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Takotsubo cardiomyopathy and neurogenic stunned myocardium: similar albeit different

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We demonstrate that in patients with stress cardiomyopathy the type of triggering event is associated with different clinical, instrumental, and laboratory features that characterize the phenotype at presentation.

Keywords Takotsubo cardiomyopathy • Neurogenic stunning • Aneurysmal-subarachnoid haemorrhage • Acute coronary syndromes • Cathecolamines

Introduction

Brain–heart connections were known since the description of the Cushing's reflex at the beginning of the 20th century. In 1950s, studies reported electrocardiographic (ECG) abnormalities mimicking acute coronary syndromes in patients with aneurysmal-subarachnoid haemorrhage (a-SAH).[1] More recently, a transient, regional, and fully reversible form of acute left ventricular (LV) dysfunction not mimicking a coronary pattern, commonly named neurogenic stunning (NS), has been described in a-SAH patients.[2] This clinical presentation resembles closely that of takotsubo (stress) cardiomyopathy (TC).[3]

Although NS is often thought to be part of TC,[3] there is some evidence that the clinical presentation, ECG changes and LV wall motion abnormalities might be different.[4]

Aim of the present study was to analyse and compare the clinical, instrumental, and laboratory features of 36 consecutive cases of NS ($n = 14$) or TC ($n = 22$) admitted to our hospital over 36 months (*Table 1*).

Methods and statistical analysis

Twenty-two of 36 patients had a diagnosis of TC, according to the revised Mayo Clinic criteria and underwent angiography that demonstrated the absence of obstructive coronary artery disease.[5] All patients with a-SAH were screened for the presence of LV wall motion abnormalities by echocardiography, and ECG and serum levels of cardiac Troponin T (TnT) were obtained. A diagnosis of NS was made in 14 patients with transient RMWA, acute ischaemic ECG changes (non-ST elevation) and low levels of cardiac TnT. Given the clinical instability of these critically ill patients, coronary angiography could not be done routinely in the acute phase.

Data are shown as mean $\pm$ standard deviation. Between-groups comparisons were carried out using two-sided paired or unpaired *t* test, as appropriate, χ^2 and Fisher exact test for categorical variables and linear regression analysis when needed. A *P*-value of <0.05 was considered statistically significant.

Results

All patients were Caucasians and all NS patients suffered from a severe a-SAH according to Hunt & Hess for clinical neurological impairment[6] and Fisher's for the amount of subarachnoid blood.[7] There was a significant age difference between the two groups and in both groups females had a significantly higher prevalence. Cardiovascular risk factors were similar in the two groups, although 35% of TC patients had a previous history of coronary artery disease (*Table 1*).

All TC patients presented with chest pain while all NS patients had signs of heart failure along with the neurological damage. The vast majority of TC, but none of NS patients, presented with ST segment elevation whilst T wave inversion was present in the majority

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Table 1 Demographic, cardiovascular risk factors, instrumental, and laboratory features

	TC (*N* = 22)	Neurogenic stunning (*N* = 14)	*P*-value
Age, mean ± SD	61.8 ± 12.3	53.0 ± 13.6	0.001
Female sex, *N* (%)	19 (86.4)	10 (71.4)	0.26
Hypertension, *N* (%)	14 (63.6)	8 (57.1)	0.57
Smoke, *N* (%)	3 (13.6)	6 (42.8)	0.06
Previous CAD, *N* (%)	7 (31.8)	0 (0)	0.01
ECG ST segment elevation	13 (59)	0 (0)	0.0002
ECG T wave inversion	6 (27.3)	9 (64.3)	0.04
TnT peak (normal <0.036 μg/l)	1.05 ± 2.05	0.40 ± 0.72	0.22
Index LV EF%	34.7 ± 10.8	45.4 ± 12.0	0.009
Apical type	17 (77%)	3 (21%)	0.007
Mid-ventricular and/or basal type	10 (45%)	13 (93%)	0.005
LVEF, at discharge	52.2 ± 7.6	56.9 ± 14.6	0.21
Clinical presentation, chest pain	22 (100)	0 (0)	–[a]
Clinical presentation, heart failure	0 (0)	14 (100)	–[a]

[a]Not applicable.

of NS patients. Left ventricular function was more severely impaired in TC compared with NS patients, although both groups showed a comparable improvement at discharge. With regard to the segmental distribution of LV wall motion abnormalities, the majority of TC patients (77%) had apical dysfunction. However, in 45% of TC cases, the dysfunction extended to or involved solely the mid and/or basal LV segments. Conversely, 93% of NS patients had basal and mid-ventricular dysfunction. Of note, in 21% of NS patients the dysfunction was extended to or involved solely the apical segments (*Table 1*). Although peak TnT levels were significantly elevated in both groups, regression analysis did not show a significant correlation between LV function impairment and TnT. Takotsubo cardiomyopathy patients had an average improvement in ejection fraction at discharge of 17.8 ± 12.07% ($P < 0.001$) and NS patients of 17.08 ± 15.79% ($P = 0.002$). One NS patient showed progressive impairment of LV function due to a severe septic complication.

Discussion

The present study provides novel data highlighting clinical and instrumental differences between patients with TC and those with NS obtained in a series of consecutive Caucasian patients admitted and treated at a single centre.

In brief, TC patients were older and presented with chest pain at variance with NS patients who had predominantly signs of heart failure associated with their neurological condition. The higher female prevalence in NS patients could be explained by the higher incidence of a-SAH known to occur in this gender. It is also worth noting that all NS patients were poor grade a-SAH, which is in line with the observation that the presence of cardiac complications is directly related with worse neurological outcomes.[8]

Important differences in clinical presentation were found between the two conditions. These are probably due to the different precipitating event: most TC patients mimicked an acute coronary syndrome while NS patients presented with signs of acute heart failure or had evidence of RMWA at echocardiography. This latter apparent discrepancy may be explained, at least in part, by the inability of most neurological patients to verbally report symptoms, because of sedation and/or the sequelae of a-SAH. In addition, a potential selection bias could derive from the fact that our hospital is a tertiary referral centre.

Over 60% of TC patients presented with ST segment elevation compared with none in NS that in the majority of cases presented with diffuse, deep negative T waves. These distinct ECG patterns are known to reflect different degrees of myocardial ischaemia: transmural in the case of ST elevation and predominantly subendocardial in the case of T wave inversion. The ECG changes associated with acute intracranial injuries are thought to result from sympathetically mediated intra-myocardial electrolyte disturbances. In turn, these may lead to myocardial cell calcium overload and enhanced cellular efflux of potassium ions and subsequent catecholamine-induced contraction band necrosis.[9]

Most TC patients presented with the typical apical ballooning due to mid-ventricular and apical a/dyskinesia with hyper contractile basal segments whilst NS patients showed hypo/akinesia affecting predominantly the basal and mid-ventricular segments. However, at variance with previous studies,[3] the degree of LV dysfunction in our series was more severe in TC than in NS.

No correlation between peak TnT and LVEF was observed, suggesting that the severity of LV dysfunction cannot be explained by extensive myocardial necrosis. This is also supported by the subsequent significant recovery of global LV function observed.

Catecholamines play a fundamental role in the pathogenesis of TC and NS. Experimental work in a canine model has demonstrated that elevated levels of plasma catecholamine immediately after SAH correlated with the severity of myocardial dysfunction and damage.[10] Similarly, a recent experimental study in a murine model of TC has demonstrated that infusion of high concentrations of epinephrine produced the characteristic reversible apical

dysfunction coupled with basal hyper-contractility while very high levels of circulating norepinephrine have no effects on myocardial contraction.[11] Plasma levels of epinephrine and norepinephrine are also higher in patients with a-SAH and evidence of transient LV dysfunction than in those without.[12] The deleterious effect of such brain–heart interactions may contribute to explain the observation that the outcome of patients with a-SAH can be predicted by measuring the levels of circulating norepinephrine.[13]

Regional differences in adrenergic receptors in the LV could contribute to explain the pattern of ventricular dysfunction: in canine LV, β_2 receptors are much more frequently expressed in apical than in basal segments while a reverse distribution is present for norepinephrine receptors and sympathetic nerve terminals of neuro-cardiac axis which are much more expressed at the base than at the apex of the LV.[11,14] Based on this evidence, we speculate that transient LV dysfunction, in both TC and NS, is a consequence of the same catecholamine-mediated myocardial damage, but with a different pattern of receptor activation: a prevalent mechanism of systemic release of epinephrine induces apical dysfunction in TC, whereas a prevalent mechanism of local release of norepinephrine induces basal dysfunction in NS. There is still debate on how adrenoceptor activation could mediate transient myocardial dysfunction: some authors sustain the hypothesis of direct cathecholamine-induced myocardial toxicity while others believe that this is caused by an episode of acute transient ischaemia caused by microvascular spasm followed by myocardial stunning. More studies are needed to ascertain whether impaired myocardial perfusion is a direct cause of the syndrome or an epiphenomenon. A myocardial PET study, by Feola *et al*., has demonstrated a reversible reduction in coronary flow reserve and a reversible impairment in metabolism in the apical segments during the acute phase of TC.[15]

The main limitation of our study is the absence of routine coronary angiography in NS. In order to minimize this bias of selection, we excluded from NS those patients with known coronary or vascular disease. The troponin × ejection fraction product (TEFP) has been proposed as an index with a 91% overall accuracy to distinguish myocardial infarction from stress cardiomyopathy.[16] A cut-off of 250 can distinguish infarction from stress cardiomyopathy: accordingly, all NS patients in our study had a TEFP < 250.

In conclusion, the results of the present study demonstrate that important differences in clinical, instrumental, and laboratory features exist between NS and TC.

Conflict of interest: P.G.C. is a Consultant for Servier.

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