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Original Contribution

Renal impairment and outcome in patients with takotsubo cardiomyopathy

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ABSTRACT

Objectives: The objectives were to ascertain the prevalence of renal impairment among patients with a takotsubo cardiomyopathy (TTC) episode and whether clinical outcomes are related to renal function.
Methods: A total of 108 consecutive subjects with TTC were enrolled in a multicenter registry and followed for a mean period of 429 days. Renal function was evaluated during hospitalization in terms of acute kidney injury/failure and estimated glomerular filtration rate (eGFR). Incidence of death, rehospitalization, and recurrence of TTC during follow-up was recorded.
Results: Raised creatinine levels can be found during hospitalizations for TTC episodes (analysis of variance $P < .001$). Incidence of acute kidney injury was 10%; that of acute kidney failure was 1%. Admission eGFR levels were proportional to the duration of hospitalization ($r = -0.28$, $P < .01$). Estimated GFR nadir values were related to adverse events at follow-up (log-rank $P < .001$). The hazard ratio of adverse events at follow-up in subjects with severe renal impairment (nadir eGFR < 30 mL/[min 1.73 m^2]) vs those with eGFR > 60 mL/(min 1.73 m^2) was 1.817 (95% confidence interval, 1.097-3.009; $P < .05$).
Conclusions: Raised creatinine levels and impaired renal function may be found in patients with TTC. Lower eGFR values during hospitalization are associated with longer hospitalizations and higher rates of adverse events at follow-up. Renal function during a TTC episode should be carefully evaluated.

1. Introduction

Renal function has been found to be an independent risk factor for cardiovascular (CV) outcome in patients with heart failure (HF) with either preserved or reduced ejection fraction [1]. About 63% of patients with HF have renal impairment [2]. Furthermore, worsening of renal function is common among hospitalized HF patients and is significantly related with higher mortality rates [3].

Takotsubo cardiomyopathy (TTC) is an acute and reversible form of HF [4] that can mimic acute myocardial infarction. Several algorithms based on the use of electrocardiogram and/or biomarkers have been proposed for the diagnostic workup of TTC [5,6], but no studies have evaluated renal function and its prognostic role among patients admitted for TTC.

The aim of the study was therefore to evaluate renal function and its potential prognostic role in this context.

2. Methods

2.1 Study population

We prospectively evaluated 108 consecutive patients with a diagnosis of TTC from July 2007 to May 2014 enrolled in a multicenter registry covering 3 hospitals, an Italian area of one and half million inhabitants (University Hospital of Foggia; "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo; and "San Paolo" Hospital, Bari, Italy).

2.2 Inclusion criteria

The diagnosis of TTC was based on Mayo Clinic criteria:(*a*) transient hypokinesis, akinesis, or dyskinesis of the left ventricular (LV) mid segments, with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present; (b) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (c) new electrocardiographic abnormalities, ST-segment elevation and/or T-wave inversion, or modest elevation in cardiac troponin; and (d) absence of pheochromocytoma and myocarditis [7].

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2.3 Clinical and echocardiographic examination

All patients underwent a clinical examination, and age, sex, medical history, kind of stressors, and electrocardiographic presentation were recorded. A 2-dimensional Doppler echocardiographic examination on the day of admission, at the third day, and at discharge was performed. The LV ejection fraction (LVEF) was calculated using the Simpson method from the apical 4-chamber and 2-chamber view [8].

2.4 Blood sample collection

Circulating levels of troponin I, blood urea nitrogen (BUN), and creatinine were obtained by venipuncture at the admission; at the second, third, and fourth day during hospitalization; and at discharge.

Normal values were as follows: <0.5 ng/mL for cardiac troponin-I, 10-50 mg/dL for BUN, and 0.61-1.24 mg/dL for creatinine.

2.5 Renal function evaluation

Degree of renal impairment was classified according to the Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure criteria [9]. *Acute kidney injury* (AKI) is defined as creatinine levels 2 times higher than the admission value or estimated glomerular filtration rate (eGFR) decrease >50%; *acute renal failure* is defined as creatinine levels are 3 times higher than the admission value or eGFR decrease >75%.

Estimated glomerular filtration rate was calculated through the use of the 4-component Modification of Diet in Renal Disease study equation incorporating age, race, sex, and serum creatinine level: eGFR $= 186 \times$ (serum creatinine level [in mg/dL]$^{-1.154}$) $\times$ (age [in years]$^{-0.203}$). For women and blacks, the product of this equation was multiplied by a correction factor of 0.742 and 1.21, respectively [10]. According with the Kidney Disease Outcomes Quality Initiative classification of the stages of chronic kidney disease [11], patients were divided into 3 groups following an evaluation of the eGFR (group 1: "normal-mild renal impairment," eGFR >60 mL/[min 1.73 m^2]; group 2: "moderate renal impairment," eGFR from 60 to 30 mL/[min 1.73 m^2]; group 3: "severe renal impairment," eGFR <30 mL/[min 1.73 m^2]).

Estimated GFR nadir was defined as the lowest value of eGFR observed during hospitalization.

2.6 Follow-up and definition of outcome

Complete follow-up data were available in all 108 patients with a follow-up of at least 3 months from the time of study inclusion. Patients were scheduled for clinical and echocardiographic examinations at the cardiomyopathy ambulatory of the cardiology department (3 months after TTC episode and every 9 months).

Clinical end points included total mortality, CV mortality (sudden and nonsudden CV death), TTC recurrence, and hospitalization for any CV cause. These clinical end points were recorded and evaluated as adverse events at follow-up.

All patients gave a written informed consent; the study was approved by local ethical committees.

2.7 Statistical analysis

Continuous variables were reported as means ± standard deviation and compared with Student *t* test for either paired or unpaired groups as required; dichotomic variables were reported as percentage and compared with χ^2 test of Fisher test as required. Normal distribution of variables was tested with Kolmogorov-Smirnov and Lilliefors test; correlations were therefore analyzed with Pearson or Spearman test as required.

Repeated measures were analyzed with analysis of variance test (ANOVA).

Survival rate was reported on Kaplan-Meier plot and analyzed with log-rank test and multiple stepwise Cox analysis, which was used for calculation of hazard ratio with 95% confidence intervals (CIs). Receiver operating characteristic curves were reported and compared with Hanley and McNeil method.

A *P* value <.05 was considered as statistically significant.

3. Results

3.1 Baseline features

One hundred and eight consecutive subjects with TTC were enrolled in the study and followed up for a mean period of 429 ± 601 days. Mean population age was 72.7 ± 10.5 years, 7% were male (n = 8), 78% had hypertension, 41% had dyslipidemia, 24% were obese, 14% were smokers, and 27% were diabetic. Mean hospital stay was 8 ± 3.5 days. Twenty-eight percent had an emotional stressor; 43%, physical; and 29%, no reported stressor. Clinical presentation of TTC episodes was typical angina in 52% of patients, atypical chest pain in 17%, and no chest pain in 28% (Table 1).

During follow-up period, 18% incurred adverse events (9% death, 5% TTC recurrence, 4% rehospitalization). Creatinine levels significantly rose up during hospitalization as shown in Fig. 1 (ANOVA $P < .001$). Peak creatinine levels during hospitalization were significantly higher than those on admission (1.42 ± 1.13 vs 1.05 ± 0.78 mg/dL, $P < .001$).

3.2 Acute renal impairment

Incidence of AKI as described above was 10% (11 patients); that of acute kidney failure as described above was 1% (1 patient). Subjects who developed AKI were significantly different from those without as for diabetes (43% vs 23%, $P < .05$) and LVEF at admission (30% ± 7% vs 37% ± 9%, $P < .05$).

Furthermore, subject who developed AKI had a longer hospitalization (10 ± 3.3 days vs 7.8 ± 3.4 days, $P < .05$) and required inotropes infusion; in all cases, patients received levosimendan infusion [12] (45% vs 14%, $P < .05$).

3.3 eGFR, hospitalization, and follow-up

The duration of hospitalization was proportional to eGFR values at admission ($r = -0.28$, $P < .01$, Fig. 2).

Table 1
Baseline and hospitalization features of patients admitted with a diagnosis of TTC

No. of pts. = 108	Mean
Age	72.7 ± 10.5
Male	7%
Hypertension	78%
Dyslipidemia	41%
Obesity	24%
Smoker	14%
Diabetes	27%
Pneumologic disease	23%
Hospitalization days	8.06 ± 3.49
No chest pain	28%
Typical chest pain	52%
Atypical chest pain	17%
Dyspnea	32%
Emotional stressor	28%
Physical stressor	43%
No stressor	29%
EF at admission	36% ± 9%
EF at discharge	50% ± 7%
Troponin I levels at admission	4.48 ± 11.10 ng/mL
Troponin I levels at discharge	0.33 ± 0.67 ng/mL
BUN levels at admission	53.50 ± 28.67 mg/dL
BUN levels at discharge	76.49 ± 37.47 mg/dL
Creatinine levels at admission	1.05 ± 0.79 mg/dL
Creatinine levels at discharge	1.23 ± 0.62 mg/dL
Creatinine peak during hospitalization	1.42 ± 1.13 mg/dL
eGFR at admission	74.16 ± 33.64 mL/(min 1.73 m^2)
eGFR nadir	56.19 ± 29.15 mL/(min 1.73 m^2)