Pathogenesis of Cardiorenal Syndrome Type 1 in Acute Decompensated Heart Failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)

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Abstract

Pathophysiological mechanisms of cardiorenal syndromes (CRS) types 1–5 are still sparsely characterized. In an attempt to address this issue, a consensus conference on CRS was held in Venice, Italy, in November 2012 under the auspices of the Acute Dialysis Quality Initiative (ADQI). Working group 1 discussed monodirectional mechanisms of CRS type 1 which is characterized by a rapid worsening of cardiac function leading to acute kidney injury (AKI). Pre-conference we performed a systematic search and review of the available literature using a modified Delphi analysis. Hereby identified and in this review discussed questions were: (i) What are the predominant pathophysiologic mechanisms of CRS type 1 in acute decompensated heart failure? (ii) Could biomarker profiling identify pathomechanisms or hemodynamic phenotype of patients with CRS type 1? Could predictive biomarkers improve renal safety of therapy in CRS type 1? (iii) How do the timing, severity

ADQI 11 Workgroup members are listed in Appendix 2.

and duration relate to the mechanisms and outcomes of CRS type 1? In summary, after discussion and appraisal of the best available evidence, working group 1 makes consensus recommendations for future research on pathologic mechanisms of CRS type 1 and recommendations for clinical practice where treatment is in either proof or disproof of a mechanism.

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Bidirectional acute and chronic disorders of heart and kidney are today classified as cardiorenal syndromes (CRS) types 1–5, however pathophysiological mechanisms are sparsely characterized with regard to correct identification and treatment at clinical presentation. In an attempt to address this issue, a consensus conference on CRS was held in Venice, Italy, in November 2012 under the auspices of the Acute Dialysis Quality Initiative (ADQI).

Working group 1 addressed these issues for CRS type 1 which is characterized by a rapid worsening of cardiac function leading to acute kidney injury (AKI) [1, 2]. CRS type 1 most frequently appears in the setting of acute decompensated heart failure (ADHF) [3] and follows ischemic (cardiac surgery, myocardial infarction) or non-ischemic (valve dysfunction, aortic dissection, pulmonary embolism, etc.) cardiac events. Up to 40% of patients hospitalized for ADHF develop AKI [4]. These patients require a more complex management and experience more complicated hospital courses and higher mortality. Preliminary data point towards the importance of timing in the development of AKI with regard to severity of the renal stressor versus iatrogenic effects.

Classical mechanisms of CRS type 1 include low cardiac output (CO) and neurohormonal activation and release of vasoactive substances resulting in low renal perfusion and possible renal ischemia with AKI. In addition, high central venous pressure (CVP), increased intra-abdominal pressure leading to venous congestion, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) and release of other vasoactive substances such as endothelin, anemia and a marked alteration of immune and somatic cell signaling have all been implicated as important contributors of kidney injury (fig. 1).

As far as understanding CRS type 1 pathophysiology is concerned, treatment approaches including agents targeting vasoactive and neurohormonal pathways and strategies to correct renal congestion through negative fluid balance are briefly discussed.

Methods

Pre-conference we performed a systematic search and review of the available literature, as described in the ADQI 11 conference summary statements elsewhere in this issue. Specifically, we focused on the identification of pathomechanisms of the acutely dys-

Fig. 1. Overview on mechanisms, histological correlates biomarkers and outcomes in CRS type 1 in the setting of acute decompensated heart failure. Reproduced with permission from ADQI [53]. ADHF = Acute decompensated heart failure; AKI = acute kidney injury (the term AKI also covers the term ‘WRF’, ‘worsening renal function’ which is usually defined as doubling in serum creatinine); AMI = acute myocardial infarction; PE = pulmonary embolism; SVR = systemic vascular resistance; HF = heart failure; CKD = chronic kidney disease; RAS = renal artery stenosis; GFR = glomerular filtration rate; NGAL = neutrophil gelatinase-associated lipocalin; IL-18 = interleukin-18; KIM-1 = kidney injury molecule 1; L-FABP = liver-type fatty acid binding protein; NAG = N-acetylglucosamine.

functioning heart damaging the kidney and their potential to be correctly identified in daily practice. Treatment effects in CRS type 1 were only considered either as proof or disproof of a mechanism. Experiments and studies were identified via Medline and Web of Science using the terms ‘cardiorenal’, ‘(acutely/acute decompensated) heart failure’, and ‘acute kidney injury (AKI)’ or ‘(worsening) renal (function)’ combined with ‘animal (experiment/model)’, ‘(patho)mechanism’, or ‘pathophysiology’, ‘pathway’ or ‘RAAS’, ‘fluid retention’, ‘sympathetic nervous system’, ‘biomarker’ or ‘immunity’. In view of the volume of the retrieved literature, only representative publications are cited in this review. Furthermore, we opted to limit this summary to clinical scenarios in which there was ample data. We did not include the specific clinical situations of cardiac surgery procedures with the use of cardiopulmonary bypass or contrast media application as we rank both scenarios as antecedents to CRS type 1.

This report is the result of a modified Delphi analysis [5] which is a structured and standardized process for collecting, summarizing and disseminating knowledge from a group of experts focused on a specific problem or task. A detailed description of the ADQI methodology is available at www.adqi.net.

Based on the literature identified prior to the conference, the following key questions were identified:

Question 1: What are the predominant pathophysiologic mechanisms of CRS type 1 in ADHF?

Question 2: Could biomarker profiling identify pathomechanisms or hemodynamic phenotype of patients with CRS type 1? Could predictive biomarkers improve renal safety of therapy in CRS type 1?

Question 3: How do the timing, severity and duration relate to the mechanisms and outcomes of CRS type 1?

At the conference, after a systematic literature review and the appraisal of the best available evidence, group 1 discussed monodirectional mechanisms of CRS type 1 generating from the heart affecting the kidney.

Results

Ad Question 1: What are the predominant pathophysiologic mechanisms of CRS type 1 in ADHF?

Hemodynamic Mechanisms

Observations from experiments and the clinical settings suggest that hemodynamic mechanisms seem to play a major if not predominant role in CRS type 1 in the setting of ADHF. Various animal studies suggest an initial hemodynamic event as a CRS type 1 trigger leading to decreased renal arterial flow, renal oxygen consumption and glomerular filtration rate (GFR) and increased renal vascular resistance whereas hemodynamic counteractive measures such as renal-selective blood perfusion restored all of these hemodynamic parameters and renal function back to normal [6].

In the general setting of ADHF, different hemodynamic profiles have been proposed based on the clinical phenotype of individual patients [7]. This approach consists of categorization of patients dependent of their systemic hemodynamics, including adequacy of perfusion (decreased CO and decreased effective circulation fluid volume (ECFV)) and extent of (pulmonary) congestion (increase in CVP or wedge pressure). As such, these can be combined into four distinct profiles deemed wet or dry and warm or cold (fig. 2).

It is within each of these profiles of ADHF where CRS type 1 may develop. Since hemodynamics, patient characteristics, treatment, and even outcome

Congestion	Yes	'Wet and cold' Renal venous pressure ↑ RBF ↓ Impaired autoregulation	'Wet and warm' Renal venous pressure ↑ Disconcordantly reduced RBF Impaired autoregulation
	No	'Dry and cold' RBF ↓ Impaired autoregulation	'Dry and warm' Disconcordantly reduced RBF Intrarenal microvascular dysregulation
		Strongly decreased	Relatively preserved
		Systemic perfusion	

Fig. 2. Systemic hemodynamic profiles of ADHF and renal hemodynamic consequences in CRS type 1. Adapted from Stevenson and Perloff [7]. This figure combines profiles of ADHF with systemic hemodynamics and possible hemodynamic renal mechanisms that can cause CRS type 1 in each of the profiles. In the 'cold' profiles, AKI may develop as a consequence of reduced RBF when autoregulation is unable to preserve GFR. In the 'dry and cold' profile, this may include anemia or stringent diuresis/ultrafiltration with associated blood pressure reductions. In the 'wet' profiles, increased central venous pressure leads to increased renal venous pressure, that reduces renal perfusion pressure, increases renal interstitial pressure, opposing filtration by collapse of tubules. In the 'warm' profiles, although systemic perfusion is relatively preserved, RBF is disconcordantly reduced, attributable to impaired or attenuated autoregulation (e.g. RAAS inhibition, excessive sympathetic nervous system activation), impaired tubuloglomerular feedback mechanisms (e.g. NSAIDs), renal artery stenosis or predisposing conditions with loss of nephrons. Note that in each of the profiles, impaired (or attenuated) autoregulation may play a key role, resulting in decreased renal perfusion pressure. Considering the fact that most ADHF patients have high blood pressure, if CRS type 1 develops as a consequence of decreased RBF (and/or decreased renal perfusion pressure), this must be at least partly attributable to autoregulatory dysfunction. ADHF = Acute decompensated heart failure; CRS = cardio-renal syndrome; AKI = acute kidney injury; RBF = renal blood flow; GFR = glomerular filtration rate; RAAS = renin-angiotensin-aldosterone system; NSAID = non-steroidal inflammatory drugs.

are different in each of the four profiles, it is likely that also the pathophysiology of CRS type 1 may differ dependent of the hemodynamic profile of ADHF [8]. In addition, the occurrence of AKI in this setting may not only be restricted to within a certain profile, but may also be related to the dynamic process of shifting between profiles during either treatment or deterioration of ADHF.

Decreased Systemic Perfusion ('Cold' Profiles)

(A) Reduced Renal Blood Flow

In the profiles that both have a cold phenotype (fig. 2), the predominant alteration in systemic hemodynamics is a strong reduction in CO and ECFV, and this may be accompanied by marked increase in CVP in the wet profile. When CRS type 1 develops in these 'cold' patients, it is more than likely associated with a reduction in renal blood flow (RBF). In an acute setting such as ADHF it is however unclear how CO relates to RBF or even intrarenal blood flow distribution in ADHF. It may be hypothesized however that with a strong decrease in ECFV as is to be expected in ADHF, neurohormonal activation including renin-angiotensin system and systemic nervous system activation result in afferent (and relatively lower efferent) vasoconstriction, leading to a decrease in RBF and renal perfusion pressure. In these 'cold' profiles, low CO and ECFV may also be associated with low systemic blood pressure. Consequently, this reduces renal perfusion pressure, even in the case of relatively normal renal venous pressure, because autoregulation may be unable to compensate for the low blood pressure in the presence of low ECFV. The finding of severely decreased RBF and GFR in the setting of reduced CO would therefore imply that autoregulation is either (i) unable to compensate, (ii) attenuated or (iii) overruled by different mechanisms, or (iv) failing because of an unknown cause. In any case, data on these mechanisms in the setting of ADHF and CRS type 1 are lacking.

(B) Increased Central Venous Pressure

For those patients who are also 'wet' and therefore have increased systemic/pulmonary congestion, different mechanisms may cause CRS type 1. High CVP is directly transmitted to the renal vein and directly influences renal perfusion pressure. Different reports have highlighted that higher CVP (either caused by intravascular hypertension or by increased intra-abdominal pressure) is associated with decreasing GFR [9–12]. Next to a direct effect on renal perfusion pressure, high renal venous pressure results in increased interstitial intrarenal pressure because the kidney has a tight capsule. This increased pressure causes collapsing of tubules, and directly opposes filtration, resulting in decreased GFR [13]. How autoregulation responds to increased renal venous pressure is unknown, although higher levels of intrarenal angiotensin II and activation of the sympathetic nervous system have been proposed, which could indirectly influence arteriolar tone [14, 15].

(Relatively) Preserved Perfusion ('Warm' Profiles)

It is essential to highlight that even in the 'warm' profiles, CO and ECFV are still reduced compared to normal values, but are relatively high compared to those in the cold profiles. It might therefore be difficult to imagine how CRS type 1 may develop as a consequence of decreased RBF. In these specific patient groups, there is no data on RBF. If CO is relatively preserved, but RBF is decreased to such an extent that is associated with a low GFR, this implies there is a disproportionate decrease in RBF compared to CO. These circumstances may develop when uni- or bilateral renal artery stenosis is present, which has been estimated to be present up to 40% in patients with chronic heart failure and chronic kidney disease [16]. Even a small reduction in CO would result in larger reductions in RBF. Other factors that may be particularly important as pathophysiologic mechanisms of CRS type 1 in these profiles are chronic use of RAAS inhibitors that limit the autoregulatory response to reductions in ECFV and associated blood pressures. In a similar fashion, concomitant non-steroidal inflammatory drug (NSAID) use may limit tubuloglomerular feedback (TGF) when in response to a decreased ECFV TGF activation causes afferent vasodilation, which may be blocked by NSAIDs. Also, a small decrease in CO may not only result in an overall reduction in RBF, but can also change intrarenal blood flow distributions, of which the importance and effect on GFR in ADHF is unknown. Finally, since patients in the warm profiles tend to present with high blood pressures, the co- and preexisting hypertension in the chronic disease state can be associated with a reduction in functional nephrons.

The warm/wet profile with increased CVP is the most frequently occurring profile in acute and advanced HF [8], and therefore the possibility that CRS type 1 occurs in especially this setting is higher beforehand compared to any other. Mechanisms of increased CVP in this profile leading to AKI are not different compared to those in the cold profiles. However, the relative impact of increased CVP on renal perfusion pressure will be much more limited, since arterial blood pressures in this profile are usually high. A small increase in CVP will therefore have less impact on renal perfusion pressure. Whether high CVP relates to lower GFR and more frequent AKI in patients with high or low CO is matter of debate. Mullens et al. [9] showed that AKI especially occurred in those with high CI and high CVP. Damman et al. [10] showed in a variety of patients with cardiovascular disease that higher CVP was associated with lower eGFR even in patients with higher CI. On the other hand, increased CVP was not associated with AKI in the ESCAPE trial [11], and lower CVP predisposed to AKI in one study [12]. Possibly, it is especially this category of patients who will be treated rigorously with high dosages of diuretics (or ultrafil-

tration). As a consequence, if this treatment is paralleled by decreases in (arterial) blood pressures, it is more frequently associated with AKI and poor outcome.

Consensus Recommendations for Future Research

- Appropriate experimental models and clinical scenarios for CRS type 1 need to be identified; combined heart/kidney transplantation with intraoperative biopsy would need to be considered.
- Prospective and systematic studies on the incidence, mechanisms and associated outcome of CRS type 1 in different hemodynamic profiles of ADHF are needed.
- Therapy aimed at restoring systemic perfusion and reducing congestion without further reducing renal perfusion pressure should be a therapeutic goal.
- Relative importance of (non-invasive) RBF in ADHF and the development of CRS type 1 need to be determined.
- Relative importance of central and renal venous pressure in ADHF and the development of CRS type 1 need to be determined.

Consensus Recommendations for Clinical Practice

- Identification of hemodynamic profiles in patients with ADHF and CRS type 1 may help in guiding therapy decisions.

Non-Hemodynamic Mechanisms

Beyond hemodynamic pathways, other mechanisms have been described to be involved in pathogenesis of CRS type 1 including activation of sympathetic nervous system and RAAS, inflammation and impaired balance of ROS versus NO production.

Systemic hemodynamic events occurring during ADHF contribute to decreased RBF, impaired autoregulation and renal congestion (fig. 2) with the latter resulting from the product of right heart function, blood volume, and venous capacity, which is largely regulated by neurohormonal systems. Specific pathobiological (back)coupling mechanisms and modifiers are activated with positive or negative feedback loops to continuously monitor and adapt to changing extracellular fluid volume and blood pressure, depending on the duration and the intensity of the insult (fig. 3).

In the setting of significant acute heart dysfunction, falling CO and decreasing ECFV of the renal arterial tree results in activation of both SNS and RAAS mediated for example through the baroreceptor reflex. Also, increased central

Fig. 3. Non-hemodynamic network of pathophysiological interactions in CRS type 1. Note the emerging potential role of macrophages/monocytes as mediator of sodium and fluid retention. Reproduced with permission from ADQI [53].

stimulation of the SNS in the paraventricular nucleus – presumably by a combination of factors including increased angiotensin II, decreased NO and increased afferent renal sympathetic nerve activity – and extracellular volume expansion/control contribute to alterations in GFR and RBF in CRS type 1 [13].

Recent data suggest a potential role of mononuclear phagocyte system in the regulation of salt-dependent volume and blood pressure by a vascular endothelial growth factor-dependent mechanism [17]. Specifically, macrophages may be protective against the development of arterial hypertension and volume overload. By implication, a dysregulation of macrophages may initiate the sequence of ADHF through volume overload and congestion even without a primary hemodynamic cardiovascular event making macrophage modulation a potentially interesting target in CRS type 1.

In line with cellular immunity potentially being critically involved in the pathogenesis of human CRS type 1, Virzi et al. [18] report that a defective regu-

lation of monocyte apoptosis and activation of inflammatory pathways occurs more frequently in patients with ADHF compared to healthy controls. Plasma-induced apoptosis was 7-fold higher in CRS type 1 patients, the activity of caspase-8 was significantly higher in monocytes incubated with plasma from affected patients and the serum concentration of two pro-inflammatory cytokines was elevated 4- to 10-fold. Therefore, immune cell apoptosis in CRS type 1 and with it premise of an immune-mediated process in the pathophysiology of CRS type 1 should be further explored.

Consensus Recommendations for Future Research

- Useful experimental and clinical models for CRS type 1 delineating bidirectional heart-kidney interactions need to be identified.
- Prospective and systematic studies with simultaneous measurement of hemodynamic and non-hemodynamic indices to determine the relative importance of pathomechanisms in initiation and maintenance of CRS type 1 in different hemodynamic profiles of ADHF are needed.
- The role of cellular immunity and resulting sodium and fluid retention in initiation and maintenance of CRS type 1 need to be further explored in clinical studies.

Consensus Recommendations for Clinical Practice

- At this stage there is no evidence to initiate specific anti-inflammatory or anti-neurohormonal treatment in CRS type 1.

Ad Question 2: Could biomarker profiling identify pathomechanisms or hemodynamic phenotype of patients with CRS type 1? Could predictive biomarkers improve renal safety of therapy in CRS type 1?

The challenge in management of CRS type 1 is relieving congestion and improving symptoms while restoring renal and systemic perfusion. Although pathophysiological understanding of ADHF and CRS type 1 increases, morbidity and mortality of the syndrome remained high over the last decades. Multiple reasons for failure of effective therapies have been implicated including the fact that (i) multiple causative factors may be involved and tackling of one pathway may be insufficient, (ii) single intervention may not cover the entire pathophysiological process, (iii) the time window between insult and development of AKI can be different in different patients, (iv) testing of drugs during their development may not reproduce their possible use in multimorbid patients, and (v) in the clinical setting AKI is often diagnosed too late, when the effects of the insult already become evident (loss of renal excretory function).

Therefore, earlier and more specific diagnosis of CRS type 1 but also allocation of predominant mechanism, site of renal injury and hemodynamic phenotype in an individual patient is needed. In this regard, biochemical cardiorenal markers, imaging techniques and monitoring of fluid and hemodynamic status will be briefly discussed.

Two important characteristics of biomarkers should be their defined role in the pathophysiology of the syndrome and their clinical actionability. Regarding the first postulated characteristic, neutrophil gelatinase-associated lipocalin (NGAL) has been implicated in the induction of cardiomyocyte apoptosis by increasing intracellular iron accumulation [19]. Also, administration of recombinant NGAL to mice induced an acute inflammatory response with compensatory changes in cardiac functional parameters reflecting its potential role as cardiorenal biomarker [19]. Such findings were in line with those reported for experimental and human myocarditis where NGAL was strongly induced in affected myocytes, vascular wall cells, fibroblasts and neutrophils [20]. High NGAL levels were initially sustained during the inflammatory stage, then decreased with recovery [20]. Beyond a potential inflammatory role of NGAL in CRS, there is first evidence for its involvement in fluid status regulation given that mineral corticoid receptor activation induces NGAL promoter in the cardiovascular system and upregulation of NGAL expression in the heart and aorta and its plasma levels [21].

Biomarker evidence of neurohormonal activation includes the natriuretic peptides, mid-regional pro-adrenomedullin, and copeptin [22, 23]. Recent studies suggest individuals with greater levels of natriuretic peptides as baseline and evidence of pulmonary congestion, in addition to increased CVP, have the greatest risk for CRS type 1 [24]. Such hemodynamic impairment of the kidney may result in a loss of autoregulation and the onset of worsened salt and water retention, reduction in renal filtration, and oliguria.

Beyond hemodynamics and neurohormonal activation, abnormal patterns of cell signaling have been linked to ADHF and possibly CRS type 1. Soluble ST-2, a recently approved blood biomarker in the risk prediction of HF hospitalization and death [25, 26], appears to be complementary to the natriuretic peptides and reflects the degree of biomechanical strain and immune cell activation and cell signaling that occurs in progressive HF [27]. ST2 is the receptor for interleukin (IL)-33, a cytokine with angiohypertrophic and antifibrotic effects on the myocardium [28]. Soluble ST is a circulating inhibitor of the ST2 receptor, and counteracts such potentially regenerative effects of IL-33. This line of reasoning illustrates how systemic cell signaling could trigger events in the kidney in the form of maladaptive TGF which cause a transient reduction in renal filtration and a rise in serum creatinine [29, 30].

The use of biochemical markers for detection of loss of GFR and development of acute tubular damage has been suggested to overcome limitations of serum creatinine. In this regard, ADQI recommended a novel unified diagnostic concept with the biochemical detection of acute tubular damage complementing acute loss of renal excretory function [31].

Beside serum creatinine, serum cystatin C, a 25-kDa glomerularly filterable protein produced by all nucleated cells at a constant rate, has been used as biochemical surrogate for renal function. Serum cystatin C measured at admission in patients hospitalized for treatment of ADHF was more predictive of long-term all-cause mortality and readmission for ADHF than serum creatinine or serum BNP [32–34]. Given the prognostic value and its biochemical characteristics, serum cystatin C may also have value for earlier diagnosis of an acute loss of renal excretory function in CRS type 1, however data in this regard are lacking. Drawing pathophysiological inferences from the serum cystatin C test result about allocation to one out of four above-mentioned specific hemodynamic phenotypes does not appear to be possible.

Among other tubular damage markers such as kidney injury molecule 1 (KIM-1), liver-type fatty acid binding protein (L-FABP), IL-18 and others, NGAL appears to be that one with most comprehensive experimental and clinical data available in ADHF at this stage. NGAL levels were found to be largely determined by underlying impairment of renal rather than myocardial function [35]. In patients with ADHF, serum NGAL strongly correlated with renal function markers [36]. Higher serum NGAL levels at hospital admission have been associated with adverse cardiovascular outcomes or death [37]. Of note, at hospital discharge, plasma NGAL level was a stronger predictor of 30-day all-cause death and ADHF readmissions than BNP (adjusted HR for NGAL: 19.9 vs. adjusted HR for BNP: 2.3) [38]. Such comparison with BNP suggests that ongoing acute tubular damage in CRS type 1 is of importance for future development of CRS type 3.

There is preliminary evidence that elevated admission serum NGAL levels predict AKI in patients with ADHF whereas serum cystatin C and even more serum creatinine were of limited value [39–41]. One study compared the value of urine NGAL with that of plasma NGAL for predicting AKI in patients with ADHF and found that both markers were similar in this regard [42].

In one study, NGAL raised slightly during diuretic treatment of ADHF in patients who subsequently developed AKI. However, NGAL predictive ability for AKI in this setting was limited [43].

Further candidate biomarkers potentially related to pathophysiology of CRS type 1 and to be tested for suitability for the early diagnosis of AKI in patients with ADHF include osteopontin, N-acetyl- β -D-glucosaminidase, stromal cell-

derived factor-1, endoglin, galectin-3 and exosomes [44]. However, at this stage, data are too limited to draw any conclusions for use of these candidate biomarkers.

A different approach from biochemical biomarkers in the differential diagnosis of CRS type 1 is the use of bioelectrical devices to measure partial or whole-body impedance and conclude from such value on the fluid status and with this allocation of a hemodynamic profile of a given patient as described above. In the absence of comprehensive data on the clinical usefulness of bioimpedance measurement in CRS type 1, several clinical studies in patients presenting with ADHF showed an association of decreased impedance values, i.e. increased body fluid volume, with adverse events including rehospitalization and death. Also, in patients presenting with dyspnea, bioimpedance measurement helped to distinguish cardiogenic dyspnea from non-cardiogenic dyspnea [45, 46]. Sequential bioimpedance measurements may contribute to achievement of adequate fluid balance status in patients with ADHF [47]. High sensitivity and specificity of reduced bioimpedance value were reported for identifying radiographic findings consistent with pulmonary edema [48]. Bioimpedance test result may be a potential criterion for discharge readiness [49].

Taken together, if acute tubular damage markers contribute to distinguishing a potentially adaptive (compensation for reduced ECFV) from a maladaptive reaction of the kidney in response to ADHF, their measurement in clinical practice might prove useful. Such approach would consider rapid reversibility of renal function loss without tubular damage. Bioimpedance measurement may guide early diagnosis of ADHF, differential diagnosis of dyspnea and therapy management on CRS type 1 but need further exploration.

Consensus Recommendations for Future Research

- Future studies should investigate the role of mineralcorticoid receptor antagonists in CRS type 1.
- Multicenter studies using a panel of acute tubular damage markers measured in urine and in plasma at admission and discharge and allocation to hemodynamic phenotype/profile are needed.
- The role of bioimpedance measurement for prevention and/or therapy of CRS type 1 needs to be investigated.

Consensus Recommendations for Clinical Practice

- Use of bioimpedance measurement may be considered in the management of patients with CRS type 1.

Fig. 4. Timing of acute kidney injury in the setting of acute decompensated heart failure. Adapted from Breidhardt et al. [50].

Ad Question 3: How do the timing, severity and duration relate to the mechanisms and outcomes of CRS type 1?

Recently, studies that had access to preadmission levels of serum creatinine revealed that AKI seems to be present already at presentation to the emergency department in about one third of consecutive patients with ADHF who have AKI at any time during hospitalization [50]. This may even be an underestimation which may arise due to the obvious dilemma of obtaining informed consent from the sickest patients.

Another 50% of AKI patients first fulfilled AKI criteria within the first 48 h in hospital, while only a minority developed late AKI after 48 h (fig. 4).

Given our incomplete understanding of the pathophysiology of CRS type 1, it may seem overzealous to differentiate predominate mechanisms according to the timing of AKI. However, we would like to highlight emerging hypothesis-generating observations of treatment effects: First, seemingly paradoxical, renal function often improves in response to standard therapy aimed to reduce filling pressures with loop diuretics and nitrates in warm and wet ADHF patients with AKI at presentation. Taken together, with the increasing recognition of increased renal venous congestion as a contributor to AKI in ADHF, this observation suggests that increased renal venous congestion may be the predominate mechanisms underlying AKI that is already present at presentation to the emergency department.

A post hoc analysis of Pre-RELAX found that drop in systolic blood pressure within the first 48 h of vasodilator therapy was an independent predictor of AKI by day 5 [51]. These data together with clinical experience support the concept that therapy-related reduction in renal perfusion pressure and/or ECFV are the predominate mechanisms underlying AKI that develops within the first days of hospitalization.

Usually, ACE inhibitors are slowly uptitrated during the course of hospitalization. The hemodynamic effect of ACE inhibitors (vasodilation of the vas efferens) and its associated drop in filtration pressure as well as ‘pre-renal’ kidney dysfunction due to the reduction in ECFV associated with intensified therapy with loop diuretics may be the predominate mechanism underlying AKI developing late during hospitalization.

Finally, severity and duration of AKI seem to relate to long-term patient outcome [52].

Consensus Recommendations for Future Research

- Confirm or rebut the hypothesis of the different ‘AKI phenotypes’ according to timing.
- Define the impact of timing of AKI on long-term outcome.

Consensus Recommendations for Clinical Practice

- Frequent (daily) monitoring of renal function during ADHF should complement clinical assessment in order to best guide therapy with diuretics and vasodilators with their profound impact on cardiorenal interactions.
- Daily assessment of limb perfusion (cold/warm extremities, recapillarization time, and others) and CVP as surrogates for renal filtration pressure and renal venous congestion as the two key hemodynamic variables determining renal function.

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