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# Renal function, electrolytes, and congestion monitoring in heart failure

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## KEYWORDS

Heart failure;  
renal function;  
monitoring;  
congestion;  
diuretics

Congestion, renal function, and electrolyte imbalance (particularly potassium) are common problems in the management of the complex multi-morbid patient with heart failure (HF). Poor control of these fundamental clinical features is associated with adverse outcomes. Close monitoring of serum potassium and renal function is recommended by most current guidelines during the management of an episode of acute decompensated HF, yet the recommendations remain poorly implemented. Physicians are advised to treat a state of euvoemia after an admission with decompensated HF and residual congestion is a marker of worse outcome, yet control of congestion is poorly assessed and managed in real-world practice. This document reflects the key points discussed by a panel of experts during a Heart Failure Association meeting on physiological monitoring of the complex multi-morbid HF patient, and here, we present to aspects related to renal function, electrolyte, and congestion monitoring.

## Introduction

In heart failure (HF) one of the main reasons for hospitalization is congestion.<sup>1,2</sup> Both the congestion itself as well as the diuretic drugs used to treat it can have a detrimental impact on renal function. As such, optimized monitoring of renal function in HF is pivotal for preventing renal failure and emergency re-hospitalization.<sup>3,4</sup> Unfortunately, due to a relative lack of studies, current guidance of renal function monitoring is largely driven by clinicians' opinions, rather than being evidence-based.<sup>5,6</sup>

A Heart Failure Association consensus meeting was held on the topic of physiological monitoring of the complex multi-morbid HF patient, and one important aspect was

monitoring of the related features of congestion status, renal function, and electrolyte levels, particularly potassium. This article reflects the key points regarding potassium, creatinine, and congestion assessment, discussed at this meeting.

## Importance of the kidney in heart failure

Data from international registries consistently show that physician adherence to guideline-recommended medications (GDMT) in HF with reduced ejection fraction (HFrEF) is associated with better outcomes.<sup>7</sup> Unfortunately, current HFrEF drug guidelines are not being optimally implemented.<sup>8,9</sup> Essential life-saving medications are frequently under-used and/or under-dosed, most often because of possibly excessive concern about adverse events.<sup>10,11</sup> Hyperkalaemia and kidney dysfunction are common

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comorbidities in HF.<sup>12-15</sup> Both are associated with the underuse and under-dosing of renin-angiotensin-aldosterone system inhibitors (RAASi).<sup>16,17</sup> Loop diuretic-induced hypokalaemia is also associated with adverse outcomes in HF with reduced ejection fraction (HFrEF).<sup>18,19</sup> Concerns about renal adverse events may be excessive in some cases, and it should be recognized that this has the potential of depriving patients of receiving full doses of life-saving therapies.<sup>20,21</sup> Down-titration of doses or discontinuation of RAASi may be warranted temporarily for persistent/severe hyperkalaemia, or worsening renal function.<sup>22</sup> However, this should not prevent attempting re-initiation or up-titration of therapy as soon as is safely possible.<sup>23</sup> The use of potassium binders may facilitate up-titration in patients prone to hyperkalaemia,<sup>24-26</sup> although, whether this may improve cardiovascular outcomes, remains to be demonstrated in adequately powered outcome trials.<sup>27,28</sup> Importantly, guidelines recommend close monitoring of serum potassium and renal function during intervals after initiation of RAASi drugs.<sup>29</sup> Unfortunately, data from major HF registries<sup>30,31</sup> show that such monitoring is poorly implemented, even after the occurrence of hyperkalaemia.

## Monitoring of renal impairment in heart failure

Renal failure is common in HF and impairment of renal function is an independent marker of poor outcome. Worsening of renal function (WRF, often defined as an increase in creatinine by  $>0.3$  mg/dL) occurs more commonly when higher-dose diuretics are used, such as in the high-dose limb of the DOSE-AHF trial. Although changes in renal function can be associated with worse outcomes, this is not always the case.<sup>32</sup> A *post hoc* analysis of the DOSE-AHF trial illustrated the diuretic-induced increase in creatinine did not predict worse outcomes.<sup>33</sup> In addition, creatinine itself can be an unreliable marker of renal impairment where in chronic illness muscle mass is reduced,<sup>34</sup> which may occur even acutely in HF.<sup>35</sup> Baseline renal dysfunction is an important predictor of diuretic response in WHF, supporting a higher starting dose of furosemide in patients with lower eGFR.<sup>36</sup>

The evaluation of renal function is of foremost importance in managing the complicated HF patient, especially in the presence of advanced disease or multiple comorbidities. Assessment of glomerular filtration rates (GFR) alone is not adequate and indeed many biomarkers and imaging techniques are available to help the clinician assess the effects of HF and its therapy on the kidney.

Renal function decline to some extent can and must be expected in the setting of decongestion, and accepted as long as the overall clinical status does not deteriorate. This is often referred to as 'pseudo worsening renal function (WRF)'. However, we have no robust data to define to what degree this is acceptable. A further decline in eGFR (especially if urinary output decreases or the clinical status of a patient simultaneously deteriorates) may represent true WRF, which is associated with substantially worse long-term outcomes and thus must be avoided.<sup>37,38</sup>

Worsening of renal function should not always be seen as a bad sign, as it can actually reflect a good response to diuretic therapy and an overall favourable prognosis, in what has been coined pseudo-WRF.<sup>39</sup> Thus the distinction between true WRF with permanent kidney damage and pseudo-WRF which can be seen in up to one-fifth of ADHF patients is an important thing to establish,<sup>33</sup> especially as being discharged with inadequate decongestion is usually far worse than the pseudo-WRF pattern.<sup>40</sup>

Markers of renal function are suboptimal to track and detect renal function decline. Creatinine tends to lag behind renal decline, and increases in creatinine may not be detected until  $\geq 24$  hours after renal function has begun to decline. However, monitoring diuresis and daily measurement of renal function and electrolytes are advocated.<sup>41-43</sup>

In routine practice, serum creatinine is the most frequently used marker of renal function, and it can be converted to GFR by one of several formulae that have been recommended in HF guidelines as part of routine HF care, although the frequency of their estimation is not discussed in detail. The Cockcroft-Gault, the simplified modification of diet in renal disease formula and the CKD-EPI formula have all been used to assess prognosis in HF, but their stability in the setting of acute changes that are frequent in acutely decompensated HF is questionable. Glomerular filtration rates are a measure of renal reserve capacity, but it also includes short-term dynamic elements which help explain why it is a good predictor of long-term outcomes in HF, but also a poor short-term predictor of hour-to-hour changes in kidney health and how to respond clinically. Glomerular filtration rates can be measured directly by exogenous indicator dilutor methods using agents such as iohalamate or inulin, but it more commonly estimated from endogenously produced factors such as creatinine or cystatin C. Cystatin C has some advantages, for unlike creatinine it is not affected by renal tubular function because it is not secreted by the tubules.<sup>44</sup> Serum urea, reflects both GFR and tubular reabsorption and is thus affected by neurohormonal status and inhibition.<sup>45</sup> Urea is a powerful predictor of outcome offering additional value independent of creatinine or GFR.

Ideally, we would also have a reliable measure of renal tubular function that can be assessed acutely during an admission for decompensated HF, and although many have been proposed none has established a cemented role in routine practice. The most studied is neutrophil gelatinase-associated lipocalin.<sup>46</sup> Others include serum  $\beta 2$ -microglobulin and fatty acid binding proteins. Urine output and electrolyte concentrations can and should be monitored in acute HF,<sup>47</sup> particularly to gauge the patient's response to loop diuretic therapy. Lastly, albuminuria can be used to assess glomerular filtration efficacy and can be abnormal in diabetes and CKD due to damage to the glomerular membrane. Albuminuria is common in HF and is linked to prognosis but the clinical implications of this remain unclear.<sup>48</sup>

Specialized imaging of the kidney, such as ultrasound, can be helpful but is not routinely recommended and certainly not for monitoring purposes. Future techniques may offer better insights into dynamic changes occurring in intra-renal blood flow and the filtering tubular functions of the kidney.

## Monitoring of electrolytes in heart failure

Electrolyte abnormalities are common in HF. They can be the result of diuretics, renal impairment neurohormonal activation, and the combination of these factors. Sodium (Na) and potassium (K) are the most commonly perturbed electrolytes<sup>49</sup> but chloride is also affected.<sup>50</sup> Hyponatraemia is common in acutely decompensated HF.<sup>51,52</sup> This is thought to be the result of impaired excretion of free water via dilution hyponatraemia, a true depletion of sodium or both. Potassium abnormalities are particularly due to the treatments given for HF with hypokalaemia complicating diuretic use and hyperkalaemia particularly associated with increasing RAAS-blockade, along with potassium-sparing diuretics and the sometime use of potassium supplements. Magnesium, deficiency frequently co-exists with hypokalaemia. Guidelines do not specially indicate when or how frequently electrolytes should be monitored as it depends on clinical circumstances, but we believe they should be estimated daily during acute decongestive therapy, during routine post-discharge follow-up and following any dose changes in HF medication.<sup>53</sup> All RAASi's can increase K levels but this is particularly noticeable after the addition of mineralocorticoid receptor antagonists (MRAs). Although the benefits of MRAs are also seen in HFrEF patients with eGFR <60 mL/min/1.73m<sup>2</sup>, despite being associated with small acute and persistent reductions in GFR,<sup>54</sup> the risk of hyperkalaemia goes up when these agents are prescribed in the presence of pre-existing renal impairment and in such patients careful repeated estimation of K is recommended.<sup>55</sup> Newly developed oral potassium binders (patiromer or zirconium cyclosilicate) might ease long-term control of K and allow patients with HFrEF to take higher RAASi doses than hitherto but whether this will be reflected in improved long-term outcomes remain unproven.

It is difficult to be prescriptive with regards to the recommended frequency of ongoing monitoring of renal function and electrolytes (usually measured together) as so much depends on individual patient characteristics and inter-current clinical events but in stable HFrEF patients it appears reasonable to measure serum creatinine, urea, eGFR, and electrolytes three times per year, supplemented by re-measurement if medication or patient condition changes.

## Monitoring of congestion in heart failure

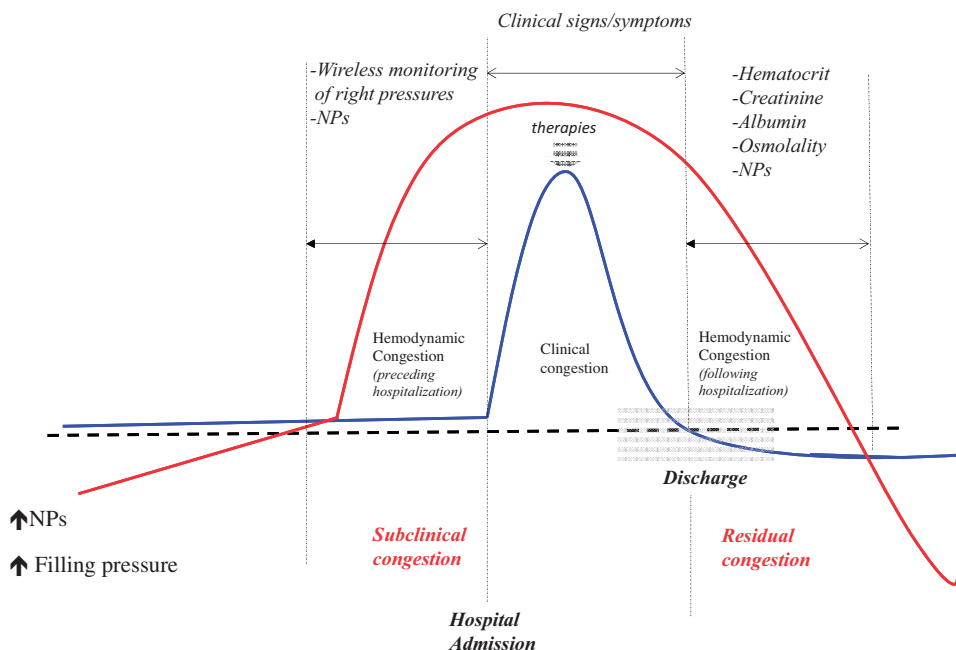
Congestion is one of the most important determinants of HF symptoms<sup>56,57</sup> and a major prognostic factor in HF.<sup>58-60</sup> It is mostly treated with loop diuretics, as recommended by major international guidelines. It is, therefore, of paramount importance to adequately determine the congestive status,<sup>61</sup> at both admission and discharge, since residual congestion at discharge is associated to higher one-year mortality and HF readmissions.<sup>62</sup> Patients with residual congestion may have been inadequately decongested during hospitalization, or even if decongested they may experience a recurrence of congestion during post-discharge

follow-up,<sup>63</sup> which may trigger subsequent deaths or readmissions in the post-discharge phase.

On the one hand, inadequately low diuretic doses may lead to persistent congestion, one major driver of the high rate of readmission after episodes of worsening HF. Conversely, inappropriately high loop diuretic doses may trigger hypokalaemia and hypovolaemia, with its associated risks of worsening renal function, the latter potentially leading to the down-titration or discontinuation of life-saving drugs i.e. RAASi. Ensuring decongestion is an essential goal during AHF hospitalization, but there is no standardized method for evaluating congestion before discharge and what defines adequate decongestion is currently unclear.<sup>59</sup> Although clinical trials have proposed a 'definition for decongestion', assessment of decongestion based strictly on trial pre-defined clinical signs may be neither sensitive nor specific, and has not been investigated in real-life clinical practice.<sup>64,65</sup> Persisting congestion should be more aggressively addressed, perhaps even at the expense of delaying discharge, and these patients should be more closely followed up. Furthermore, other biological variables as surrogate markers of haemodynamic congestion, a <30% change in NP concentrations, or decreased haematocrit during hospitalization, decreasing serum osmolality, add significant prognostic information beyond residual clinical congestion.<sup>59</sup>

Several routinely assessed biological parameters, such as serum protein, albumin, haemoglobin,<sup>66</sup> and haematocrit (considered in isolation or in combination, enabling the indirect estimation of plasma volume)<sup>67,68</sup> have been proposed as surrogate markers of (de)congestion and have been found to be associated with cardiovascular endpoints.<sup>28,69</sup> The gold standard measure of haemodynamic congestion in HF is invasive measurement of pulmonary capillary wedge pressure<sup>1</sup> yet this is impractical for routine care.<sup>1</sup> Non-invasive assessments of congestion have been validated but with variable sensitivities and specificities.<sup>1</sup> Physical signs of congestion can be unreliable and difficult to assess, especially in obesity. Newer techniques such as lung ultrasound offer advantages over older techniques including chest X-ray.<sup>70</sup> The reader is referred to the paper on imaging of cardiac function for discussion of indirect estimation of cardiac filling pressures (*Figure 1*). Most guidelines suggest the measurement of natriuretic peptides (NPs) in selected clinical settings, but this is more measure of ventricular stress or dilatation than of congestion per se, even though the two may be mechanistically linked in many cases. NPs have a high negative predictive value for ruling out acute HF with congestion but routine monitoring of NP levels in long-term follow-up has not proven to be beneficial on outcomes or cost-effective.

Other potential biomarkers of congestion that can be monitored include sCD-146<sup>71</sup> and the monitoring of haemoglobin concentration through estimation of Hb after decongestive therapy thereby giving an estimate of the degree of relative decongestion rather than the absolute level of congestion at any point in time.<sup>72</sup> Although increasing creatinine levels are frequently interpreted as worsening kidney function, leading to reductions in HF therapy, during active decongestion an increase in creatinine is to be expected, and being discharged with ongoing congestion seems worse



**Figure 1** As result of pressure/volume overload, filling pressures and NPs, will increase (red) and its variation precedes worsening of congestion (blue). This pattern may be useful to identify early subclinical decompensation. In spite of clinical improvement as result of in-hospital therapies, for a subset of patients, filling pressures and NPs levels are still persistent during hospitalization and in early post discharge period, suggesting residual congestion. Also, decrease in serum osmolality as result of the high plasma volume may signify haemodynamic congestion. Identification and monitoring of haemodynamic congestion is crucial for preventing early post-discharge adverse events.

compared with the apparent WRF as measured by temporary increases in creatinine.<sup>73</sup>

### Telemedicine for monitoring congestion, renal function, and potassium levels

Dynamic therapy optimization using a telemedicine solution based on frequent non-invasive assessments of congestion (as assessed by haemoglobin), renal function, and blood potassium may enable safe optimization of GDMT.<sup>74</sup> Concomitant changes in haemoglobin, blood potassium, and renal function and their interplay are probably the most clinically relevant actionable parameters for assessing congestion and the crucial cardio-renal balance. One such system, the remote CardioRenal<sup>®</sup> monitoring solution integrates a pragmatic disease management programme and combines the following components: (i) an innovative microfluidics technology of accurate home monitoring of haemoglobin, potassium, and creatinine concentrations, using a finger-prick 3  $\mu$ L blood-drop; (ii) remote monitoring using modern data transfer and data processing methods; (iii) a comprehensive patient-centred disease management, including a medically staffed call-centre; (iv) an innovative algorithmic decision support expert system delivering personalized therapeutic advice to the physician, guided by the monitored variables and the expert system analysis of the patients' electronic health record.

The planned CARE-MOST HF trial (Cardiorenal Assessments and REmote Monitoring for the OptimiSation of Therapy in Heart Failure) is a prospective randomized open blinded end-point evaluation (PROBE) design trial to assess the effectiveness of the CardioRenal<sup>®</sup> telemonitoring loop

vs. usual care in the early follow-up phase of HFrEF patients enrolled before discharge after an acute decompensation. The primary end-point of the study is the cumulative number of HF hospitalizations and cardiovascular deaths. These results will shed new light on the effectiveness of this telemonitoring system in HFrEF patients.

### Conclusions

Renal function, congestion, and electrolyte disturbances are both inter-dependent and strong predictors of outcome in HF and can rapidly change depending on the clinical context. Accurate monitoring is essential both in the dynamic situation of acute HF as well as in up-titrating and maintaining optimized RAASi dosages. Accurate individualized monitoring of potassium, renal function, and congestion can facilitate both HF therapy optimization and hospitalization reduction. Telemedicine, in particular, may allow a dynamic optimization of therapy over time. Clinical trials specifically aimed at evaluating the optimal frequency of renal function monitoring in patients with HF are strongly needed.

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