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TAKOTSUBO CARDIOMYOPATHY AFTER CRYOBALLOON PULMONARY VEIN ABLATION IN A PATIENT WITH PERSISTENT ATRIAL FIBRILLATION: CLINICAL CASE

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We present a case of takotsubo cardiomyopathy characterized as acute transient left ventricular systolic dysfunction in a patient with persistent atrial fibrillation, that occurred after cryoballoon pulmonary vein ablation procedure.

Keywords: takotsubo cardiomyopathy; left ventricular systolic dysfunction; echocardiography; cryoballoon pulmonary vein ablation; atrial fibrillation

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Takotsubo cardiomyopathy (TTC) or stress-induced cardiomyopathy represents a clinical syndrome characterized by acute transient systolic dysfunction of the left ventricular (LV) apex of the heart against a background of relatively intact contractility or hyperkinesis of the basal segments. The syndrome was first described by H.T.Sato in Japan in 1990 in predominantly postmenopausal women [1]. The syndrome was named 'tako-tsubo' by Japanese researchers due to the similarity of the configuration of the LV in systole to the shape of the traditional Japanese squid fishing jar (tako-tsubo). Typical of the disease is the balloon shape of the LV, which results from akinesia of the apex and narrowing of the basal area due to hyperkinesis. In the 30 years since the first case was described, the number of publications on TTC patients has steadily increased, but the mechanisms of development remain poorly understood.

It is generally believed that severe emotional stress or depression, physical pain, severe somatic illness and surgical procedures of all kinds are the most common triggers for TTC [2]. The presence of this association is reflected in synonyms for the condition, such as «broken heart syndrome» and stress-induced cardiomyopathy.

The transient nature of LV dysfunction and the absence of irreversible myocardial damage initially suggested a favourable prognosis. However, current long-term follow-up and registry data show comparable mortality and complication rates in the acute phase of TTC and acute coronary syndrome (ACS). Factors that worsen the prognosis of TTC include age, male sex, physical exertion, type 2 diabetes mellitus, cardiogenic shock and reduced ejection fraction (EF) [2]. According to the TTC consensus paper, cardiac arrhythmias are one of the most important factors determining the clinical outcome of this syndrome [3]. According to recent publications, the presence of atrial fibrillation (AF) in patients with TTC may be an independent predictor of in-hospital mortality and worse long-term prognosis [4, 5]. The present paper presents the clinical case of a patient with TTC after elective cryablation of the pulmonary veins for persistent AF.

Patient P., 66 years old, was admitted to hospital with complaints of palpitations with rapid, irregular heartbeat, accompanied by severe dyspnoea and weakness. The occurrence of cardiac arrhythmia has been known since 2016 and has led to repeated pharmacological cardioversions with amiodarone. Allapinin, propafenone and bisoprolol were administered as prophylactic antiarrhythmic therapy without significant clinical effect. Since 2019, the patient has been receiving amiodarone at a dose of 200 mg/day with a positive effect. However, after 1.5 years, autoimmune thyroiditis with nodularity, amiodarone-induced thyrotoxicosis, was diagnosed and the drug was discontinued. Prednisolone and thiamazole were administered, whereupon thyrotropic hormone and free thyroxine levels normalized over the course of 6 months of antithyroid therapy. Given the symptomatic AF (EHRA score III), failure of antiarrhythmic drug therapy and development of side effects with antiarrhythmic drugs, the patient was indicated for interventional treatment - pulmonary vein (PV) cryablation.

Preoperative examination revealed dyslipidemia (total cholesterol 6.93 mmol/l, LDL 4.87 mmol/l, HDL 1.45 mmol/l) and subclinical drug-induced hypothyroidism (thyrotropic hormone 7.6 μIU/ml, free thyroxine normal) with thiamazole administration. The electrocardio-

gram (ECG) on admission recorded sinus rhythm with a heart rate of 60 beats per minute, deviation of the electrical axis of the heart to the left, left bundle anterior branch block, no abnormal ST -T segment changes (Figure 1).

Transthoracic echocardiography (Echo) showed that the left atrium was undilated (antero-posterior dimension 4.0 cm, volume 58 ml), volume index of the left atrium 30.9 ml/m², LV contractility preserved, no signs of LV local contractility disturbances, no signs of pulmonary hypertension and increased central venous pressure. On admission, the patient was taking apixaban 5 mg b.i.d., atorvastatin 20 mg q.d. and thiamazole 10 mg q.d. The preliminary diagnosis was: «Cardiac arrhythmias: persistent AF, tachysystole. Autoimmune thyroiditis with nodularity, drug-induced subclinical hypothyroidism».

Cryoablation (isolation) of the pulmonary veins

Based on the indication, the patient underwent PV cryoablation [6]. The procedure was performed after pre-sedation with Sibazone 5 mg and Promedol 20 mg once under combined anesthesia with bolus injection IV of propofol and endotracheal anesthesia. The right femoral vein was punctured twice. A diagnostic multipolar lead was inserted into the coronary sinus under fluoroscopic control, and the left atrium was accessed by puncture of the atrial septum under transoesophageal Echo monitoring. When mapping the PV with a circular multipole electrode, all potentials of the PV were recorded. Cryoballoon ablation was performed once in the antral part of each PV with an exposure duration of 240 seconds and temperatures between -40 and -55 °C. To avoid cold damage of diaphragm innervation, exposure to the right LV was controlled by stimulation of the phrenic nerve. After cryoablation, repeated mapping confirmed evidence of isolation of all PV (pulse input and output). Hypocoagulation was maintained throughout the procedure with IV heparin and monitored with an activated clotting time of at least 350 seconds.

After surgery, the patient was transferred to the intensive care unit (ICU) in a hemodynamically stable condition, where she was observed for 24 hours. Immediately after transfer to the ICU, the patient had moderate chest pain that increased on the left side. However, the ECG recorded 10 minutes after the onset of pain showed no coronary dynamics in the form of ST -T increase/decrease. With two-dimensional bedside Echo, no reduction in local and global LV contractility was detected in the ICU. The pain syndrome is partially controlled with non-steroidal anti-inflammatory drugs.

On the morning of the second day after the operation, the patient still had the above-mentioned complaints. The ECG showed an inversion of the T waves in leads I, II, aVL, aVF, V1-V6, a prolongation of the QTc interval up to 540 ms. (Figure 1). According to two-dimensional Echo on the morning of the second day after surgery, there was a zone of dyskinesia with deformation in the apical LV segments with concomitant hyperkinesia of the basal and middle LV segments; LV EF decreased to 42-43%. (Figure 2). Blood tests showed a moderate increase in troponin T to 821 pg/ml, C-reactive protein to 97 mg/l, LDH to 422 U/L.

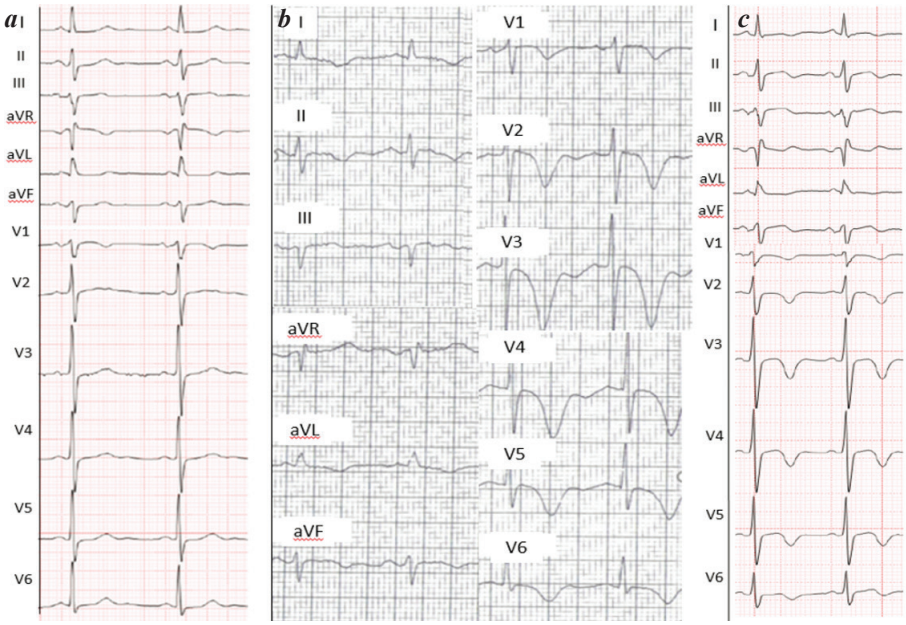

Fig. 1. ECG of patient P.: a - on admission to hospital; b - on the second day after PV cryoablation (against a background of sinus rhythm with a heart rate of 78 beats per minute, an inversion of the T waves in leads I, II, aVL, aVF, V1-V6 and a prolongation of the QTc interval to 540 ms were noted); c - on the seventh day after PV cryoablation (inversion of T waves in leads I, II, V1-V6 with lower amplitude than on the second day, shortening of the QTc interval to 470 ms persisted). Note: PV - pulmonary vein.

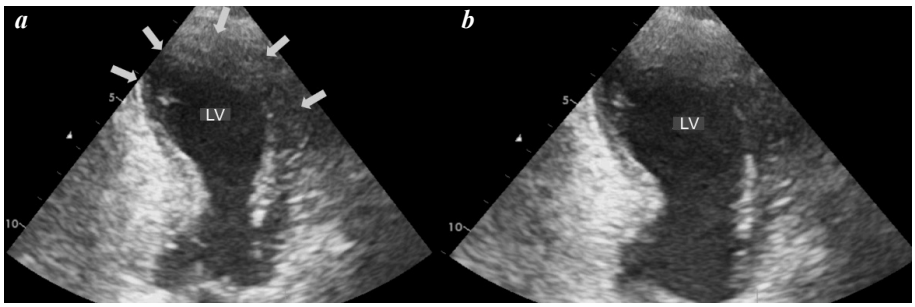

Fig. 2. Two-dimensional Echo of patient P. after PV cryoablation (the revealed zone of dyskinesia (marked by arrows) corresponds to the apex segments of LV of all its walls with marked LV cavity deformation, hyperkinesis of the basal segments): A - two-chamber position in the apex approach, LV systole; B - two-chamber position in the apex approach, LV diastole. Note: LV - left ventricle, PV - pulmonary vein.

In view of the pain syndrome, presence of potential risk factors for coronary heart disease, differential diagnosis and exclusion of acute myocardial damage in ACS and visualization of the coronary artery, coronary angiography (CAG) was performed. CAG showed 'borderline' coronary artery stenoses: 70% stenosis of the anterior descending artery, 70% stenosis of the right coronary artery, 60% stenosis of the circumflex artery (Figure 3).

Considering the ECG changes (inversion of T waves in all thoracic leads), the characteristic LV deformation in systole (apical «ballooning» of LV in combination with basal hyperkinesis) according to Echo, the discrepancy between angiographic and Echo image (no obstructive lesion and coronary thrombosis), a diagnosis of takotsubo cardiomyopathy of apical type was established.

During further dynamic follow-up, the patient's condition remained hemodynamically stable. A sinus rhythm with a heart rate of 65-80 bpm was maintained, BP remained within 100-110/60-70 mmHg and there were no signs of circulatory failure. Brain natriuretic peptide level was 118.6 pg/ml. Holter monitoring showed sinus rhythm with a mean / maximum / minimum heart rate of 78 / 99 / 68 bpm, no rhythm or conduction abnormalities. By the third day, the patient's chest pain had completely resolved. Further ECG recordings showed a decrease in the amplitude of the inverted T waves, the QTc interval was 470 ms (Figure 1).

Due to the circular nature of the local contractility abnormalities, myocardial dyssynchrony and deformation were investigated with speckle tracking imaging [7]. The method showed a decrease in Global Longitudinal Strain Average-GLPS Avg to -10.9% (standard -21.6±2.3%) (Figure 4). On the fourth day of acute TTC, a repeat Echo was performed, which showed positive dynamics in the form of a decrease in LV asynergy, an increase in LV ejection fraction from 42 to 51%.

Anticoagulant therapy with apixaban 5 mg b.i.d and adjusted hypolipidaemic therapy with atorvastatin to 40 mg q.d. were continued in the unit. Angiotensin-converting enzyme inhibitors were prescribed as pathogenetic therapy for TTC. The patient was discharged on the 7th day after LV cryoablation in satisfactory condition and was advised to take the above medications.

After 1 month, a repeat Echo study was performed which showed LV EF normalized to 60% and no areas of local LV contractility abnormalities. The study also showed no dilatation of the heart cavities and no signs of pulmonary hypertension. Speckle tracking Echo showed improvement in LV myocardial deformation characteristics with a GLPS Avg of -16.4% (Figure 4). Given the coronary artery stenoses detected with CAG, a negative stress Echo was performed to rule out myocardial ischaemia. Palpitations did not recur during the following 6 months of follow-up. No rhythm or conduction abnormalities were detected during repeated daily checks at 3 and 6 months.

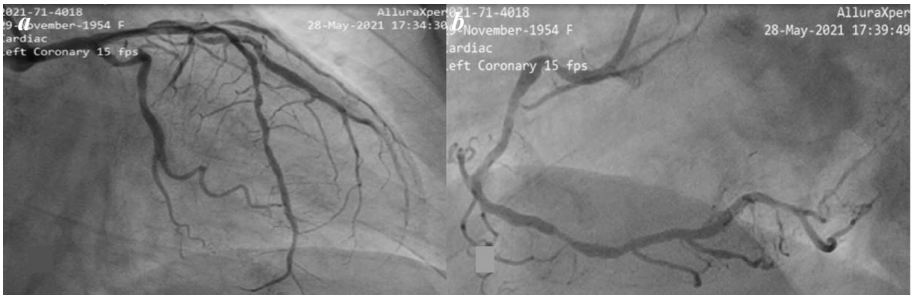

Fig. 3. Coronary angiography of patient P. after PV cryoablation, a diffuse atherosclerotic coronary artery disease was found: a - the anterior descending artery is 50% narrowed at the orifice, 60% narrowed in the proximal segment and 70% narrowed in the middle segment, the circumflex artery is 60% narrowed in the proximal third (right caudal projection); b - in the proximal segment of the right coronary artery multiple stenoses with a narrowing of up to 70%, in the middle segment a narrowing of 40%, in the distal segment a narrowing of 65-70% (left caudal projection). Note: PV - pulmonary vein.

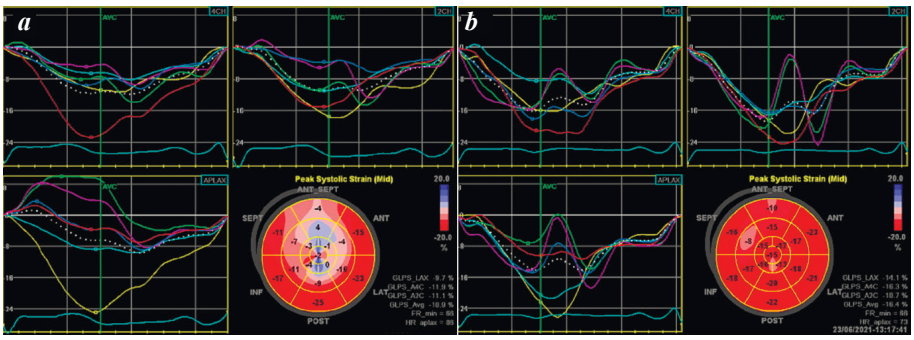

Fig. 4. Speckle tracking echocardiography with evaluation of curves and indices of longitudinal myocardial deformation in 17 segments, maximum systolic deformation for each of the 17 LV segments in the form of a «bull's eye»: a - evaluation of indices on the fourth day after PV cryoablation (significant decrease in segmental longitudinal deformation in the LV apex of all its walls, typical for apical TTC, GLPS avg -10.9%); b - in dynamics 1 month after PV cryoablation (a significant decrease in the area of segmental longitudinal deformation in the LV apex is noted, GLPS avg -16.4%). Note: GLPS - Global Longitudinal Strain, LV - left ventricle, PV - pulmonary vein, TTC - takatsubo cardiomyopathy.

DISCUSSION

Data on TTC collected over the past decades allow timely detection of the disease and its potential complications. According to a follow-up registry of 3.265 patients, 1% of patients admitted to hospital urgently with a diagnosis of ACS were found to have TTC. Based on the US Nationwide Inpatient Sample database, most TTC patients are women (5.2 per 100,000 women versus 0.6 per 100,000 men) [8].

The primary diagnostic criteria for TTC scanning, formulated by the Mayo Clinic in 2008, have subsequently been repeatedly updated and revised [9]. A 2018 European Society of Cardiology consensus paper established the following diagnostic criteria for the diagnosis [3]: 1) transient LV dysfunction (hypokinesia, akinesia or dyskinesia) in apical or middle segments not corresponding to the blood supply zone of a single coronary artery, often leading to circular changes in LV segments; 2) previous physical or emotional stress (optional condition); 3) significant coronary artery lesion not refuted by the presence of CT; 4) ECG changes in the form of ST-segment elevation/reduction, inversion of T waves, prolongation of the QTc interval in the acute phase of the disease; 5) moderate troponin elevation, increased plasma natriuretic peptide level; 6) no evidence of infective endocarditis; 7) predominance of post-menopausal women; 8) recovery of systolic function from LV in dynamic cardiac imaging.

It is still unclear whether TTC is exclusively a cardiovascular disease. A significant proportion of patients with TTC have extracardiac pathology, particularly pheochromocytoma and acute cerebral disorders. Previous surgical procedures or administration of sympathomimetics, which act as triggers of TTC, also suggest a polypathogenetic nature of the disease [3, 10].

The understanding of the pathogenetic mechanisms of TTC is based on several hypotheses, and the available approaches to the treatment of the syndrome are not supported by randomized trials. The presence of emotional or physical stress as a trigger of TTC has been the basis for the hypothesis of a central role of catecholamines in the development of the syndrome [10]. Activation of the sympathetic nervous system can lead to spasms of the coronary arteries and disruption of the microcirculation. The characteristic shape of the LV on the TTC may be due to the different density of beta-adrenoceptors in the apex and basal regions. Stimulation of beta-adrenoceptors by catecholamines leads to a negative inotropic effect, local hibernation and myocardial dysfunction, which recovers completely within a few weeks or months [11].

Despite transient LV dysfunction in TTC, there is a risk of serious, even life-threatening, complications. It is important to note that the initial perception of a favourable course of TTC has not been confirmed in several registries and studies. The mortality rate in the acute phase of TTC is similar to that of acute myocardial infarction, at 5.6% at one year follow-up [2]. Potentially dangerous complications of TTC include cardiogenic shock (up to 10% of cases), LV thrombosis, LV outflow tract obstruction and LV wall rupture [12,13]. Life-threatening arrhythmias, including Torsade de Pointes ventricular tachycardia (TdP) and ventricular fibrillation, were observed in 3.4-9% of patients in the acute phase of TTC. Prolongation of the QTc interval of more than 500 ms over several days (as in our patient) is to be expected and significantly increases the risk for these arrhythmias [14].

Patients with TTC are not only prone to ventricular tachyarrhythmias but also to supraventricular arrhythmias. The prevalence of AF in patients with TTC is between 5 and 25%. According to a retrospective analysis by I. El-Battrawy et al. (2017) of patients with TTC, AF was associated with an increased risk of in-hospital mortality and was the worst long-term predictor of adverse disease outcomes [4]. In addition, AF increases the risk of acute heart failure and thromboembolic events, which is more pronounced in patients with LV wall hypo- and akinesia in TTC. Similar prognostic results reported by L. Jesel et al. (2019) showed that markers of myocardial damage and systemic inflammatory response (C-reactive protein, troponin I, BNP) were significantly more frequent independent predictors of cardiovascular mortality in patients with TTC at AF. Thus, the results may suggest a significant role of inflammation in the development of AF in the cohort of patients with TTC [15]. Coronary artery disease is found in 10-29% of patients with TTC [16]. Therefore, the presence of a stenotic coronary artery lesion does not exclude a diagnosis of TTC in the patient.

Circular systolic LV dysfunction, detected by Echo in the form of apical «ballooning» of the LV apex, which does not correspond to the coronary blood supply of the LV, combined with basal segment hyperkinesis, is the most characteristic feature for distinguishing TTC from ACS and other diseases. In acute TTC, this circular pattern of LV local contractility abnormalities is usually accompanied by a significant decrease in regional longitudinal deformation from the base towards the LV apex, where the most marked changes are seen [17]. These abnormalities of LV local contractility are not only detectable by two-dimensional Echo, but can be particularly clearly visualized by assessing LV deformation using speckle tracking technology and determining LV «bull's-eye» diagrams [7, 17].

CAG and contrast-enhanced magnetic resonance imaging are also important diagnostic techniques. CAG can exclude the presence of thrombosis or «complicated» coronary artery plaque. Magnetic resonance imaging with contrast agent makes it possible to distinguish TTC in the acute phase from the development of myocarditis.

Many patients cannot be completely excluded from ACS by Echo and CAG, especially in clinically stable patients with TTC and no ST -T-segment elevation. The InterTAK diagnostic score, proposed by the European Society of Cardiology in 2018, provides a specific way to confirm a TTC diagnosis and determine the method of coronary imaging [3]. Our patient had an intermediate risk of TTC (56 points), which also warranted CAG.

The most important approaches to the management of TTC in the acute phase are timely diagnosis and prevention of potentially dangerous complications. The question of long-term drug therapy for TTC, which influences the course and prognosis of the disease, remains unresolved. There is evidence of a beneficial effect of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on the prognosis of cardiovascular events for 1 year before the function of LV is restored [2].

The initial description of TTC as a «stress-induced» cardiomyopathy suggested a possible involve-

ment of the beta-adrenergic system in the development of the syndrome. Experimental *ex vivo* heart models of TTC patients demonstrated increased beta-adrenergic activity of cardiomyocytes in response to catecholamine exposure [10]. Based on this work, the potential benefit of prescribing beta-blockers for patients with TTC has been suggested. However, according to the InterTAK registry, 60% of patients with recurrent TTC have received beta-blockers, and these are predominantly β1-specific. There are also no data on the effect of beta-blockers on mortality in patients with TTC. Routine prescription of these drugs to prevent TTC recurrence is therefore not advisable [2, 18].

The clinical case we studied demonstrates the importance of early diagnosis of TTC developing in the postoperative period after LV cryoablation and the importance of ruling out irreversible myocardial damage in ACS. There are only 2 cases of TTC after LV cryoablation in the literature [19, 20]. The clinical case we describe shows the development of TTC after intervention for persistent AF combined with widespread atherosclerotic coronary artery disease. The correlation with the surgical intervention, the pathological changes in the ECG and the apical LV dyskinesia in the Echo are classic signs of the disease. Due to the prolongation of the QTc interval to a maximum of 540 ms in our patient, continuous cardiac rhythm monitoring was performed in ICU during the acute phase of TTC. This allowed possible causes of QTc prolongation (bradycardia, hypokalemia and hypomagnesaemia) to be corrected if necessary to prevent life-threatening arrhythmias. Although our patient did not experience any serious complications in the manifestation of TTC, the cryoballoon isolation of the pulmonary veins performed at follow-up enabled the patient to avoid symptomatic recurrences of AF and improve her quality of life.

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