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Transient left ventricular dysfunction syndrome: Patho-physiological bases through nuclear medicine imaging

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ABSTRACT

Background: Takotsubo cardiomyopathy (TTC) is a novel heart disease, mimicking acute myocardial infarction. The term "transient left ventricular dysfunction syndrome" (TLVDS) seems to be more appropriate since variant forms of TTC sparing apical segments (mid-ventricular ballooning syndrome (MVBS) and inverted TTC) have been described. Patho-physiological bases of TLVDS remain poorly understood and its optimal management is until now empirical. Our aim was to characterize patho-physiological mechanisms of TLVDS by means of nuclear medicine procedures and to discuss the clinical usefulness of isotopic imaging for a non-invasive diagnosis of TLVDS.

Methods and results: During the sub acute phase, eighteen patients with TLVDS (13 TTC and 5 MVBS) underwent myocardial ^{99m}Tc-tetrofosmin or ^{201}Thallium Gated Single Photon Emission Computed Tomography (G-SPECT) ($n=11$), ^{123}I-mIBG SPECT ($n=8$) and ^{18}F-FDG Gated Positron Emission Tomography (G-PET) ($n=15$), assessing respectively LV perfusion, sympathetic innervation and glucose metabolism. Hypocontractile LV segments were characterized by normal perfusion but reduced uptake of ^{18}F-FDG and ^{123}I-mIBG. Topography and extent of metabolic defects and innervation abnormalities were largely overlapping. Follow-up ^{123}I-mIBG SPECT and ^{18}F-FDG G-PET were performed in selected patients showing rapid normalization of LV motion and progressive improvement of both glucose metabolism and sympathetic innervation.

Discussion: With the hypothesis of neurogenic stunned myocardium as the central causative mechanism of TLVDS, ^{123}I-mIBG SPECT seems to be the most specific diagnostic technique. Sympathetic function and glucose metabolism seem to be strictly correlated in the hypocontractile LV segments. Finally, our results underline the role of nuclear imaging in the setting of patho-physiological mechanisms of TLVDS.

1. Introduction

Transient apical ballooning syndrome or Takotsubo cardiomyopathy (TTC), represents 1–2% of troponin-positive acute coronary syndromes [1]. TTC affects predominantly postmenopausal women and a stressful event commonly precedes most cases [2]. Symptoms, laboratory and electrocardiographic (ECG) findings mimic closely those of acute myocardial infarction. The acute phase of disease is characterized by akinesis or dyskinesis of left ventricle (LV) apex, which is associated to basal hypercontractility in patients without significant stenoses of epicardial coronary arteries. TTC is transient and wall motion abnormalities are completely reversible in a few weeks. Nevertheless, complications and death have been reported in 18.9% and 3.2% of patients, respectively [2] and a recurrent episode occurs in 3.5–6% of cases [1,3].

Variant forms of TTC sparing LV apex have been described and called "mid-ventricular ballooning syndrome" (MVBS) and "inverted Takotsubo" [4–7]. Thus, "transient left ventricular dysfunction syndrome" (TLVDS) without coronary artery disease was recently proposed as a new and more appropriate definition for TTC [1].

Patho-physiological bases of TLVDS remain still poorly understood. Neurogenic myocardial stunning that is mediated by stress-induced catecholamine acute release seems to be the most relevant hypothesis. Nevertheless, multivessel coronary spasms [8], impaired coronary microcirculation [9] or inflammatory process [10] have been proposed as causative mechanisms for TLVDS.

To improve the knowledge of this interesting myocardial disease, a cohort of patients with TLVDS was investigated by means of nuclear medicine techniques. The clinical usefulness of isotopic imaging for a non-invasive diagnosis of TLVDS was also discussed.

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2. Study population

Between January 2006 and May 2008, we retrospectively included in our study 18 consecutive patients admitted to our Cardiology Department for clinical suspicion of acute myocardial infarction, satisfying the following criteria:

(1) All patients met the Mayo criteria for the clinical diagnosis of TLVDS [11]:
   a. transient akinesis or dyskinesis of the LV apical and/or midventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution;
   b. absence of obstructive coronary disease or angiographic evidence of plaque rupture;
   c. new electrocardiographic abnormalities, either ST-segment elevation or T wave inversion;
   d. absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, obstructive epicardial coronary artery disease or myocarditis;
(2) All patients underwent at least one myocardial isotopic procedure 3 to 20 days after the onset of symptomatology (subacute phase), assessing LV perfusion, sympathetic innervation or glucose metabolism.

Thirteen out of 18 patients were women (72%). The median age of the studied population was 67 years (age range: 13–87 y). Typical TTC was observed in 13 out of 18 TLVDS patients (72%) as compared to the midventricular pattern assessed in the remaining 5 cases. The onset of symptoms was preceded by manifest acute emotional stress in 5 out of 18 patients (28%). Right arm acute ischemia, acute bupirenorphine withdrawal and acute hyponatremia complicated by confusional syndrome, anticipated TLVDS symptomatology in 3 patients (17%). Potential iatrogenic causative mechanism of TLVDS was suggested in 5 patients (28%). Four of them had an adrenalin IV injection for treating cardiogenic shock secondary to anaphylaxis, sepsis, tricyclic antidepressants abuse for suicidal purpose and general anesthesia. The overdose of β2-mimetic for treating severe asthma exacerbation was probably the cause of TLVDS in the last one. Finally, no identifiable triggering event was identified for the remaining 5 patients (28%).

Patient population characteristics are summarized in Table 1.

3. Methods

3.1. Non-isotopic procedures

Troponin I and Creatine Phosphokinase (CPK) were measured using standard procedures from blood samples obtained from an antecubital vein at admission and subsequently every 8 h until the recovery of normal values.

Two-dimensional transthoracic echocardiography (TTE) was performed on admission and 1 month after the acute phase, using a VIVID 7 (GE Medical System LLC, Waukesha, Wisconsin) with a 2.5-MHz transducer.

Emergency coronary angiography was performed by femoral approach in all included patients using Judkins technique with a 4F or 6F catheter. Standard projections were obtained. Coronary artery disease was defined as more than 50% reduction in lumen diameter.

LV ejection fraction (LVEF) was calculated by Simpson's method for both TTE and left ventriculography as expressed as mean ± SD.

3.2. Scintigraphic procedures

Myocardial perfusion Gated Single Photon Emission Computed Tomography (G-SPECT) began 60 min after ^{99m}Tc-tetrofosmin injection (740 MBq) or 10 min after ^{201}Thallium injection (74–111 MBq), using a double-head gamma camera (ECAM, Siemens Medical Systems, Erlangen, Germany) equipped with low-energy, high-resolution parallel-hole collimators, a 180° rotation arc, 32 projections, 30 (^{99m}Tc-tetrofosmin) or 40 (^{201}Thallium) s/projection, 8 frames/heart cycle and 64×64 matrix. The studies were reconstructed using filtered back-projection without attenuation or scatter correction and realigned along the heart axis.

^{123}I-metalodoBenzyl-Guanidine (^{123}I-mIBG) scintigraphy was performed 4 h after IV injection of 220 MBq ^{123}I-mIBG using the same gamma camera. Medical therapy and drugs known to influence ^{123}I-mIBG uptake were discontinued for at least 24 h before tracer injection. Projections data were obtained from a 64×64 matrix in 32 views for 60 s each. The studies were reconstructed using ordered-subsets expectation maximization iterative technique without attenuation or scatter correction and realigned along the heart axis.

^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Gated Positron Emission Tomography (G-PET) was performed after oral glucose loading [12]. G-PET acquisition began 45 min after ^{18}F-FDG injection (250 MBq) using a combined PET/Computed Tomography (CT) technology (Discovery ST; GE Medical Systems, Milwaukee, Wisconsin), at 6–12 frames/heart cycle. A thoracic low-dose CT scan was performed before 15-minute 3-dimensional PET acquisitions. PET data were reconstructed with and without CT-based attenuation correction by use of iterative technique. PET reconstructed images were realigned along the short-axis, vertical and horizontal long-axis and qualitatively interpreted.

To facilitate the comparative analysis among perfusion SPECT, ^{123}I-mIBG SPECT and ^{18}F-FDG PET, a 17 segments-model of polar map presentation was obtained from LV short-axis slices. Hence, myocardial uptake defects were quantified as a percentage of the whole LV wall. Two experienced nuclear medicine physicians (CS, IA) interpreted PET and SPECT images, blindly and separately, using QPS-QGS software (Cedars-Sinai, Los Angeles, California). Physicians were uninformed of the results obtained by the conventional diagnostic approach. The final interpretation of images with disagreement was made as a consensus reading.

Table 1
Summary of patient population clinical characteristics.

Pt n°	Sex (M/F)	Age (y)	TLVDS type	Trigger event	Symptoms	ECG	Troponin I (N<0.14 ng/mL)	CPK (N<200 IU/L)	LVEF (%)		
									VTG-St	TTE-St	TTE-Fu
1	F	83	TTC	Right arm ischemia	Chest pain, dyspnea	ST elevation	4.6	390	40	40	55
2	F	83	TTC	Unknown	Pulmonary edema	T-waves inversion	3.1	182	45	40	55
3	F	69	TTC	Emotional stress	Syncope	T-waves inversion	4.3	230	50	40	55
4	M	17	TTC	Adrenalin injection	Dyspnea	ST elevation	7.1	208	55	45	70
5	F	64	TTC	Adrenalin injection	Pulmonary edema	T-waves inversion	3.2	251	na	30	50
6	F	82	MVBS	Unknown	Dyspnea	T-waves inversion	6	100	na	25	60
7	M	84	TTC	Hyponatremia	Dyspnea	ST elevation	0.2	120	35	40	70
8	F	39	TTC	Bupirenorphine withdrawal	Pulmonary edema	T-waves inversion	4.2	135	20	20	55
9	F	82	TTC	Emotional stress	Chest pain, dyspnea	ST elevation	4.9	246	25	25	50
10	F	87	TTC	Emotional stress	Chest pain, dyspnea	ST elevation	2.8	113	41	40	70
11	F	79	TTC	Emotional stress	Chest pain	ST elevation	1.8	828	20	25	50
12	F	64	TTC	Adrenalin injection	Chest pain, dyspnea	T-waves inversion	2.6	150	40	35	60
13	M	13	MVBS	Adrenalin injection	Shock	T-waves inversion	3.5	175	na	45	60
14	M	72	TTC	ß2 mimetic	Chest pain, epistaxis	ST elevation	0.3	482	32	30	60
15	F	67	MVBS	Unknown	Chest pain	ST elevation	4.1	302	35	40	60
16	F	60	MVBS	Emotional stress	Chest pain	ST elevation	2.5	109	45	42	55
17	M	86	TTC	Unknown	Syncope	ST elevation	4.3	120	na	40	55
18	F	81	MVBS	Unknown	Syncope	ST elevation	4.8	153	48	35	60

TLVDS: Transient Left Ventricular Dysfunction Syndrome; TTC: Takotsubo Cardiomyopathy; MVBS: Midventricular Ballooning Syndrome; ECG: Electrocardiography; CPK: Creatine Phosphokinase; LVEF: Left Ventricular Ejection Fraction; VTG: ventriculography; TTE: 2D-Transthoracic Echocardiography; St: primary staging; Fu: follow-up; na: not available.