive FB was associated with increased mortality |

**Table II (Continued).** Studies on the impact of positive fluid balance on outcomes

| Author | Year | Study Design | Population | Number | Key Findings |
|---|---|---|---|---|---|
| Lee, J., et al. **[78]** | 2015 | Single-center retrospective longitudinal | ICU patients | 15395 | • Positive FB during hospitalization had increased risk of mortality in the 90 days post ICU discharge; this association was stronger in patients with AKI and CHF at discharge<br>• Trend towards decreased mortality in patients with CHF and AKI in patients with negative total FB |
| Cunha, A.R., et al. **[94]** | 2015 | Prospective observational single-center | Septic shock patients | 40 | • Positive FB was common is patients with septic shock<br>• Higher FB during shock or at 7 days was associated with greater ICU length of stay<br>• -In patients with higher FB, FB tends to increase during the shock period and after recovery |
| Mitchell, K.H., et al. **[88]** | 2015 | Retrospective single-center | Septic shock patients | 247 | • Volume overload was more common in patients more severely ill, with higher fluid resuscitation and blood transfusions<br>• Blood product administration was associated with volume overload<br>• There was an association between volume overload and the inability to ambulate<br>• Patients with volume overload were more likely to be on mechanical ventilation longer, have longer hospital stays, and readmission and mortality |
| Kelm, D.J., et al. **[91]** | 2015 | Retrospective single-center | Severe sepsis and septic shock patients treated with EGDT | 405 | • Fluid overload was common after EGDT<br>• FO was associated with higher in hospital mortality<br>• Clinical evidence of FO was associated with more medical interventions |
| Koonrangsesomboon, W., et al. **[92]** | 2015 | Retrospective single-center | Septic shock patients in the ICU > 24h | 1048 | • Mean cumulative FB at the 3rd day was independently associated with ICU and hospital mortality<br>• Higher mean cumulative FB at the 3rd day was associated with greater length of stay |
| Han, M.J., et al **[230]** | 2016 | Retrospective single-center | Patients treated with continuous RRT in the ICU | 100 | • There was a significant relationship between system dysfunction (nervous, cardiovascular, respiratory, coagulation) and daily FB<br>• Daily FB before RRT initiation was proportional to 28-day mortality |
| Pittard, M.G., et al. **[89]** | 2017 | Retrospective multicenter | Septic shock patients | 186 | • - There was a strong association between more positive FB and hospital or ICU mortality |
| Chen, Y. C., et al. **[79]** | 2020 | Retrospective multicenter | Patients with cancer requiring ICU care | 942 | • Positive FB through days 1-4, higher APACHE II score and shock were independently associated with increased 1-year mortality<br>• The impact of positive FB was mainly seen in patients with shock |
| Fong, K. M., et al. **[80]** | 2020 | Retrospective single-center | ICU patients who received ECMO | 123 | • Non-survivor had a greater positive FB<br>• Cumulative FB was associated with mortality in day 7, but not day 3<br>• There was no association between RRT and cumulative FB<br>• Positive FB was more associated with decreased urine output than increased fluid intake |
| Yoo, M.S., et al. **[93]** | 2021 | Retrospective multicenter | Non-critically ill patients with sepsis | 32 | • There was no correlation between positive FB at discharge and 30-day readmission |
| Wang, T., et al. **[77]** | 2022 | Retrospective single-center | Medical ICU patients | 4610 | • Positive FB in the 1st week was associated with greater long-term mortality in patients with shock<br>• Positive FB in the 4th to 7th day was associated with long-term mortality in patients without shock |

**Table III.** Studies on the impact of central venous pressure or positive fluid balance on acute kidney injury outcomes

| Author | Year | Study Design | Population | Number | Key Findings |
|---|---|---|---|---|---|
| Payen, D., et al. **[105]** | 2008 | Secondary analysis of the SOAP database [231] | Critical patients who developed AKI >24h after ICU admission | 1120 | • AKI patients had higher mortality rates than patients without AKI (35,7% vs 16.4%)<br>• Early and late AKI had similar mortality rates<br>• Mean FB was as independent predictor of mortality in patients with early AKI (54% risk 60-day mortality)<br>• In oliguric patients and patients treated with RRT mean FB was significantly more positive than in non-oliguric and non-RRT patients; oliguric and RRT patients had higher 60-day mortality rates<br>• Patients treated with RRT earlier had better outcomes |
| Bouchard, J. et al. **[108]** | 2009 | Multicenter observational | Critical patients with AKI | 610 | • 30-day mortality (37% vs 25%) and at discharge (46% vs 32%) was significantly higher in patients with fluid overload<br>• Progression and longer duration of fluid overload were associated higher mortality<br>• Correction of fluid overload by dialyses had lower mortality |
| Teixeira, C., et al. **[110]** | 2013 | Retrospective multicenter | ICU patients | 573 | • AKI patients had higher mean FB and lower mean urine volume (MUV)<br>• AKI patients had higher mortality compared to non-AKI patients<br>• MUV was lower in all groups of patients except non-oliguric<br>• Higher MFB and lower MUV were associated with increased 28-day mortality<br>• Diuretic use was associated with better survival |
| Macedo, E., et al **[112]** | 2010 | Prospective observational | Critical patients with AKI | 253 | • Fluid accumulation increased as kidney function declined<br>• Positive FB can lead to underestimation of AKI severity |
| Heung, M., et al. **[111]** | 2012 | Retrospective single-center | Patients with AKI who underwent RRT | 170 | • Fluid overload at RRT initiation was higher in patients who did not recover renal function compared to patients who recovered function<br>• Fluid overload was ≥ 10% higher in the non-recovery group<br>• Fluid overload at RRT initiation was a predictor of lack of renal recovery |
| Liu, K. D., et al. **[113]** | 2012 | Secondary analysis of a randomized clinical trial | Patients with ARDS who developed AKI without RRT | 1000 | • Adjusting SCr to FB showed increased incidence of AKIN stage 1 AKI<br>• Patients with "unrecognized" AKI have similar mortality rates to patients with AKI before FB adjustment |
| Garzotto, F., et al. **[109]** | 2016 | Prospective multicenter | ICU patients who had AKI at admission or developed AKI during hospitalization | 1734 | • Patients with AKI had positive FB 3 days prior and 3 days after diagnosis<br>• Patients with AKI requiring RRT had the highest degree of fluid overload<br>• Non-survivors in overall critical patients had more fluid accumulation, and there was progressive fluid increase in the 4 days prior to death<br>• Mean fluid overload was an independent risk of mortality<br>• Velocity of fluid accumulation was associated with mortality |

**Table IV.** Studies on the correlation between central venous pressure or positive fluid balance and acute kidney injury in patients with heart failure (ADHF: Acute Decompensated Heart Failure; AHF: Acute Heart Failure; AKI: Acute Kidney Injury; BNP: B-type Natriuretic Peptide; CI: Cardiac Index; CVP: Central Venous Pressure; eGFR: Estimated Glomerular Filtration Rate; LVEF: Left ventricular Ejection Fraction; PAC: Pulmonary Artery Catheterization; RAP: Right Atrial Pressure; SBP: Systolic Blood Pressure; WRF: Worsening Renal Function)

| Author | Year | Study Design | Population | Number | Key Findings |
|---|---|---|---|---|---|
| Nohria, A., et al. **[126]** | 2008 | Multicenter retrospective | From the ESCAPE trial cohort[232]: Patients with LVEF ≤30%, recent hospitalization or escalation of out-patient diuretic therapy and SBP ≤125 mmHg. | 433 | • Impaired baseline renal function is associated with adverse outcomes in advanced HF, more than WFR during hospitalization<br>• RAP had a weak correlation with baseline renal function |
| Mullens, W., et al. **[12]** | 2009 | Single-center observational prospective | ADHF patients with class NYHA III-IV symptoms | 145 | • Baseline CVP was the strongest hemodynamic predictor of WRF<br>• Impaired CI and CI improvement had poor correlation with WRF<br>• Follow-up: mean CI and mean CVP were higher in patients who had WRF |
| Uthoff, H., et al. **[46]** | 2011 | Prospective interventional | AHF patients with dyspnea at rest/minor exertion, chest radiography AHF signs and BNP >500 ρg/mL | 13 | • Presentation and discharge CVP did not correlate with eGFR<br>• Higher CVP at presentation in patients with low SBP was associated with lower eGFR<br>• CVP did not correlate with eGFR in normal to high SBP patients<br>• Low presentation CVP was associated with AKI within 24h, but between 24-96h, incidence of WRF was higher in patients with higher CVP |
| Aronson, D., et al. **[127]** | 2013 | Randomized multicenter trial | ADHF patients from the VMAC study[233] | 475 (238 underwent right heart catheterization) | • Baseline RAP correlated with baseline eGFR<br>• RAP did not predict WRF<br>• Inverse association between net fluid removal in the 1st 24h and risk of WRF<br>• Amount of fluid removal did not correlate with decrease in RAP<br>• Greater RAP reduction did not associate with lower WRF risk<br>• Decrease in RAP was not a reliable surrogate to assess decongestion<br>• Greater drops in SBP should anticipate WRF |
| Hanberg, J.S., et al. **[11]** | 2016 | Multicenter retrospective | HF patients undergoing PAC | 575 | • Inverse correlation between baseline CI and baseline eGFR; also, no correlation between CI and improvement of indicators of renal function<br>• Static CI or changes in CI did not correlate with WRF<br>• RAP was inversely related to eGFR |

**Table V.** Studies in on the impact of central venous pressure on sepsis-related acute kidney injury (AKI: Acute Kidney Injury; CO: Cardiac Output; CVP: Central Venous Pressure; DAP: Diastolic Arterial Pressure; FB: Fluid Balance; MAP: Mean Arterial Pressure; MPP: Mean Perfusion Pressure; SA-AKI: Sepsis-related Acute Kidney Injury)

| Author | Year | Study Design | Population | Number | Key Findings |
|---|---|---|---|---|---|
| Legrand, M., et al. **[14]** | 2013 | Single-center retrospective observational | Septic ICU patients | 137 (69 with new or persistent AKI) | • CVP was the hemodynamic parameter most associated with development or progression of AKI<br>• Higher mean CVP in the 1st 24h is associated with higher risk of AKI<br>• CO and MAP were not significantly different between the groups with and without AKI, except DAP |
| de Oliveira, F.S., et al. **[146]** | 2015 | Retrospective single-center | Severe sepsis and septic shock patients | 116 | • Higher positive FB 24h and 58h post-sepsis diagnosis and the presence of AKI were associated with increased mortality<br>• FB between 24-48h and reduced urine output after shock onset related to mortality in shock patients<br>• Positive FB was not associated with the risk of AKI or protection from AKI |
| Wong, B.T., et al. **[143]** | 2015 | Single-center retrospective observational | Septic shock ICU patients | 107 | • Time-weighted MAP and MPP over 1st 24h were similar in patient with and without severe AKI, but time-weighted CVP was higher in patients with severe AKI<br>• Relative MAP deficit was similar in patients with and without AKI<br>• Relative MPP deficit was greater in patients with severe AKI, determined mostly by CVP excess<br>• Mean CVP in the 1st 24h was associated with AKI progression<br>• MAP, MPP, relative MAP, MPP deficits were not associated with AKI progression |
| Huo, Yan, et al. **[15]** | 2022 | Longitudinal retrospective multicenter | Critical patients with SA-AKI | 1377 | • Lower CVP was associated with decreased mortality and higher CVP was associated with higher mortality<br>• Lower CVP is a protective factor in SA-AKI patients |

**Table VI.** Alterations in hepatic, portal veins Doppler, and intrarenal venous Doppler according to the severity of systemic congestion. Pulsatility fraction is the variation of velocity in Doppler during a cardiac cycle. Adapted from *Quantifying systemic venous with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system* [40] (S: Systolic Component of the Waveform; D: Diastolic Component of the Waveform)

| | **Normal** | **Mild Abnormality** | **Severe Abnormality** |
|---|---|---|---|
| **Hepatic Vein Doppler** | S is higher than diastolic component D | S is lower than D, but still towards the liver | S lower than D with reversed (towards the heart) |
| **Portal Vein Doppler Pulsatility Fraction** | <30% | 30-49% | >50% |
| **Intrarenal Venous Doppler** | Continuous pattern | Discontinuous pattern with a systolic and a diastolic phase | Discontinuous pattern with only a diastolic phase |

**Table VII.** VExUS scoring according to the grading of congestion in Doppler ultrasound. Adapted from *Quantifying systemic venous with Point-Of-Care ultrasound: development of the venous excess ultrasound grading system* [40] (IVCd: Diameter of the Inferior Vena Cava)

| | ***VExUS A*** | ***VExUS B*** | ***VExUS C*** | ***VExUS D*** | ***VExUS E*** |
|---|---|---|---|---|---|
| ***Grade 0*** | IVCd < 2 cm | IVCd < 2 cm | IVCd < 2 cm | ---------- | ---------- |
| ***Grade 1*** | IVCd ≥ 2 cm + Normal patterns | IVCd ≥ 2 cm + Normal patterns | IVCd ≥ 2 cm + Normal or mild abnormalities | Normal patterns | Normal patterns or mild abnormalities |
| ***Grade 2 – Mild congestion*** | IVCd > 2 cm + Mild abnormalities in ≥1 patterns | IVCd > 2 cm + Mild or severe abnormalities in ≥1 patterns | IVCd > 2 cm + Severe abnormalities in ≥1 patterns | Mild or severe abnormalities in ≥1 patterns | Severe abnormalities in ≥1 patterns |
| ***Grade 3 – Severe congestion*** | IVCd > 2 cm + Severe abnormalities in ≥1 patterns | IVCd > 2 cm + Mild or severe abnormalities in multiple patterns | IVCd > 2 cm + Severe abnormalities in multiple patterns | Mild or severe abnormalities in multiple patterns | Severe abnormalities in multiple patterns |

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