Renal kinetics in acute heart failure

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ABSTRACT

Aims Worsening renal function (WRF) in acute heart failure (AHF) has multifactorial pathophysiological mechanisms and heterogeneous prognostic impacts. The aim of this study was to determine the characteristics and renal kinetics of this phenomenon.

Methods and results We prospectively enrolled a cohort of 196 patients admitted for AHF to the Cardiology Department at Nhan Dan Gia Dinh Hospital, from July 2016 to March 2017. AHF was defined using the 2012 European Society of Cardiology criteria. The definition and severity of WRF were based on the 2012 Kidney Disease Improving Outcome criteria for acute kidney injury. Renal recovery was classified using the 2017 Acute Disease Quality Initiative 16 Workgroup Consensus. Among the 196 patients studied, WRF developed in 43.4%. In 80.0% of patients, WRF occurred within 48 hours of admission. In the WRF group, 89.4% were at stage 1, consistent with a relative increase in median serum creatinine of 49.5%. A total of 76.5% of the patients with WRF recovered at discharge, while rapid recovery occurred in 20.0% of patients.

Conclusions Most cases of WRF were mild, and WRF was correlated with a high rate of recovery during hospitalisation. However, rapid renal recovery was not common.

INTRODUCTION

Worsening renal function (WRF) is a common comorbidity in acute heart failure (AHF), since 10%–40% of these patients develop WRF during hospitalisation.1 2 While most recent studies have indicated that venous congestion or an increase in the central venous pressure is the main pathophysiology of WRF,3 other conditions, such as concurrent infection, neurohormonal activation or heart failure medical treatments, could also cause significant changes in renal function. By using implantable haemodynamic monitors, studies have suggested that venous congestion often occurs many days prior to the patient experiencing heart failure-related events.4 This fact supports a recent finding where a considerable number of patients with WRF were first diagnosed at admission for heart failure.5 This early presentation has a distinctive pathophysiological pathway and prognostic impact on heart failure.6

In addition, in contrast to ‘true WRF’, in which intrinsic renal injury does occur, most of the cases of WRF in AHF are considered ‘pseudo-WRF’, relating to a transient functional decrease in the glomerular filtration rate.7 Pseudo-WRF is believed to have a considerably faster recovery rate and better prognostic impact compared with ‘true-WRF’. The characteristics of WRF regarding the severity or the time point of renal dysfunction development, and renal kinetics of WRF concerning the rate of kidney function recovery will, therefore, provide insight into the differential diagnosis of the pathophysiological mechanisms of cardiorenal interaction. It should be acknowledged that most studies evaluating cardiorenal syndrome have been focusing on the incidence and risk factors of WRF in AHF, and the evidence base for renal reversal is still lacking. Thus, we performed a prospective study to determine the features of renal dysfunction and renal kinetics of WRF in AHF.

METHODS

Study population
We prospectively recruited 196 patients admitted to the Cardiology Department at Nhan Dan Gia Dinh Hospital (a tertiary hospital in Ho Chi Minh City, Vietnam) from July 2016 to March 2017. To be eligible for enrolment, patients had to be over 18 years of age and they presented with signs and symptoms of AHF. AHF was defined (online...
supplementary appendix A), classified into four clinical profiles (online supplementary appendix B), and the patients were managed according to current European Society of Cardiology (ESC) guidelines. The exclusion criteria included patients who presented with (1) cardiac tamponade, (2) acute aortic dissection, (3) septic shock, (4) acute coronary syndrome, (5) indications for coronary angiography, (6) admission serum creatinine ≥3.0 mg/dL, (7) indications for emergency haemodialysis for acute kidney injury and (7) postrenal acute kidney injury. WRF was defined as one of the following: (1) increase in serum creatinine ≥0.3 mg/dL within 48 hours; or (2) increase in serum creatinine to ≥1.5 times baseline, which was known or presumed to have occurred within the prior 7 days. The severity of WRF was classified according to the Kidney Disease Improving Outcome (KDIGO) criteria. Among patients that developed WRF during hospitalisation, kidney function recovery within 48 hours of its onset was defined as a rapid reversal. A time period of 48 hours was proposed to separate transient versus persistent acute kidney injury.10 Renal recovery was assessed at discharge by a decrease in the serum creatinine level after its peak to within 10% of its baseline serum level. The standard treatment of heart failure, including ACE inhibitors and angiotensin receptor blockers (ACEi/ARB), vasodilators, beta-blockers and diuretics, was left to the attending physician.

Study assessment
At enrolment, all patients underwent an initial clinical assessment including a clinical history, physical examination, chest X-ray and blood tests including N-terminal B-type natriuretic peptide (NT-proBNP). Transthoracic echocardiography was performed during hospitalisation using the biplane method of disc formula to calculate left ventricular ejection fraction. An abdominal ultrasound was indicated at the physicians’ discretion. Serum urea and creatinine were measured at presentation, every 48 hours thereafter, and at discharge from the hospital. The eGFR was calculated using the simplified Modification of Diet in Renal Disease formula to estimate the baseline and follow-up kidney function in all patients. Baseline creatinine was recorded as the lowest value in 3 months before the admission for AHF when the patient was in a stable state of health.

Statistical analysis
Data are provided as the mean±SD when normally distributed, as the median and IQR for skewed distributions, and as frequencies and percentages for categorical variables. Associations between baseline variables were evaluated by means of one-way analysis of variance, and χ² or Fisher exact tests, as appropriate. The independent t-test or Mann-Whitney test was used to compare the differences between two independent groups. Logistic regression model analysis adjusting for age, New York Heart Association (NYHA) class, AHF clinical phenotypes, comorbidities, medications before admission ACE-i/

RESULTS
Incidence of WRF
The clinical characteristics of the study population with and without WRF are represented in table 1. The mean age of the patients was 68.3 years, and 40.3% were men. While all of the patients admitted for AHF were in NYHA III (44.9%) and NYHA IV (55.1%), 90.3% were classified as having a wet-warm phenotype. In both patients with or without WRF, cardiac type was the most common type of congestion. The mean serum creatinine level was 1.5 mg/dL, and the mean eGFR was 54.0 mL/min/1.73 m², whereas two-thirds of patients with AHF had eGFR below 60 mL/min/1.73 m² at admission.

Eighty-five (43.4%) patients with AHF developed WRF during hospitalisation, which was more likely to occur in older patients, those with acute decompensated heart failure or chronic kidney disease, those who had a lower sodium level, those using renin-angiotensin system blockers and those on oral loop diuretics before admission. These patients also experienced more severe AHF, in which inotropes and intravenous vasodilators and furosemide were used more often than in patients without WRF.

Renal kinetics
Time of WRF occurrence
Among the 85 patients with WRF, the incidence of WRF decreased with the time of hospitalisation, with 80.0% developing within the first 48 hours and 92.9% occurring during 96 hours after admission. Of note, WRF was first diagnosed at presentation in 49.4% based on the baseline creatinine value (figure 1).

In relation to the severity of WRF, the majority of WRF cases were graded as KDIGO stage 1 (89.4%). KDIGO stage 2 and stage 3 were defined in 9.4% and 1.2% of cases, respectively. KDIGO stage 1 comprised 90.5% of
# Heart failure and cardiomyopathies

## Table 1 Baseline characteristics according to the presence of worsening renal function (WRF)

| Characteristics                        | WRF (n=85) | No WRF (n=111) | P value |
|----------------------------------------|------------|----------------|---------|
| Age                                    | 71.9±12.7  | 65.5±15.9      | 0.033   |
| Male sex                               | 36 (42.4%) | 43 (38.7%)     | 0.609   |
| Oedema                                 | 39 (45.9%) | 41 (36.9%)     | 0.207   |
| Hepatomegaly                           | 76 (89.4%) | 99 (89.2%)     | 0.960   |
| Hepatoujugular reflux sign             | 78 (91.8%) | 104 (93.7%)    | 0.603   |
| Bibasilar crackles                     | 60 (70.6%) | 72 (64.9%)     | 0.397   |
| NYHA                                    |            |                | <0.001  |
| III                                    | 24 (28.2%) | 64 (57.7%)     |         |
| IV                                     | 61 (71.8%) | 47 (42.3%)     |         |
| AHF haemodynamic phenotype             |            |                | 0.868   |
| Dry warm                               | 9 (10.6%)  | 7 (6.4%)       | 0.264   |
| Wet warm                               | 74 (87.1%) | 103 (93.6%)    |         |
| Dry cold                               | 0 (0%)     | 0 (0%)         |         |
| Wet cold                               | 2 (2.3%)   | 1 (1%)         |         |
| Congestion type                        |            |                | 0.038   |
| Vascular type                          | 8 (9.4%)   | 10 (9.0%)      |         |
| Cardiac type                           | 77 (90.6%) | 101 (91%)      |         |
| AHF clinical phenotype                 |            |                |         |
| De novo                                | 19 (22.4%) | 40 (36.0%)     |         |
| Acute decompensated                    | 66 (77.6%) | 71 (64.0%)     |         |
| Heart rate (beats/min)                 | 99.2±25.5  | 100.0±23.2     | 0.941   |
| SBP (mm Hg)                            | 134.9±34.1 | 135.1±31.6     | 0.686   |
| DBP (mm Hg)                            | 77.4±17.3  | 79.0±18.4      | 0.803   |
| Comorbidities                          |            |                |         |
| Hypertension                           | 74 (87.1%) | 88 (79.3%)     | 0.154   |
| Chronic heart failure                  | 66 (77.6%) | 71 (64.0%)     | 0.038   |
| Atrial fibrillation                    | 27 (31.8%) | 40 (36.0%)     | 0.532   |
| Diabetes                               | 32 (37.6%) | 26 (23.4%)     | 0.031   |
| Chronic kidney disease                 | 14 (16.5%) | 6 (5.4%)       | 0.011   |
| Baseline creatinine (mg/dL)            | 1.21       | 1.14           | 0.032   |
| Medications before admission           |            |                |         |
| ACE-i/ARB                              | 49 (57.6%) | 47 (42.3%)     | 0.034   |
| Loop diuretics                         | 26 (30.6%) | 14 (18.0%)     | 0.040   |
| NSAIDS/corticosteroids                 | 6 (7.0%)   | 5 (5.0%)       | 0.441   |
| Laboratory tests at admission          |            |                |         |
| Urea (mg/dL)                           | 53.9±25.3  | 39.7±15.1      | <0.001  |
| Creatinine (mg/dL)                     | 1.5±0.4    | 1.1±0.3        | <0.001  |
| eGFR (mL/min/1.73 m²)                  | 44.7±16.3  | 61.1±17.7      | <0.001  |
| eGFR-60 mL/min/1.73 m²                 | 73 (85.9%) | 58 (51.3%)     | <0.001  |
| Serum sodium (mmol/L)                  | 135.2±4.7  | 136.6±4.7      | <0.001  |
| Haemoglobin (g/L)                      | 117.0±21.4 | 121±21.5       | 0.220   |
| NT-proBNP (pg/mL)                      | 9673.90 (429.9 to 18917.9) | 7569.2 (1017.2 to 14121.2) | 0.349 |
| LVEF<40%                               | 51 (60.0%) | 65 (58.6%)     | 0.839   |

Management during hospitalisation

Continued
Table 1 Continued

| Characteristics                        | WRF (n=85) | No WRF (n=111) | P value |
|----------------------------------------|------------|----------------|---------|
| Intravenous furosemide                 | 65 (76.5%) | 82 (73.9%)     | 0.677   |
| Inotropes                              | 11 (12.9%) | 4 (3.6%)       | 0.015   |
| Intravenous vasodilators               | 49 (57.6%) | 16 (14.4%)     | <0.001  |
| Mechanical ventilation                 | 8 (9.4%)   | 4 (3.6%)       | 0.093   |
| Duration of hospitalisation (days)     | 13.3±7.3   | 9.3±4.7        | <0.001  |
| NT-proBNP decrease at discharge ≥30%  | 69 (81.2%) | 102 (91.9%)    | 0.026   |

ACE-i, ACE inhibitor; AHF, acute heart failure; ARB, angiotensin II receptor antagonist; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; LVEF, left ventricular ejection fraction; NSAIDS, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

WRF at admission, 80.8% of WRF at day 2 and all the WRF cases in the following days.

In the subgroup of WRF, the median relative increase in serum creatinine was 49.5%, with an absolute value of 0.6 mg/dL. The mean incremental changes in serum creatinine level when WRF developed at admission, day 2, day 4 and day 6 were 58.0%, 47.0%, 37.3% and 34.4%, respectively (Figure 2). There was no significant difference among the mean variations of serum creatinine by days during hospitalisation (p=0.522).

Renal recovery

At discharge, in the WRF group, renal recovery occurred in 65 patients (76.5%). Our data demonstrated that there was an inverse relationship between the day when WRF was first diagnosed and the likelihood of kidney function improvement. While 90.5% of patients with WRF occurring at admission had renal recovery, only 58.8% of patients developing WRF after day 4 had serum creatinine levels decrease to within 10% of their baseline values at discharge. In general, rapid reversal of WRF (within 48 hours) occurred in only 20% of patients, and there was no considerable difference regarding the rate of rapid reversal when WRF was confirmed at admission or in the following days (19.0% vs 20.9%, p=0.828). The rate of renal recovery within 96 hours since WRF was first diagnosed was 42.4% (Figure 3).

In comparison with the preserved ejection fraction subgroup, patients with AHF characterised by LVEF <40% had similar renal events and renal outcomes regarding the relative variation in serum creatinine during hospitalisation, the incidence of early WRF and renal recovery.

**DISCUSSION**

In this prospective study of AHF, we demonstrated that WRF was common and severe acute kidney dysfunction (KDIGO stage 2 and stage 3) was rare. While nearly half of the patients with WRF had developed it before

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**Figure 1** The time points of worsening renal function (WRF) occurrence in acute heart failure. Serum urea and creatinine were measured at admission and every 48 hours after that. WRF was defined as one of the following criteria: (1) increase in serum creatinine ≥ 0.3 mg/dL within 48 hours; or (2) increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days. If a patient did not have baseline serum creatinine, the lowest serum creatinine value during hospitalisation is assumed to be the baseline value.

**Figure 2** Relative increase in serum creatinine by day worsening renal function (WRF) occurring. % serum creatinine increase (%)=(serum creatinine at the day WRF was first diagnosed – baseline serum creatinine) x 100/ baseline serum creatinine.
Incidence of WRF

There are inconsistent definitions of WRF among clinical trials in relation to how serum creatinine was measured as well as the absolute changes (0.3–0.5 mg/dL) and relative variations. While the incidence of WRF was rather low in retrospective studies, they remained in the 30%–40% range in prospective investigations, in which serum creatinine was evaluated periodically during hospitalisation for AHF. In addition, in relation to nephrology criteria, if the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, Acute Kidney Injury Network (AKIN) or KDIGO classification were used to define WRF, its incidence could increase to nearly 45%. The high incidence of WRF (43.4%) in our study can be explained by the strategy of kidney function monitoring and the study design. While 20% of patients with WRF would recover within 48 hours and WRF could occur at both, the early and late stages, our study indicates that serial checks for renal dysfunction can unmask a considerable number of instances of WRF in patients with AHF.

Renal kinetics

The pathophysiological mechanisms underlying acute kidney dysfunction in AHF appear to be multifactorial. All conditions, including superimposed infection, inflammation, neurohormonal activation, medical treatment, pump failure and especially venous renal congestion, have been linked to the vicious cycle between the heart and the kidney. However, most changes in serum creatinine in AHF are mild. Investigating the incremental changes in serum creatinine, Smith et al. concluded that 75% of patients had serum creatinine increase by ≥0.1 mg/dL, and only 24% of patients had this incremental change ≥0.5 mg/dL. Logeart et al. showed that the mean increase in serum creatinine in WRF was 0.64±0.4 mg/dL. However, an absolute incremental variation in serum creatinine cannot represent the severity of WRF. Relative change has been used instead in recent studies. Classifying WRF according to the KDIGO criteria, Roy et al. highlighted that nearly 75% of cases of WRF in patients with AHF were stage 1. In addition to previous data, we discovered that the severity of WRF and the relative changes in serum creatinine were not significantly different among the days when WRF was first diagnosed. Our study also suggested that among patients with WRF, only 1.2% had an increase in serum creatinine to more than three times the baseline. These data can be translated in clinical practice to demonstrate the causes of acute kidney injury in AHF. In patients with AHF with an acute increase in serum creatinine by more than two or three times, physicians should be cautious in determining whether haemodynamic congestion has a causal effect on the worsening of kidney function as the acute deterioration of renal function in a majority of AHF cases is mild.

The more severe the haemodynamic congestion, the more likely the WRF to appear. The time to development of WRF is important because different pathophysiological pathways are reflected by different stages after the admission day on which WRF is first diagnosed. WRF occurring during the first few days of admission is mainly caused by renal hypoperfusion, neurohormonal activation and renal venous congestion. In the Prospective Outcomes Study in Heart Failure, the median time to WRF was 4 days, while the WRF rates at day 7 were 80% and 90% in studies by Forman et al. and Krumholz et al. respectively. Since these previous studies used serum creatinine levels at admission as baseline values, they could not represent haemodynamic changes in heart failure several days before heart failure-related events, as recognised by Zile et al. The study by Breidthardt et al. has been one of the few studies addressing this problem, in which 32% of patients with acute kidney injury were first diagnosed at presentation. In our study, as 91.8% of patients with AHF were classified as having a wet phenotype, we observed that nearly half of the patients with a significant increase in serum creatinine had WRF before admission, and 92.9% of these patients with WRF were diagnosed in the first 96 hours. The median time to WRF was 2 days. Moreover, it can be said that the wet presentation does not only have enough potential to cause WRF, but the severity of wet presentation (the severity of dyspnoea; OR 2.8, 95% CI 1.29 to 6.16, p=0.009) and baseline kidney function (OR 21.1, 95% CI 3.10 to 143.73, p=0.002) have cumulative impacts on the development of WRF. When WRF occurred in the first 2 day after admission, our study indicated that neither ACE-i/ARB treatment (OR 1.64, 95% CI 0.29 to 9.42, p=0.580) nor the cumulative dose of furosemide (OR 1.01, 95% CI 0.99 to 1.01, p=0.095) in the first 48 hours after admission contributed significantly to the deterioration of kidney function. In contrast to early WRF, later serum creatinine changes may be more likely to be related to iatrogenic factors such as ACE-i/ARB treatment, loop diuretics therapy and the interventional procedures. However, considering that our study had similar outcomes to the study of Breidthardt et al., we only found a few cases of WRF after day 4, and the
extent of serum creatinine changes was not significantly different between different points of time at which WRF was first diagnosed. The majority of patients with WRF in the later days were also in KDIGO stage 1. These data suggested that the severity of WRF in AHF cannot be used to distinguish whether haemodynamic changes or iatrogenic factors are the main cause, and AHF regimens may not seriously affect the occurrence of WRF compared with congestion.

Our study is the first to evaluate renal recovery according to a nephrology criterion. With a mean duration of hospitalisation of 13.5 days, approximately 75% of WRF cases recovered fully at discharge. Although 80.0% of WRF cases in our study were diagnosed in the first 2 days and early WRF in AHF is supposed to be caused by haemodynamic abnormalities, rapid renal reversal appeared in only 20% of patients. In particular, the rate of rapid reversal was not distinctive among different days when WRF appeared. In the Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE) trial, the rate of kidney function recovery reached 11% after 72 hours. However, early WRF has the characteristics of pseudoacute kidney injury because the rate of renal recovery was 1.5 times higher than the rate in the subgroup of patients with WRF occurring after day 4, a difference that was significant. These data suggested that: (1) early WRF in AHF is not merely due to haemodynamic changes (renal hyperfusion or venous congestion), and (2) the speed of renal recovery can be delayed by medical treatments or comorbidities.

Limitations
In addition to the fact that it was a single-centre study, the haemodynamic congestion in this study was not evaluated and followed up by pulmonary catheterisation; hence, we could not confirm the causes of late occurrence of WRF. We acknowledged that WRF implicates a poor prognosis in congestive AHF only in the case of diuretics resistance; however, data regarding cumulative urinary output or urine creatinine value to address this phenomenon were not available. Moreover, the number of patients in KDIGO stage 2 and 3 was rather small, so further analysis in this subgroup would be considered.

Conclusion
In this prospective study of AHF, when WRF was defined according to a specific nephrology criteria, we found that the incidence of acute kidney function deterioration was high. Although the majority of WRF had the typical features of pseudo-WRF which occurred daily during hospitalisation with a mild relative increase in serum creatinine, the rapid recovery rate was not as high as expected. Further studies should seek to demonstrate the differential mechanisms of WRF during days after AHF admission and the incidence of true-WRF.

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Contributors GMN designed the study, performed the analysis, interpreted the results and drafted the manuscript. HHN enrolled subjects, and drafted the manuscript. N-HC performed critical revision of the manuscript.

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Heart failure and cardiomyopathies

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