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Inflammatory patterns in Takotsubo cardiomyopathy and acute coronary syndrome: A propensity score matched analysis

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ABSTRACT

Background and aims: Systemic inflammatory activation can be observed in both Takotsubo cardiomyopathy (TTC) and acute coronary syndrome (ACS). The aim of this study was therefore to compare circulating cytokine levels during the acute and subacute phase of TTC and ACS.
Methods: One hundred thirty-six consecutive patients were enrolled in the study; after a propensity score matching, 32 TTC patients were compared with 32 subjects with ACS. Clinical baseline features and circulating levels of interleukin(IL)-1β, IL-1α, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, MCP1, EGF, VEGF, TNFα were obtained at admission (t_0) and after 120 h (t_1).
Results: At t_0, several circulating IL levels were higher in subjects with TTC (IL-2 2 *vs.* 0.5 pg/ml, IL-4 1.5 *vs.* 0.82 pg/ml, IL-10 3.34 *vs.* 1.62 pg/ml, TNF-α 5 *vs.* 2.3 pg/ml, IFN-γ 0.92 *vs.* 0.32 pg/ml, EGF 84.8 *vs.* 10.7 pg/ml, $p < 0.05$ in all cases), while IL-6 levels were higher in patients with ACS (25.4 *vs.* 12.4 pg/ml $p = 0.03$).
At t_1, IL-2 and EGF levels were still higher in patients with TTC *vs.* those with ACS (IL-2 4.6 *vs.* 0.72 pg/ml, $p = 0.01$; EGF 36.3 *vs.* 18.5 pg/ml, $p = 0.03$), while IL-6 serum levels were higher in ACS patients (19.6 *vs.* 7.35 pg/ml, $p = 0.02$).
Conclusions: Different inflammatory patterns can be observed during the acute and subacute phase of TTC when compared to ACS. Increased levels of anti-inflammatory interleukins can be found during the acute phase of TTC while ACS is featured by higher levels of IL-6 during the acute and sub-acute phase.

1. Introduction

Takotsubo cardiomyopathy (TTC) is an acute heart failure syndrome, featured by transient and reversible left ventricular dysfunction [1]. The mechanism leading to transient systolic dysfunction characteristic of TTC is still unclear; increased serum levels of catecholamines may be one of the drivers [2].

Clinical presentation of TTC, including symptoms, electrographic presentation and serum biomarkers, may resemble acute coronary syndrome (ACS); an invasive assessment with coronary angiography is therefore important for the diagnosis and therapeutic management.

Systemic inflammation has been extensively evaluated in ACS [3,4,5] and could represent a novel target for treatment in patients with stable coronary atherosclerosis [6]. However, there are limited data on inflammatory activation in TTC, Pirzer et al. evaluated only serum levels of interleukin 6 and 7 between TTC and ACS patient [7], while Santoro et al. evaluated serum levels of interleukin 6 and 10 only in TTC patients [8]. Moreover, in an animal model of TTC, mononuclear cell infiltration has been found during the acute phase [9] and cardiac magnetic resonance studies in patients with TTC showed during hospitalization evidence of transient myocardial edema consistent with acute inflammation [10].

Aim of the study was therefore to evaluate differences between

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inflammatory patterns in TTC and ACS and potential insight into the pathophysiology of TTC. We thus compared circulating levels of inflammatory (interleukin(IL)-1β, IL-1α, IL-6, Interferon (IFN)-γ, Tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF)) and anti-inflammatory (IL-2, IL-4, IL-10) cytokines, chemoattract component (endothelial growth factor (EGF)) and chemokines (IL-8, monocyte chemoattractant protein-1 (MCP1)) during the acute and subacute phase of TTC in comparison to ACS.

2. Materials and methods

2.1. Study population

Seventy-five consecutive patients with TTC and 61 with ACS were prospectively enrolled in the study at the Department of Cardiology, Ospedali Riuniti University Hospital, Foggia, from January 2012 to December 2015. A propensity scoring method was used to identify 32 matched couples of TTC and ACS, comparable for principal risk factors.

The diagnosis of TTC was based on Mayo Clinic criteria: a) transient hypokinesis, akinesis, or dyskinesis of the LV mid segments, with or without apical involvement; b) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; c) new electrocardiographic abnormalities, either ST-segment elevation and/or T-wave inversion, or modest elevation in cardiac troponin; d) absence of pheochromocytoma and myocarditis [11]. The diagnosis of ACS was based on the third universal definition of myocardial infarction [12].

2.2. Exclusion criteria

Patients with chronic inflammatory (systemic lupus erythematosus, rheumatoid arthritis, and Crohn's disease) or neoplastic disease, recent infectious disease, fever, immunosuppressive drug therapy (steroids, cyclosporine, or methotrexate), or immunologic disorder were excluded from the study.

2.3. Clinical examination

All patients underwent clinical examination; age, gender, medical history and kind of stressors were recorded.

2.4. Echocardiograph examination

A two-dimensional Doppler echocardiographic examination, on the day of admission and at discharge was performed. The left ventricular ejection fraction (LVEF) was calculated using the Simpson's method from the apical four-chamber and two-chamber view.

2.5. Coronary angiography

All patients underwent coronary angiography at admission.

2.6. Blood sample collection and laboratory

Circulating levels of NT-proBNP, troponin-I, IL-1β, IL-1α, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, MCP1, EGF, VEGF, TNFα were evaluated by venipuncture at admission (t0) and after 120 h (t1), on the base of prior data already evaluating the earlier phase of ACS [13]. NT-proBNP levels were measured by an enzyme immunoassay (Biozol). The upper limit of normal for apparently healthy persons (95th percentile) is 125 pg/ml for NT-proBNP in these assays. Troponin I plasmatic concentrations were evaluated using a particle-enhanced turbidimetric immuno-assay (PETIA). Normal values, provided by furnisher (Immulite, Siemens, Deerfield, IL, USA) were <0.5 ng/ml. Blood samples for cytokines analysis were immediately centrifuged and serum separated after coagulum retraction by centrifugation at 2000 rpm for 10 min; it was then frozen at −20 °C until laboratory assay. All cytokines were standardized by inclusion of a titration of the appropriate purified recombinant cytokines of known concentration. The analytes of interest were quantified with a biochip array analyzer. Normal values, provided as range values by furnisher (Immulite, Siemens, Deerfield, IL, USA) were: Il-1β 0.5–1.6 pg/ml, IL-1α 0.8–1.45 pg/ml, IL-2 4.8–8.7 U/ml, IL-4 0.5–6.6 pg/ml, IL-6 1.20–1.95 pg/ml, IL-8 7-9-14.38 pg/ml, IL-10 0.1–1.8 pg/ml, IFN-γ 0.5–0.34 pg/ml, MCP1 68.83–500 pg/ml, EGF 2.9–271 pg/ml, VEGF 14.6–372.5 pg/ml, TNF-α 0.5–4.98 pg/ml.

2.7. Ethics statement

All patients gave a written informed consent. The study was conducted according to the Declaration of Helsinki and the study protocol was approved by the local ethics review board.

2.8. Statistical analysis

Continuous variables were reported as means ± standard deviation and compared with Student's *t*-test for either paired or unpaired groups as required, dichotomic variables as percentage and compared with χ^2 test of Fisher test as required. Seventy-five consecutive patients with TTC and 61 with ACS were enrolled in the study. A propensity scoring method was used to identify an ACS cohort, matched on the basis of age, gender, admission ejection fraction and cardiovascular risk factors [14]. A p value < 0.05 was considered as statistically significant.

3. Results

3.1. Baseline features

Patients with TTC did not differ from those with ACS in term of age (73 ± 11 *vs.* 74 ± 12 $p = 0.55$), sex (male 9% *vs.* 15% $p = 0.45$), ECG presentation at admission (ST elevation 44% *vs.* 56% $p = 0.45$), cardiovascular risk factors and admission left ventricular ejection fraction (37% *vs.* 37% $p = 0.71$); however, admission troponin serum levels were higher in patients with ACS (3.3 ± 4 vs 34 ± 37 ng/ml $p = 0.01$) (Table 1).

Table 1
Baseline features of study cohort.

	TTC	N = 32	ACS	N = 32	
	Mean	Std.dev.	Mean	Std.dev.	*p*
Age, years	73	±11	74	±12	0.55
Male sex	9%		15%		0.45
Hypertension	84%		81%		0.74
Diabetes	38%		34%		0.79
Angina pectoris	47%		66%		0.13
Atypical chest pain	16%		22%		0.52
No chest pain	31%		13%		0.07
Admission LVEF%	37%	±9	37%	±10	0.71
Discharge LVEF%	49%	±6	40%	±9	**0.01**
NTproBNP adm. pg/ml	10692	±11227	13300	±21173	0.54
cTnI admission ng/ml	3.21	4.4	34.4	37	**0.01**

ACS = acute coronary syndrome, TTC = Takotsubo cardiomyopathy, LVEF = left ventricular ejection fraction, cTnI = cardiac troponin I.