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Association of renal tubular damage with cardio-renal anemia syndrome in patients with heart failure

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ABSTRACT

Background: Cardio-renal anemia syndrome (CRAS) has begun to gather attention as a vicious circle since chronic heart failure (CHF), chronic kidney disease (CKD), and anemia are all able to be caused and exacerbated by each other. However, it remains unclear whether renal tubular damage (RTD), another type of kidney dysfunction, is associated with this vicious circle. The aim of the present study was to assess the association of RTD with CRAS in patients with CHF.

Methods and results: We included 300 consecutive patients with CHF. RTD was defined as a urinary β_2-microglobulin to creatinine ratio ≥300 μg/g. Patients with RTD had lower serum iron and higher levels of high sensitivity C-reactive protein than those without it. Multivariate logistic analysis showed that RTD was closely associated with anemia in patients with CHF, after adjustment for confounding factors. During a median period of 1098 days, there were 86 cardiac events, including 14 cardiac deaths and 72 re-hospitalizations for worsening heart failure. Net reclassification improvement was significantly improved by addition of RTD to the model including age, New York Heart Association functional class, brain natriuretic peptide, anemia, and CKD. All patients were divided into 3 groups: CRAS + RTD group, CRAS group, and control group. Kaplan–Meier analysis demonstrated that CRAS + RTD had the greatest risk in patients with CHF.

Conclusions: RTD was associated with normocytic anemia, accompanying iron deficiency and inflammation. RTD added prognostic information to conventional CRAS, suggesting the importance of RTD in cardio-renal anemia interaction.

1. Introduction

Heart failure remains a major and increasing public health problem with a high mortality [1]. Recent reports indicate that cardio-renal anemia syndrome (CRAS) is closely associated with extremely poor outcomes in patients with chronic heart failure (CHF) since CHF, chronic kidney disease (CKD), and anemia are all able to be caused and exacerbated by each other [2–6]. Previous reports show that CKD is an important factor in the development of the cardio-renal anemia interaction. Recently, we reported that, as with CKD, renal tubular damage (RTD), another type of kidney dysfunction, is also a risk factor for cardiovascular disease [7,8].

Renal tubule cells have diverse regulatory and endocrine functions and the renal tubules play a pivotal role in modulating acid base balance, active vitamin D synthesis, and reabsorption of sodium, water and bicarbonate [9]. Erythropoietin, a primary regulatory hormone in the hematopoietic system, is synthesized in renal tubule cells [10]. RTD induced by cadmium intoxication was reported to be closely associated with the development of anemia through erythropoietin suppression [11]. Although CKD is reportedly associated with anemia, primarily due to decreased erythropoietin production [12], there is currently no clinical evidence for an association of RTD with anemia.

Anemia is a well-known risk factor for cardiovascular mortality [13,14]. Several factors, such as chronic inflammation and iron status, are responsible for the development of anemia in patients with CHF [15,16]. Iron status is noted in cardio-renal anemia interaction since serum iron is an important material of haem, an oxygen-carrying component of hemoglobin [17–19]. However, the relationship between kidney function and iron status in patients with CHF is not clear.

The aim of the present study was to examine 1) whether RTD is associated with normocytic anemia in patients with CHF; and 2) whether RTD can add prognostic information to conventional CRAS in patients with CHF.

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2. Methods

2.1. Study subjects

This was a prospective study of 300 consecutive patients who were admitted to our hospital for the diagnosis or treatment of CHF. The diagnosis of CHF was made by two cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, with signs of pulmonary congestion or peripheral edema, and radiological or echocardiographic evidence of left ventricular enlargement or dysfunction [20].

Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data. The diagnoses of hypertension, diabetes mellitus, and hyperlipidemia were established on the basis of the patient's medical records or history of current or previous medical therapy. Fifteen patients were excluded due to microcytic or macrocytic anemia and twenty two patients were excluded due to acute coronary syndrome within three months preceding admission, hemodialysis, active hepatic disease, pulmonary disease, or malignant disease.

Demographic and clinical data including age, gender, and New York Heart Association (NYHA) functional class were collected from patient's medical records and patient interviews. Medications at discharge were recorded from the hospital medical records.

2.2. Biochemical markers

Urine and venous blood samples were obtained in the early morning within 24 h after admission. Urinary β_2-microglobulin concentrations were determined by the latex agglutination method (BML, Inc., Tokyo, Japan). We quantitatively measured urinary albumin by immunoturbidimetry in a single spot urine specimen collected in the early morning. β_2-Microglobulin levels and urinary albumin levels were corrected for urinary β_2-microglobulin to creatinine ratio (UBCR), and urinary albumin to creatinine ratio (UACR). N-acetyl-β-D-glucosamidase (NAG) levels, a marker of early RTD, were measured in single spot urine specimens. Since UBCR, UACR and NAG were not normally distributed, we utilized $\log_{10}$ UBCR, $\log_{10}$ UACR and $\log_{10}$ NAG for all analyses. We detected urinary protein with albumin-specific dipsticks at the same time. We defined proteinuria as a positive dipstick test (1+ or more). The estimated glomerular filtration rate (GFR) was calculated by using the modification of diet in renal disease's equation with the Japanese coefficient, as previously reported [21].

2.3. Definition of RTD, CKD, anemia, and CRAS

RTD was defined as a UBCR ≥ 300 μg/g ($\log_{10}$ UBCR ≥ 2.47 μg/g), as previously reported [22]. Chronic kidney disease (CKD) was defined as a reduced eGFR (<60 mL/min/1.73 m^2), or the presence of proteinuria according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical guidelines [23,24]. Anemia was defined as hemoglobin <13 g/dL in males and <12 g/dL in females according to the World Health Organization (WHO) guidelines. CRAS was defined as patients with anemia and CKD.

2.4. Endpoints and follow-up

Patients were prospectively followed for a median period of 1098 days (range 789 to 1244) by telephone or by using medical records twice a year. There were 14 patients who were not followed due to non-cardiac death. The end points were cardiac death, defined as death due to progressive heart failure, sudden cardiac death, acute myocardial infarction and progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was confirmed by the attending physician.

The study was approved by the institutional ethics committee and all patients gave written informed consent.

2.5. Statistical analysis

All values are expressed as means ± SD, or medians. The *t*-test and chi-square test were used for comparison of continuous and categorical variables, respectively. Comparisons between kidney markers and hemoglobin were analyzed by single linear regression analysis. Differences among groups were analyzed by analysis of variance (ANOVA) with the Scheffe post hoc test. The logistic analysis was performed to identify the risk factor for anemia. The Cox proportional hazard analysis was performed to identify the independent predictors for cardiac events. Predictors that were significant by univariate analysis were entered into the multivariate analysis. The receiver operating characteristic (ROC) curves for all cardiac events were constructed and used as a measure of the predictive accuracy of RTD on all cardiac events. In addition, we calculated the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) to measure the quality of improvement for the correct reclassification according to the addition of RTD to the model. Cardiac event-free curves were constructed according to the Kaplan–

Table 1
Comparisons of clinical characteristics between patients with and without anemia.

Variables	All patients n = 300	Anemia (−) n = 150	Anemia (+) n = 150	P value
Age (years)	72 ± 11	68 ± 12	76 ± 9	<0.0001
Men/women	171/129	88/62	83/67	0.5598
NYHA functional class (I/II/III/IV)	77/108/79/36	50/49/36/15	27/59/43/21	0.0242
Hypertension	188 (63%)	89 (59%)	99 (66%)	0.2326
Diabetes mellitus	90 (30%)	39 (26%)	51 (34%)	0.1306
Hyperlipidemia	91 (30%)	48 (32%)	43 (29%)	0.5300
Etiology				0.0980
Ischemic heart disease	68 (23%)	28 (19%)	40 (27%)	
Non-ischemic heart disease	232 (77%)	122 (81%)	110 (73%)	
Blood examination				
eGFR (mL/min/1.73 m^2)	63 ± 26	69 ± 20	57 ± 30	0.0003
BNP (pg/mL)	357 (129–882)	276 (102–702)	466 (166–1023)	0.0048
Urinalysis				
$\log_{10}$ UBCR (μg/g)	2.25 ± 0.95	1.95 ± 0.77	2.55 ± 1.03	<0.0001
$\log_{10}$ UACR (mg/g)	1.50 ± 0.65	1.30 ± 0.57	1.70 ± 0.68	<0.0001
Proteinuria (%)	57 (19%)	17 (11%)	40 (27%)	0.0007
$\log_{10}$ NAG (U/g)	1.04 ± 0.32	0.94 ± 0.31	1.15 ± 0.28	<0.0001
CKD (%)	162 (54%)	59 (39%)	103 (69%)	<0.0001
RTD (%)	114 (38%)	30 (20%)	84 (56%)	<0.0001
Echocardiography				
LVEDD (mm)	55 ± 10	56 ± 10	55 ± 9	0.5502
LVEF (%)	49 ± 17	49 ± 17	48 ± 17	0.8807
E wave (m/s)	0.87 ± 0.37	0.81 ± 0.35	0.93 ± 0.39	0.0221
E/e′ ratio	16 ± 9	14 ± 8	17 ± 9	0.0147
Medicine				
ACEIs or ARBs	230 (77%)	117 (78%)	113 (75%)	0.5851
β-Blockers	196 (65%)	95 (63%)	101 (67%)	0.4667
Aldosterone blockers	95 (32%)	43 (29%)	52 (35%)	0.2640
Loop diuretics	196 (65%)	85 (57%)	111 (74%)	0.0016
Statins	105 (35%)	54 (36%)	51 (34%)	0.7165

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
NYHA, New York Heart Association; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; Hb, hemoglobin; UBCR, urinary β_2-microglobulin–creatinine ratio; UACR, urinary microalbumin–creatinine ratio; NAG, N-acetyl-beta-D-glucosamidase; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; E, mitral inflow E wave; E/E′, the ratio of the mitral inflow E wave to the tissue Doppler e′ wave; CKD, chronic kidney disease; RTD, renal tubular damage; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.