Ivabradine in Takotsubo Cardiomyopathy

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Abstract:

AIM: The aim of this review is to present a case report of Takotsubo cardiomyopathy and to review the current literature. The second aim is to describe the role of ivabradine in the management of Takotsubo cardiomyopathy when intolerance for beta blockers occurs.

MATERIALS: Case report and literature review of Takotsubo cardiomyopathy.

RESULTS: A 52-year-old Caucasian female presented with Takotsubo cardiomyopathy triggered by severe emotional stress. Dmission electrocardiogram mimicked acute ST-segment elevation myocardial infarction , coronary angiography excluded significant coronary stenosis and left ventriculogram showed a typical Takotsubo cardiomyopathy apical ballooning appearance. Due to beta blocker intolerance, “off-label” treatment with ivabradine was initiated because of symptomatic sinus tachycardia. Echocardiography revealed normalization of the ejection fraction at outpatient follow-up. In the recent literature, ivabradine has been used in the management of different entities such as stable angina pectoris, congestive heart failure, inappropriate sinus tachycardia syndrome, postural tachycardia syndrome and Takotsubo cardiomyopathy.

CONCLUSION: Takotsubo cardiomyopathy may be induced by witnessing a robbery. The patient was intolerant for beta blockers and had a favorable response to treatment with ivabradine. Ivabradine may be an alternative choice in cases where there is an intolerance of beta blockers. We present an exceedingly rare case of Takotsubo cardiomyopathy induced by uncommon severe emotional stress, catching her colleague stealing money from the cash register, which was associated with sinus tachycardia in a female patient with intolerance for beta blockers. The patient responded well to treatment with oral ivabradine. The literature is briefly reviewed

Keywords: Takotsubo Cardiomyopathy, Stress Cardiomyopathy, Coronary Angiography, Ventriculography, Ivabradine

Introduction:

Recently, the incidence of Takotsubo cardiomyopathy (TTC) has been estimated to be 29.8 per million inhabitants [1]. TTC has been recognized since 1990 and is characterized by chest pain, the elevation of cardiac markers, dynamic ECG changes characterized by negative T-waves [2] or mimicking ST-segment elevation myocardial infarction in some cases, transient apical and mid-ventricular wall-motion abnormality, and the absence of significant obstructive coronary artery disease. TTC is highly related to and triggered by sudden severe psychological or physical stress. TTC may occur in Asian and Caucasian subjects [3] and may be subsequent to aneurysmal subarachnoid hemorrhage (SAH) [4], or triggered by paroxysmal supraventricular tachycardia [5] and following uncomplicated pacemaker implantation [6].

Medical therapy is only supportive with beta blockers and angiotensin-converting enzyme inhibitors [7;8]. TTC has a good long-term prognosis and recovery as the systolic left ventricular function occurs in the majority of cases. Increased awareness of the condition is also witnessed by the increased number of publications in 2013 (n=1879) [9]. We present here a female patient with TTC triggered by severe emotional stress and treated with off-label ivabradine (procoralan) due to intolerance for beta-blockers. The current literature is briefly reviewed.

Clinical case:

A 52-year-old Caucasian female was admitted to our cardiac care unit because of acute chest pain. Her medical history contained percutaneous coronary intervention (PCI) of the left circumflex coronary artery (LCx) due to Non ST-elevation myocardial infarction (Non STEMI) 2-years earlier with normal ejection fraction. Her cardiac medication included a statin, metoprolol (which was discontinued on admission due to extreme fatigue), aspirin, and perindopril. One day prior to the chest pain she had caught her younger colleague stealing money from the cash register, which led to disturbed emotional status during that day. Physical examination was unremarkable, beside symptomatic tachycardia. Admission ECG showed sinus tachycardia of 112 beats per minute with minimal ST-segment elevation in the infero-lateral leads suggestive of STEMI. Blood tests revealed increased levels of creatine kinase (CK) (283 U/l, normal range < 170) and hs-troponin T (565 ng/l, normal range < 14). An emergent coronary angiography (CAG, video 1 and 2) excluded significant coronary stenosis and showed a patent stent in the LCx. Contrast ventriculogram (Fig. 1, video 3) revealed a severely depressed left ventricular function (Ejection Fraction (EF) around 20%) with severe hypokinesia of the antero-lateral, apical and infero-posterior

Figure 1: Left ventricular angiogram: (A) during diastole, (B) mid-systole and (C) systole showing akinesia of the apical region with basal sparing and demonstrating the typical TTC features denoting apical ballooning with apical hypokinesia.

segments with hyperkinesia of the basal segments. Because of beta-blocker intolerance (extreme fatigue) and persistent, symptomatic sinus tachycardia during the clinical course, off-label ivabradine (5 mg twice daily) was prescribed. The patient had a favourable response to treatment with ivabradine. The clinical condition stabilized after the initiation of treatment. Finally, follow-up transthoracic echocardiography after several months showed complete recovery of left ventricular function (EF, 0.63%) and the patient remained well.

Discussion:

TTC is a transient condition, with a high prevalence in post-menopausal women, with depressed systolic LV function, which may occur classically following psychological and emotional [10;11] stressors or after surgical interventions and medical conditions or physical trauma [12;13]. Reports of TTC associated with opiate withdrawal [14] or cocaine use [15], acute respiratory failure [16], following pulmonary resection [17], after cholecystectomy [18], related to motor vehicle accidents [19] or associated with pheochromocytoma [20] have recently been published. TTC may be precipitated by eclampsia during pregnancy [21]. Rarely, TTC may have the tendency to be recurrent [22].

TTC is responsible for 1.2-2.2% of total hospital admissions for suspected acute coronary syndrome [23;24]. TTC is not only common complication (25%) in the critically ill patients and in intensive care population [13;25-28] but also in subarachnoid hemorrhage (33%) subjects [26;29;30]. It has been observed during epileptic seizures and may be the cause of sudden death in some cases [31].

A recent publication has suggested that TTC is an acute heart failure syndrome associated with a significant in-hospital death that is comparable with acute coronary syndrome patients [32].

Criteria required for establishing the diagnosis TTC:

The following criteria are required for establishing the diagnosis of classic TTC: transient left systolic ventricular dysfunction frequently emerging following a stressful trigger, not associated with significant obstructive coronary artery disease, novel and dynamic ECG changes with ST-segment elevation or T-wave inversion [2;33], usually accompanied with the slight elevation of cardiac markers and no signs of myocarditis or pheochromocytoma and in the absence of cerebrovascular accident, head trauma and intracranial hemorrhage [8;34-37]. The current patient fulfilled the above-mentioned criteria. Recently, pericardial effusion has been reported in the setting of TTC [38].

Diagnostic work-up:

The diagnostic work-up of TTC may include history, ECG, echocardiography, coronary angiography (CAG), ventriculography and, less frequently, cardiac magnetic resonance imaging (MRI)[39]. It recognized that TTC predominantly affects post-menopausal women [37]. Recent study have shown that emotional stress was more prevalent in women and physical triggers were more common in men. In our current case, an emotional trigger played a pivotal role and coronary angiography was distinctive for the diagnosis illustrating an apical type. The apical type is most common (81.7%) in TTC followed by mid-ventricular

configuration (14.6%), basal form (2.2%) and finally focal presentation (1.5%) [32]. When the basal segments are involved, TTC is defined as inverted stress-induced cardiomyopathy [40].

Acute performed CAG reveals either normal epicardial coronary arteries [41] or, as was the case in our presenting patient, they may show insignificant lesions [42;43].

Postulated etiopathogenetic mechanisms of TTC: The exact pathogenesis of TTC is unknown, but various hypotheses have been suggested, among these catecholamine-induced cardiotoxicity and microvasculature dysfunction are the most supported ones [8].

While the pathogenesis of TTC is not fully understood and remains to be elucidated, several hypotheses, including first multivessel epicardial coronary artery spasm [41], second acute microvascular spasm and micro-vascular dysfunction with subsequent myocardial apical stunning [44-46], third storm of catecholamine excess and release of cardiac catecholamine [47;48] associated with catecholamine-induced myocardial stunning and effects mediated by epinephrine on β -2 adrenoreceptors [49-51] and fourth spontaneous coronary thrombus lysis of occlusive coronary artery thrombus [52-54], have been proposed. It has been postulated that whatever the etiology of TTC, reversible coronary microvascular dysfunction occurs as a common pathophysiological determinant [55]. Recently it was suggested that "there is a brain-heart connection in TTC, which contributes to the disease mechanism" [32] and other studies have shown that mental stress may cause endothelial dysfunction and impairment of the coronary microcirculation [56;57].

Management and prognosis of TTC:

Reversible TTC cases have been reported [58;59]. Observed complications associated with TTC are, among others, acute heart failure [40], LV thrombus [60;61], significant arrhythmias [62] are uncommon in TTC accounting for 5,7% found in a retrospective study by Dib et al. [63]. None of these complications was found in our patient who had sinus tachycardia. Generally, this transient condition has a good prognosis and may recover spontaneously without the need for pharmacological or intra-vascular device interventions, but, in some cases, invasive supportive management including inotropic agents, intra-aortic balloon pump (IABP) and left ventricular assist devices (LVADs) may be indicated. Initial pharmacological support including angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, diuretics and beta blockers may be required in the short-term (weeks-months) [7;24;33]. Recently, the findings of the International Takotsubo registry have indicated a favorable outcome with improved survival when angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors are used [32]. Anticoagulation for the prevention of thromboembolism may be added [64]. β -blockers and non-dihydropyridine calcium channel blockers (diltiazem and verapamil) reduce heart rate effectively, but their use may be limited by adverse reactions, intolerance or contraindications. In the case of intolerance to β -blockers, ivabradine, with the selective lowering of heart rate and cardiac oxygen consumption, has emerged.

Mechanisms of action of ivabradine:

Ivabradine (caused no hypotension and has no negative inotropism)

decelerates the gradient of diastolic depolarization, causing a reduction of the intrinsic pacemaker activity in the sinoatrial node; it counteracts dobutamine-induced sinus tachycardia [65], and may be advantageous through more than one mechanism: first, by counteracting sinus tachycardia, second, by possible modulating role in perivascular and interstitial inflammatory reactions in MI and acute myocarditis [66;67], and third, by acting as a vasodilator to abolish microvascular vasospasm postulated as one of the pathogenic mechanisms of TTC [68;69]. TTC may be caused by microvascular vasoconstriction with subclinical coronary microvascular dysfunction [69].

Profile of ivabradine: Ivabradine obtained a European marketing authorization on 25th October 2005, and is available in 102 countries. Ivabradine is a selective If current blocker with heart rate-reducing effects [70], which has been indicated for chronic stable angina pectoris in patients with normal sinus rhythm who are not able to tolerate β -blocker therapy and for congestive heart failure.

Ivabradine is a selective If channel blocker [71]. It has no negative inotropic or lusitropic effects, reduces resting heart rate, heart rate during exercise and rate-pressure product without affecting resting and exercise blood pressure. It provides a reduction of cardiac workload and energy consumption that may be beneficial in patients with ischemic heart disease [72], stable angina pectoris [70] and/or congestive heart failure [73]. Furthermore, it has no negative dromotropic consequences, does not influence the QT interval [70] and causes no coronary vasoconstriction [74]. As it has been postulated that vasospasm is one of the pathogenic mechanisms of TTC [68], ivabradine may act as a vasodilator and/or spasmolytic.

Clinical trials:

Ivabradine has a proven efficacy for the treatment of stable angina pectoris [72] and congestive heart failure [73]. Ivabradine treatment demonstrated a reduction of the incidence of cardiovascular death and hospitalization in a heart failure population in the Systolic Heart Failure Treatment with If inhibitor Ivabradine (SHIFT) trial [72] and of coronary events in a subgroup of chronic stable angina pectoris with heart rates ≥ 70 bpm in the ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL) study [73]. On the contrary, the SIGNIFY trial (including 12,049 patients with activity-limiting angina randomly assigned to placebo or ivabradine (Procoralan), at a dose of up to 10 mg twice daily), showed that a subgroup of patients had a significant increase (3.4% vs 2.9% yearly incidence rates) in the combined end-points of risk of cardiovascular death or non-fatal myocardial infarction compared with placebo [75]. Furthermore, the data indicated a higher risk of bradycardia with Ivabradine (Procoralan) compared with placebo (18.0% vs. 2.3%, $P < 0.001$) [75].

Ivabradine use in different disorders:

Ivabradine has been prescribed for the treatment of inappropriate sinus tachycardia [76-79], postural tachycardia syndrome (PoTS) [79-82] and takotsubo cardiomyopathy [83]. In a retrospective study ($n = 20$), McDonald et al. reported symptomatic improvement in 60% of PoTS patients [80]. Recently, it has been demonstrated in

a single center trial that ivabradine has improved the quality of life in patients undergoing coronary artery bypass grafting associated with conduction abnormalities (first degree atrioventricular block or bundle branch block) or left ventricular dysfunction with relative or absolute contraindications to β -blockers [84].

In acute heart failure due to myocarditis: In a few cases [65], ivabradine was administered as an adjuvant off-label to patients with acute heart failure and multiorgan failure due to myocarditis; it has proven to be beneficial in supporting hemodynamic stabilization [66]. Furthermore, in cardiac allograft recipients, ivabradine showed a reduction of left ventricular mass index by significant heart rate reduction [85].

In the current case, TTC symptoms recovered during ivabradine use; however, a causal relation between ivabradine and left ventricular recovery cannot be proven as the recovery of TTC-induced left ventricular dysfunction may occur spontaneously; however, the condition-related symptoms showed good clinical response.

Profile of Ivabradine: Electrophysiological properties:

Ventricular arrhythmias: In experimental animal studies, ivabradine reduced the incidence of reperfusion ventricular tachycardia (VT) by 50% and ventricular fibrillation (VF) by 70% following regional ischemia. These antiarrhythmic effects were produced due to its selective influence on heart rate reduction [86].

Atrial fibrillation (AF): Martin et al. performed a meta-analysis of 21,571 patients which demonstrated that ivabradine treatment was associated with a relative risk of 15% of developing AF [87]. On the other hand, Ivabradine in combination with Metoprolol was more effective (7.6%) than ivabradine (17.1%) or metoprolol (11.5%) alone in the prevention of postoperative atrial fibrillation in patients undergoing coronary artery bypass surgery [84].

Currently, guidelines regarding the treatment recommendations and follow-up of TTC are lacking. No randomized clinical trials on treatment of TTC have been conducted.

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