Biomarkers and Physiopathology in the Cardiorenal Syndrome

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Introduction

Patients with acute heart failure (HF) often develop acute worsening renal function (WRF) in the course of the disease. Their condition is then called acute cardiorenal syndrome (CRS) (1). In this review, we have limited the discussion to the cardiorenal syndrome of type 1. Managing patients with HF is already challenging, but the presence of associated WRF can greatly increase mortality and morbidity (2). Early diagnosis and treatment are the keys to decrease mortality, to prevent re-hospitalizations and to reduce healthcare costs. Biomarkers have been established as highly sensitive and may be considered as specific tools to help in the diagnosis and to get a prognosis for patients with HF. Reflecting distinct physiopathological pathways and types of cellular insults, they have been proven superior to conventional laboratory tests.

Acute heart failure (AHF) is the leading cause of hospitalizations in patients aged 65 and over and represents a significant economic cost (3). The prevalence of HF is about 2% in Europe and in the United States (3). The time window between renal insult and development of acute kidney injury (AKI) in AHF can vary.

AKI is often diagnosed too late, only when the effects of the insult become evident with a loss or decrease of renal function. The development of renal injury is responsible for the increasing mortality of patients with HF (4). AKI is indeed an independent risk factor for 1-year mortality in acute decompensed heart failure (ADHF) patients (5). According to certain databases, renal dysfunction is the most frequent comorbidity in AHF patients, associated with high in-patient mortality (6).
Type 1 CRS occurs in approximately 25% to 33% of patients admitted with ADHF, depending on the criteria used (7).

The mortality rate for ADHF is dependent of the presence or absence of impairment renal function. Annual mortality rates are 26% in patients without renal dysfunction, 41% in patients with any impairment of renal function and 51% in patients with moderate to severe impairment (8).

Definition-Classification

Combined disorders of heart and kidney are classified as cardiorenal syndromes (1). The primary failing organ can either be the heart or the kidney, and the syndrome is divided into five distinct subtypes. In **types 1** and **2, CRS**, worsening of HF in acute (type 1) or chronic HF (type 2), leads to worsening kidney function. In **types 3** and **4** (termed acute and chronic renocardiac syndromes, respectively), AKI or chronic kidney disease (CKD) leads to worsening HF. In **type 5 CRS**, systemic conditions cause simultaneous dysfunctions of the heart and kidney (1).

A patient with known HF, who is admitted to hospital for an episode of ADHF and either a mild elevation in serum creatinine at baseline or a temporary need for dialysis, would be classified as type 1 CRS since the HF was the initial, predominant problem and the renal failure the consequence (9). Because of the complexity of interaction between acute heart and kidney failure, type 1 CRS is subdivided into 4 categories (10):

- De novo cardiac injury leading to de novo kidney injury
- De novo cardiac injury leading to acute-on-chronic kidney injury
- Acute-on-chronic cardiac decompensation leading to de novo kidney injury

- Acute-on-chronic cardiac decompensation leading to acute-on-chronic kidney injury

CRS type 1 is characterized as the development of AKI in a patient with acute cardiac illness. The acute cardiac insults commonly include acute coronary syndrome (ACS), ADHF, cardiogenic shock and can appear in the post procedure of cardiopulmonary bypass surgery . There is evidence to support a multiple pathophysiological mechanism, resulting in a clinical syndrome characterized by a rise in serum creatinine, oliguria, diuretic resistance, and in many cases, worsening of ADHF symptoms.

The new criteria for the diagnosis of AKI include a minor change in renal function, including a rise in creatinine of 0.3 mg/dL in 48 hours or 0.5mg/dL in 7 days and a decrease in urinary output (11). In addition, these new criteria suggested that the diagnosis of AKI should be based on a reduction of kidney function occurring within a time window of 48 hours. Early detection of AKI is not possible with the use of plasma creatinine and there is a need for more precise markers, able to show renal damage while it is happening.

In most cases, patients with AHF are admitted with clinical signs and symptoms of congestion and fluid overload. Loop diuretics, used to induce a diuresis in these congested patients, are often associated with a subsequent decrease in glomerular filtration rate (GFR), and cause a creatinine increase that is apparent within 48 to 72 hours.

Numerous factors can independently predict the development of WRF at the admission of patients with clinical manifestations of ADHF. These factors include baseline renal function, history of coronary artery disease, hypertension, diabetes mellitus, and history of prior HF (12). In addition, the presence of systolic hypertension, tachycardia, pulmonary edema, and the use of high doses of diuretics at admission were independently related to the development of type 1 CRS during treatment (13).

Physiopathology

It is well known that HF is characterized by complex interactions between cardiac, renal, and vascular systems, mediated through hemodynamic, neurohormonal mechanisms and endothelial dysfunction. The kidney plays a crucial role to maintain hemodynamic balance, which is often disrupted in HF patients (14).

The acute cardiac insult often results in reduced cardiac output (CO), which leads to decreased renal perfusion pressure, increased renal venous resistance, and as a consequence reduced GFR. When AHF is characterized by diminished left ventricular systolic function and poor CO, compensatory mechanisms are stimulated, such as an activation of the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and a production of other local mediators, which interact to maintain the fluid volume (15). Endothelial dysfunction contributes to vasoconstriction and increased afterload. The imbalance between these compensatory mechanisms, unable to maintain adequate CO, results in volume overload. Furthermore, decreased renal perfusion, in addition to nephrotoxic agents and over-diuresis, eventually leads to AKI in such patients (10).

As the rise of serum creatinine takes some time to become apparent, novel techniques such as the use of biomarkers have received considerable attention in the diagnosis and prognosis of

patients with WRF secondary to HF. These biomarkers are secreted in response to increased stress and are widely used to monitor the progression and the severity of the disease.

Renal dysfunction in acute HF

As already mentioned, a deep interaction exists between the heart and the kidneys, altered in patients with AHF leading to CRS type 1. The mechanism of renal insult is different in case of low or high CO. The paragraph below details the hemodynamics and neuro-hormonal abnormalities involved in this interaction (See table 1).

Hemodynamic dysfunction

In the Acute Decompensated Heart Failure National Registry (US), the majority of patients were brought to the hospital because of pulmonary congestion. Most of them had normal blood pressure (140 mm Hg or higher of systolic blood pressure). Only 2% of the patients had a systolic blood pressure of 90 mm Hg (16). Renal function can be maintained with a CO as low as 1.5 l/min/m ² (17). The fall in renal function in case of AHF is related to the reduction of left ventricular function only in 20% of the cases.

When low CO appears, a systemic venous congestion and renal arteriolar vasoconstriction develop. They increase central venous pressure and further reduce renal blood flow. Renal hypoperfusion triggers the SNS and activates the RAAS to maintain plasma volume by retaining sodium and water (18).

Venous congestion is one of the most important hemodynamic determinants of CRS and is due to a decrease of effective arterial blood volume (EABV). It has been associated with the development of renal dysfunction in the setting of ADHF, with normal or low CO. In HF patients, increased central venous pressure (CVP) can be transmitted to the kidney circulation by the glomerular efferent arteriole, with a reduction of the glomerular filtration pressure gradient that causes a fall of GFR (19). Damman *et al.* found that higher CVP was inversely related to GFR and independently associated with all-cause mortality (20). This effect is probably due to an increase in renal venous pressure which decreases the arteriovenous pressure gradient across the kidney (21). The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found no relationship with baseline hemodynamic parameters like CO, pulmonary capillary wedge pressure, or systemic vascular resistance (SVR) correlated with baseline renal function. Only venous or right atrial pressure was significantly but weakly correlated with serum creatinine and GFR (22). Venous congestion also leads to the development of visceral oedema and ascites with increased intra-abdominal pressure (IAP). Elevated IAP is prevalent in patients with ADHF and is also associated with impaired renal function (23).

Moreover, it is frequently observed that renal dysfunction may complicate the treatment course of HF because of the use of diuretics. Even if the use of intravenous loop diuretics often decreases venous congestion, the cost to pay is a WRF within a few days of hospitalization. Although loop diuretics provide prompt diuresis and relief of congestive symptoms, they provoke a marked activation of the SNS and RAAS systems, resulting in renovascular reflexes and sodium retention. They are thus considered as a primary precipitant of CRS. This places the patient with ADHF at risk for CRS in a narrow therapeutic management.

Neurohormonal activation

The RAAS has thus an important role in the initiation and maintenance of vascular, myocardial, and renal dysfunction leading to oedema in HF (10). This activated mechanism occurs as an initial protection mechanism for renal hypoperfusion, which leads to stimulation of angiotensin II. This peptide is also known to be a stimulator of the SNS, which increases SVR and congestion. Angiotensin II has direct trophic effects on cardiomyocytes and renal tubular cells that promote cellular hypertrophy, apoptosis, and fibrosis (24). Constriction of afferent arterioles by angiotensin II and the SNS reduces renal blood flow and GFR, and causes increased proximal tubular sodium reabsorption (See table 1).

This systemic vasoconstriction induced by RAAS and SNS activation compensates the initial decrease in stroke volume associated with low CO. The arterial under-filling occurs secondary to a decrease in CO in low-output HF and arterial vasodilatation in high-output HF, both of which increase the stimulation of SNS, enhancing the stimulation of RAAS. Hence, a vicious cycle of worsening HF and oedema formation occurs (10).

As a result of SNS activation, catecholamines are also increased and play an important role on the progression of HF. It is well known that elevated plasma norepinephrine levels in patients with HF correlate with increased mortality (25). Stimulation of adrenergic receptors on proximal tubular cells also enhances the sodium reabsorption, whereas adrenergic receptors in the juxtaglomerular apparatus stimulate the RAAS (26). All these neuro-hormonal activations can appear in low or maintained CO.

Hypothalamic-pituitary and humoral stress reaction

ADHF is a major activator of the hypothalamus-pituitary-adrenal axis. This activation leads to an increase in concentration of the adrenal stress hormone cortisol. Another hormone, which is increased by AHF condition, is vasopressin. This hormone is derived from a larger precursor peptide (preprovasopressin) along with copeptin, which is released from the posterior pituitary in an equimolar ratio to vasopressin. Copeptin levels have been found to closely mirror the production of vasopressin and have been proposed as a prognostic marker in acute illness (10).
Vasopressin stimulates the V1a receptors of the vasculature and increases SVR. The activation of the V2 receptors in the principal cells of the collecting duct increases water reabsorption and leads to hyponatremia (22). The clinical consequences of these changes include sodium and water retention, pulmonary congestion, and hyponatremia, which occurs both in low-output and high-output cardiac failure.

Diagnostic and prognostic biomarkers of renal dysfunction in acute HF

To limit the injury at the kidney level in an acute phase of HF, an early diagnosis is necessary. This is not the case when using the creatinine parameter. There is actually a delay of approximately 48 hours between the kidney injury and the rise in serum creatinine level. Several urinary and serum biomarkers of structural kidney injury have been investigated to identify AKI earlier, in order to improve the diagnosis and the treatment of AKI and to get a good prognostic evaluation of patients admitted to the hospital.

Creatinine

GFR estimation is usually based on serum creatinine (SCr). The development of AKI, defined by acute changes in serum creatinine, associates with a higher risk of long-term mortality (27). SCr is known to be a rather insensitive GFR biomarker. Many factors independent of kidney function affect creatinine, including: age, gender, muscle mass and metabolism (both already modified during AHF and AKI periods), medications, and level of hydration (28). There is also an exponential relation between SCr level and estimated GFR. WRF may therefore be better defined by either an absolute increase or a relative increase of baseline creatinine value. When GFR is declining, the damage has already occurred and few things can be done to prevent or to protect the kidney from further damage.

Currently, as indicated by the RIFLEs (Risk-Injury-Failure-Lost-End stage kidney disease) criteria and the AKIN (Acute Kidney Injury Network), creatinine is one of the major markers used to detect kidney dysfunction. A patient may fall into one of the categories of the RIFLE depending on the time of development of the kidney failure, on the change of creatinine, and/or on the urinary output (29).

SCr is unable to rapidly reflect changing GFR, i.e. in a non steady state. Additionally, creatinine becomes abnormal when more than 50% of GFR is lost, and it takes up to 24 hours before increases in blood concentration are detectable. Moreover, SCr is not exclusively cleared by glomerular filtration but is also partially secreted by renal tubules. This well-known phenomenon may account for substantial GFR overestimation (30).
SCr level is more a marker of renal function than kidney injury. Increased SCr levels are not always representative of kidney injury. An increased SCr level is strongly associated with impaired clinical outcome, but with significant shortcomings for accurate assessment of GFR (31).

Neutrophil gelatinase-associated lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2 (LCN-2), is a small 25-kDa protein with 178 amino acids. It belongs to the lipocalin family of proteins (32). Because of its small molecular weight, plasma NGAL is fully filtered though the glomerulus and totally reabsorbed in the tubules.

NGAL has been shown to be involved in immune modulation, inflammation, and neoplastic transformation. It is expressed in immature neutrophils and epithelial cells (33). NGAL is physiologically expressed and secreted in the lung, kidney (proximal tubule), trachea, stomach, and colon. NGAL is thought to be bacteriostatic in pathological states by forming complexes with iron-binding siderophores. The physiological role of NGAL in renal ischemia or toxin induced kidney injury may be to decrease injury by reducing apoptosis and increasing the normal proliferation of kidney tubule cells (34).

Plasma NGAL levels are less specific for renal disease, as higher levels are also found in inflammation, sepsis, or cancer. Urine levels are much less affected by these situations, since the NGAL that appears in the urine is secreted only from the tubules (35).

The performance of the ARCHITECT urine NGAL assay is reliable and reproducible to determine urine NGAL (36). The biological variations of NGAL and NGAL-to-creatinine ratio are 84% and 81% respectively, for first morning urine samples, suggesting that a 2-fold

increase in NGAL concentrations is required to confirm AKI (37). Plasma NGAL may increase its usefulness in the diagnosis and prevention of CRS if a curve of plasma values in function of time is used rather than a single plasma measurement. Current commercial immunoassays are not able to distinguish between the monomer, homodimer, or heterodimer forms of NGAL. Therefore, further work still needs to be done to resolve the analytical issues before large-scale prospective clinical trials can be performed to determine the diagnostic utility of NGAL as a biomarker of AKI (38).

Recently, investigators explored the role of NGAL in cardiovascular pathology. In this particular condition, some studies showed that NGAL values were higher in those with hypertension compared to controls (normotensives) (39). In multivariate analysis, serum NGAL is correlated with serum creatinine, urine NGAL, duration of hypertension, measured GFR, cystatin C, and other parameters.

NGAL in AKI

Serum and urine NGAL have been well demonstrated to increase dramatically in renal failure underlining their potential role as a marker for kidney injury.

A meta-analysis by Haase *et al*. demonstrated that NGAL was an early predictor of subclinical AKI, with early elevations in plasmatic NGAL levels compared to serum creatinine. Moreover, in-patient mortality was highest in those patients with elevated NGAL levels, with or without elevated serum creatinine (40).

Some authors demonstrated that on post cardiac surgery in paediatric and using a cut-off of 150 ng/mL to detect AKI, plasmatic NGAL achieved 84% sensitivity and 94% specificity. It can detect AKI within 2 hours (41).

In a multicentre AKI biomarkers study, both urine and plasma NGAL were linearly associated with a composite outcome of in-hospital death or dialysis, and also with the length of hospital and intensive care unit stay (42).

NGAL in HF

In a study of 119 patients admitted with AHF, elevated plasma NGAL at time of admission predicted the development of type 1 CRS. Above a cut-off value of 170 ng/mL, NGAL was associated with development of type 1 CRS within 48 to 72 hours with a sensitivity of 100% and a specificity of 86.7% (43).

Others studies have found that among patients admitted for ADHF, those who subsequently developed WRF (defined as creatinine rise > 0.3 mg/dL) had significantly higher NGAL values than those who maintained steady renal function. Patients with an admission NGAL > 140 ng/mL were at 7.4-fold increased risk of developing worsening kidney function during hospitalization (sensitivity = 86%, specificity = 54%), validating the accuracy with which NGAL can predict kidney injury (44).

Furthermore, it was reported that both serum and urine NGAL levels correlate with various markers of renal function, such as serum creatinine, cystatin C, and albuminuria (20).

Serum NGAL is a robust marker for detecting early AKI and carries high diagnostic and prognostic usefulness both in ADHF and on hospitalized patients. Many studies have shown

that NGAL rises 24 to 48 hours before creatinine, and thus shows promise in being a powerful marker for early detection of kidney damage (45,46).

In contrast to the serum value of NGAL and its predictive value, some studies demonstrated that urinary NGAL did not reliably predict persistent renal impairment or all-cause mortality in ADHF (47). Some authors have suggested that serum and urinary NGAL represent different aspects of the nephron's function. Whereas higher serum NGAL correlates well to reduced glomerular filtration function, urinary NGAL is more a marker of impaired natriuresis and diuresis in the setting of ADHF (48).

Cystatin C

Another marker also has its place in the early detection of AKI with performance superior to creatinine. This biomarker is Cystatin C (CysC). This marker is a low-molecular-weight protein (13.3kDa) and belongs to the family of cysteine proteinase inhibitor proteins (49). Its production is constant, and it is present in all types of cells. CysC is freely filtrated through the glomerulus and completely reabsorbed by tubular cells. CysC is then fully catabolized and not secreted in the urine, except after tubular injury. Its levels are unaffected by age, sex, race, muscle mass, steroid therapy, infection, liver disease, or inflammation (49).
Serum CysC (SCysC) concentration is thus strongly related to GFR, although a urinary CysC concentration is near to zero in healthy subjects. Higher urinary CysC concentrations can be observed in case of renal tubular damage.
CysC has a half-life of 1.5 hours (compared with 4 hours for creatinine). Therefore, after kidney injury, CysC concentration increases earlier than creatinine concentration, enabling faster identification of AKI (50).

CysC is measured using liquid agglutination of latex particles coated with polyclonal antibodies against CysC. There is no reference method available and significant interassay variation has been reported (51).

The diagnostic usefulness of CysC is well documented in the acute setting. SCysC performs significantly better than SCr in order to detect critically ill patients with measured GFR below 60 ml/min (30).

Cystatin C in HF

CysC appears to be a useful marker of early AKI in patients hospitalized for AHF. A decline in renal function detected by SCysC during the first 48 hours after hospitalization occurs frequently in AHF, with an AUC of 0.92 for detection of CRS type 1, and has a negative impact on prognosis (52).

Most of the studies testing performance of urinary versus serum CysC markers have demonstrated a superiority of the latter. Soto *et al*. conducted a study to evaluate diagnostic potential of SCysC for detecting AKI in patients presenting to the emergency department. To detect AKI, CysC achieved an AUC of > 0.86 compared to SCr (53). Moreover, SCysC was able to discriminate between those with initial elevations in SCr, which returned to baseline in 48 hours, and those that went on to develop AKI (52).

Haase *et al*. demonstrated that plasma NGAL and SCysC were the strongest predictors of developing AKI (defined with RIFLE criteria) in patients post-cardiac surgery (40). CysC achieved an AUC of 0.76, compared to NGAL 0.77 in detecting AKI on arrival. Overall, CysC and NGAL performed better in detecting early AKI and predicting duration of stay in the hospital.

Several studies have also evaluated the performance of CysC in detecting early AKI, a clinical entity that needs to be dealt with rapidly to prevent progression to CRS in patients with acute HF. An increase in SCysC greater than 0.3 mg/dL 48 hours after admission had a specificity of 90% and a sensitivity of 77% for developing an AKI (54).

It has been shown that the plasma level of CysC was a strong and independent marker of CRS and mortality in AHF (55). In patients with chronic systolic heart failure, SCysC levels were directly correlated with ventricular dysfunction and were suggested as a prognostic factor (56).

Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with an immunoglobulin and mucin domain. KIM-1 is markedly induced in response to renal injury and is expressed on the proximal tubule apical membrane. It is involved in the differentiation of T-helper cells and expressed on the proximal tubule apical membrane cilia with injury, but not in the normal kidney.

A number of studies have demonstrated KIM-1 to be a marker of AKI occurring after cardiopulmonary by pass surgery (CPB) and cardiac catheterization (57). Urinary KIM-1 was also associated with increased risk of death or hospitalization, independent of GFR in patients with chronic heart failure (58).

In a recent study, urinary levels of KIM-1 in the immediate postoperative CPB period provide additional prognostic information for 3-year mortality risk in patients with and without clinical AKI (59).

Urinary KIM-1 levels decrease in response to anti-hypertensive treatment with a combination of either thiazides, a low salt diet or angiotensin receptor blockade. The reduction in KIM-1 is correlated with a reduction in proteinuria (60).

Fatty acid binding protein (FABP)

Fatty-acid binding proteins (FABPs) are a family of 15-kDa cytoplasmic proteins that are involved in the intracellular transport of long-chain fatty acids. They facilitate the transfer of fatty acids between extracellular and intracellular membranes. Nine different FABPs have been identified and named according to the tissues in which they were firstly identified (61).

Two types of FABPs are interesting in AKI management. The first is the kidney heart-type (H-FABP), located in the distal tubular cells, and the second is the liver-type (L-FABP), which is located in the proximal tubular cells. L-FABPs may also have a role in the reduction of cellular oxidative stress, binding fatty acid oxidation products, and limiting the toxic effects of oxidative intermediates on cellular membranes (62).

Urinary L-FABP is undetectable in healthy control urine. Under ischemic conditions, the proximal tubular reabsorption of L-FABP is reduced. The performance of urinary L-FABP has been demonstrated in small series of intensive care unit (ICU) patients with promising results to predict outcome (63).

Performance of urinary L-FABP for AKI diagnosis in cardiac surgery patients is good. Urinary L-FABP showed high sensitivity to detect AKI on post-operatory period, with high specificity (64).

N-acetyl-β-D-glucosaminidase (NAG)

The enzyme N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal brush border enzyme found predominantly in proximal tubular cells. It has a large molecular weight (>130 kDa) and is therefore not filtered by glomerular filtration. It sheds into the urine in response to tubular injury. When combined, NAG and L-FABP could detect AKI with higher accuracy than either biomarker measurement alone (64).

Urinary NAG has been shown to be a marker of kidney injury, particularly tubular damage, in patients with nephrotoxicity due for instance to radio contrast media, environmental toxins, and ischemia (65).

It was reported that urinary NAG is increased in postoperative AKI patients with cardiac surgery but not in stable renal function (66).

In patients with HF, urinary NAG levels are associated with an increased risk of death or HF hospitalizations regardless of GFR (58). In addition, NAG levels are correlated with GFR and effective renal plasma flow, suggesting that this marker can detect decreased renal perfusion in patients with low cardiac output.

Interleukin-18 (IL-18)

Interleukin-18 (IL-18) is an 18-kDa pro-inflammatory cytokine originating from proximal tubular cells. It is detected in the urine after acute proximal tubular damage. It probably has a role in mediation of ischemic renal failure (67). IL-18 levels precede the rise in creatinine, but the rise in IL-18 is slower compared to the rise in NGAL.

Few data highlighted the role of IL-18 as predictor of outcome in ischemic heart disease and, as such, as predictor of the incidence of HF (68). IL-18 is a relatively modest predictor of AKI in ADHF (47). Further investigations regarding the prognostic value of urinary IL-18 are expected.

In patients with kidney transplantation, the urine level of IL-18 has been studied as a biomarker for delayed graft function (69).

Recently, IL-18 has been shown to be a good urinary biomarker of kidney injury in the immediate postoperative period, providing additional prognostic information for 3-year mortality risk in patients with and without clinical AKI (59).

Combinations of renal biomarkers

A new injury criterium incorporating the new damage biomarkers for diagnosis of AKI was proposed. Under this new diagnostic approach, AKI can be defined by abnormal levels of kidney injury biomarkers even in the absence of oliguria or elevated serum creatinine, thus defining a new spectrum of AKI (70).

It is possible that a combination of biomarkers such as NGAL, KIM-1, and CysC could be applied for the early detection of postoperative AKI in CRS. It was reported that using combined biomarkers (KIM-1, NAG, and NGAL) for early detection of postoperative AKI enhanced the sensitivity compared to using only one biomarker (57). A recent study by Coca *et al.* demonstrated that, in a population of patients that were at high risk for AKI and underwent cardiac surgery, elevated levels of urinary kidney injury biomarkers in the postoperative period are independently associated with an increased risk for long-term mortality over a median 3-year follow-up (59).
These results indicate that urinary biomarkers not only provide added prognostic information in those with clinical AKI, but also potentially support a revised paradigm in which even subclinical AKI may confer increased risk for adverse outcomes (59).

Albuminuria

In CKD, albuminuria has been advocated as an important therapeutic target. The degree of reduction in albuminuria was strongly correlated with cardiovascular outcome and, more importantly, incident HF (71). Albuminuria not only reflects glomerular damage, it is also thought to be a marker of generalized endothelial dysfunction, reflecting the pathophysiology of the interactions between the cardiovascular and renal systems, but only in chronic circumstances. Albuminuria is not a good marker of AKI because not sensitive and specific enough.

There are suggestions that albuminuria in HF is frequent and may be associated with impaired renal perfusion and increased venous congestion, in analogy to decreased GFR (72).
In large sub studies of the CHARM and GISSI-HF trial, micro and macro-albuminuria were not only prevalent, but also associated with a strongly increased mortality rate (73,74).
This is also apparent in patients without decreased GFR, which suggests that albuminuria is a very early sign of renal damage as it has been reported in the general population, or that different mechanisms may contribute to reduced GFR and increased albumin excretion.
However, albuminuria may serve as marker of prognosis in patients with HF, and as a predictor of HF and a reflection of comorbidities even more than a diagnostic marker.

Table 2 summarizes the advantages and inconvenients of the different biomarkers.

Conclusions

The management of HF patients developing a renal failure is very complicated. New biomarkers are increasingly used as diagnostic tools of renal failure in HF patients, and also to improve clinical decisions and reduce future re-hospitalizations. The superiority of urinary or serum biomarkers or both of these is not demonstrated yet.
These biomarkers are however not cost effective when used in bedside management to limit the over-diuresis that decreased the congestion symptoms of patients with HF and AKI.
Research should focus on developing specific urinary or serum biomarkers, to detect the different types of renal damage and the time of appearance of these lesions, in the hope to prevent kidney injury progression and perhaps to reduce the bad prognosis of these patients.

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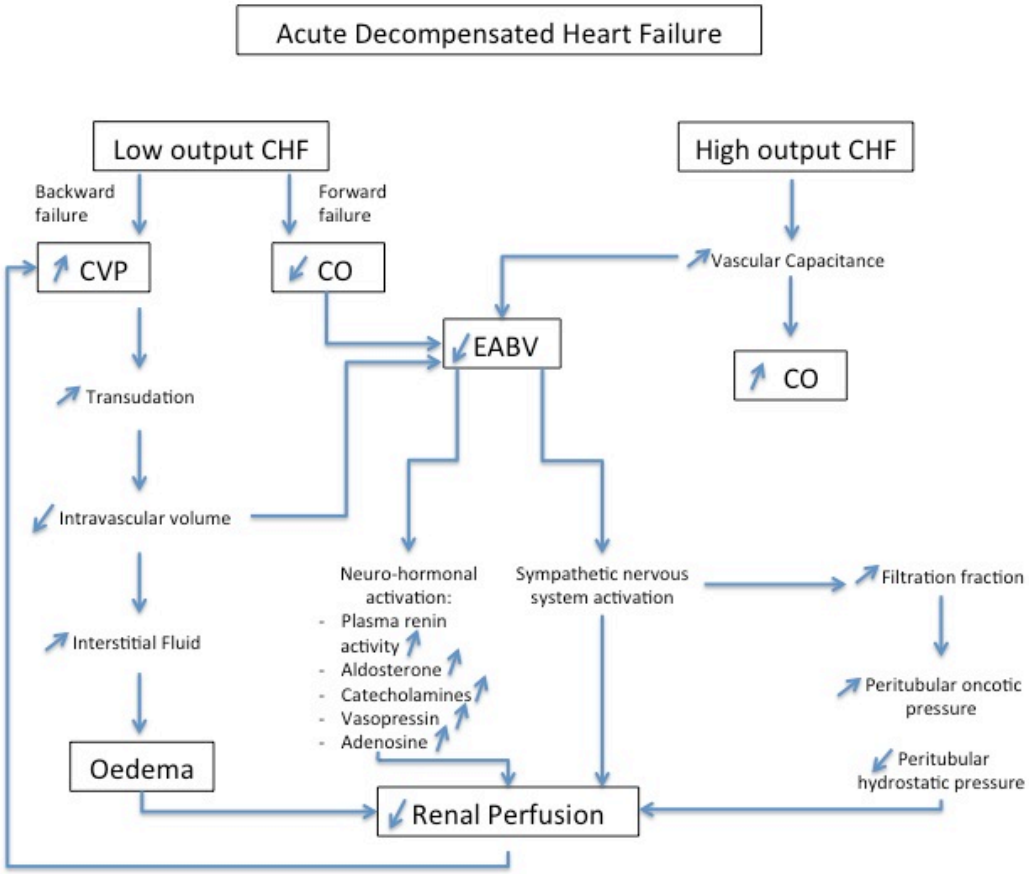
Tables

Table 1: Physiopathology of Type 1 CRS (6,14,15)



CHF: Cardiac Heart Failure, CO: Cardiac Output, CVP: Central Venous Pressure, EABV: Effective Arterial Blood Volume

Table 2 : Propreties of different biomarkers in AHF patients (75–77)

Marker	Detection	Relation with prognosis	Advantages	Inconvenients
Creatinine	Serum	Prognosis of mortality in AHF	Easy, Cheap. Marker of renal function	Dependent of lot of variables. Exponential relation with GFR. GFR overestimation
NGAL	Serum/Urine	Prognosis of mortality in AHF	Early indicator of AKI and specific for AKI	Low specificity for urine NGAL in case of ADHF vs plasma NGAL
Cystatin C	Serum/Urine	Prognosis of mortality in AHF	Unbiased, Very reliable	Expensive. Difficulty of interpretation
KIM-1	Urine	Prognosis of mortality in CHF	Highly senstive and specific for AKI detection	Costs
FABP	Urine	Prognosis of mortality in ICU patients	Utility in setting of preclinical and clinical AKI	Elevated in sepsis
NAG	Urine	Increase risk of death in CHF	Easy, Strong marker of AKI	Costs. Low specificity
IL-18	Serum/Urine	Predictor of the incidence of HF	Early marker of AKI	Increased in inflammation
Albuminuria	Urine	Strong relation with prognosis	Easy, Cheap	Lack of specificity for AKI may limit its utility

FABP: Fatty Acid Binding Protein, IL-18: Interleukin 18, KIM-1: Kidney Injury Molecule 1, NAG: N-Acetyl-beta-D-Glucosaminidase, NGAL: Neutrophil Gelatinase-Associated Lipocalin, AKI: Acute Kidney Injury, ADHF: Acute Decompensed Heart Failure, AHF: Acute Heart Failure, CHF: Chronic Heart Failure, ICU: Intensive Care Unit