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Pathophysiological association of catecholamine stress in a patient with Takotsubo cardiomyopathy and chronic kidney disease: a case report

Patofiziološka povezanost katekolaminskog stresa kod pacijentice s Takotsubo kardiomiopatijom i kroničnim zatajenjem bubrega: prikaz slučaja

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Abstract. ***Aim:*** Takotsubo cardiomyopathy is a transient dysfunction of the heart muscle that occurs in response to a stressful event. A working diagnosis is mostly made for acute ischemic heart disease due to similar clinical presentation and differential diagnostic doubts. Although it is a reversible disorder of cardiac contractility, mortality rate is similar to that of an acute coronary syndrome due to the development of complications. We report the case of a patient with chronic kidney disease and the consequent development of Takotsubo cardiomyopathy, a possible pathophysiological link that has not been reported in the significant number in literature so far. ***Case report:*** An 83-year-old patient on a chronic hemodialysis program, due to the development of anginal symptoms specific for the acute coronary syndrome and with a significant increase in cardiospecific enzymes, was transferred to the Coronary care unit for the necessary invasive cardiac treatment. Echocardiographic and coronarographic findings confirmed the diagnosis of Takotsubo cardiomyopathy, which was the first case in a patient on chronic hemodialysis program in our institution. ***Conslusions:*** According to available data, about 30 cases of Takotsubo cardiomyopathy have been reported so far, indicating that transient myocardial dysfunction is a rare cardiomyopathy in patients with chronic kidney disease. A small number of literature-recorded cases do not support the similar pathophysiological basis of increased sympathetic activity present in Takotsubo cardiomyopathy and chronic kidney disease.

Key words: catecholamines; chronic renal insufficiency; hemodialysis; pathophysiology; Takotsubo cardiomyopathy

Sažetak. ***Cilj:*** Takotsubo kardiomiopatija prolazna je disfunkcija srčanog mišića koja nastaje kao odgovor organizma na stresorni događaj. Radna se dijagnoza većinom postavlja za akutnu ishemijsku bolest srca radi slične kliničke prezentacije i diferencijalnih dijagnostičkih dvojbi. Iako se radi o reverzibilnom poremećaju srčane kontraktilnosti, smrtnost je slična akutnom koronarnom sindromu uslijed razvoja komplikacija. Izvještavamo slučaj pacijentice s kroničnom bubrežnom bolesti i posljedičnim razvojem Takotsubo kardiomiopatije, moguće patofiziološke poveznice koja do sada literaturno nije zabilježena u značajnom broju. ***Prikaz slučaja:*** 83-godišnja pacijentica na programu kronične hemodijalize, uslijed razvoja anginoznih tegoba specifičnih za akutni koronarni sindrom te uz značajan porast kardiospecifičnih enzima, premještena je u koronarnu jedinicu radi potrebne invazivne kardiološke obrade. Ehokardiografski i koronarografski nalaz potvrdio je dijagnozu Takotsubo kardiomiopatije, što je ujedno prvi zabilježen slučaj u pacijenta na programu kronične hemodijalize u našoj ustanovi. ***Zaključci:*** Prema dostupnim podatcima, do sada je zabilježeno oko 30 slučajeva Takotsubo

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kardiomiopatije kod bubrežnih bolesnika, što pokazuje da je prolazna disfunkcija miokarda rijetka kardiomiopatija u pacijenata s kroničnom bubrežnom bolesti. Mali broj literaturno zabilježenih slučajeva ne ide u prilog sličnoj patofiziološkoj osnovi povećane simpatičke aktivnosti prisutne kod Takotsubo kardiomiopatije i kronične bubrežne bolesti.

Ključne riječi: hemodijaliza; katekolamini; kronična bubrežna insuficijencija; patofiziologija; Takotsubo kardiomiopatija

In the acute setting, the presentation of Takotsubo cardiomyopathy is often similar to the presentation of acute coronary syndrome with ST elevation. The mortality rate of both diseases is similar due to the development of complications such as left ventricular free wall rupture.

INTRODUCTION

Takotsubo cardiomyopathy (TCM) is a cardiac syndrome manifested by transient dyskinesia, hypokinesia or akinesia of the left ventricular (LV) wall (midventricular part) with or without involvement of the apex of the heart, or involving the walls of the heart supplied by more than one coronary artery and without the presence of coronary artery disease[1]. The incidence of TCM is the most common in postmenopausal women (90%), on average between 62 and 76 years of age[2,3]. The most common trigger for the development of such a transient cardiac dysfunction is psychological or emotional stress[4]. The genesis of the emotional or psychological component is supported by a slightly higher incidence of depression and anxiety in patients who develop TCM[5,6]. Due to the older age at which TCM typically occurs, patients are more likely to have other comorbidities such as arterial hypertension, hyperlipidemia, nicotinism, and diabetes, which in turn lead to cardiovascular complications and mortality similar to those seen in acute myocardial infarction with ST-elevation (STEMI)[2,7,8].

The diagnosis of TCM is based on the clinical signs, electrocardiogram (ECG), blood markers, echocardiographic and coronarographic findings. The most common clinical symptoms are shortness of breath and chest pain, coinciding with the symptoms of other ischemic heart diseases, as well as with the symptoms of heart failure[2]. ECG changes correspond to the changes found in STEMI with the difference that ST elevation is present diffusely, most pronounced in precordial and lateral leads, i.e. in leads that represent the supply area of several coronary arteries[9]. The most important blood marker, cardiospecific enzyme troponin, has a dynamic of increasing up to 60 times above the upper limit of normal (unlike STEMI where an increase of > 400 times above the upper limit of normal occurs)[10]. Echocardiography, which is usually routinely performed before coronary angiography in patients with suspected STEMI, is manifested by dyskinesia, hypokinesia or akinesia of the apical and middle ventricular segment – or areas of the heart that extends beyond the network of one coronary artery[11]. Of the other non-invasive imaging methods, cardiac magnetic resonance (CMR) shows promising results in TCM diagnostics but due to its cost and unavailability in many healthcare facilities has not yet found its place in the acute diagnostic algorithm[12]. Probably the most significant feature of TCM that distinguishes it from ischemic heart disease is the coronarographic finding of absent obstructive coronary artery disease and the ventriculographic finding of the "ballooning" phenomenon in the area of lowest myocardial resistance (site of akinesia and myocardial hypokinesia, most often presented apically)[13].

Several electrocardiographic and echocardiographic criteria may serve to aid in the diagnostic differentiation of TCM from STEMI including: troponin-ejection fraction product (TEFP), lenght of corrected QT interval (QTc), transient LV dysfunction and the degree of increase in cardioselectric enzymes (troponins) (table 1)[10,14,15]. TEFP is obtained by multiplying the ejection fraction (EF) of LV with peak troponin levels and values ≥ 250 have a sensitivity of 95%, a specificity of 87%, and an overall accuracy of 91% to distinguish STEMI from stress cardiomyopathy. Peak troponin levels due to myocardial necrosis in patients with STEMI are higher than in patients with stress cardiomyopathy, so the use of TEFP may serve to distinguish obstructive from non-obstructive heart disease[15].

In patients with chronic renal failure (CKD) there is an increased activity of the autonomic nervous

Table 1. Diagnostic differentiation of Takotsubo Cardiomyopathy from acute myocardial infarction with ST elevation (STEMI)

Diagnostic differentiation of TCM from STEMI:
• length of corrected QT interval (QTc) > 500 ms in the acute phase[14]
• recovery of LV contractile function in 2-4 weeks[14]
• increase in cardiac enzymes (troponin) up to 60 times above the upper limit of normal (in STEMI increase of > 400 times above the upper limit of normal)[10]
• TEFP ≥ 250[15]

LV – left ventricle, STEMI – acute myocardial infarction with ST-elevation, TEFP – troponin-ejection fraction product.

system (sympathetic component) and consequently elevated plasma catecholamine levels (adrenaline, noradrenaline, dopamine)[16,17]. Similar changes in catecholamine levels (predominantly adrenaline) were also found in TCM[18]. Increased catecholamine activity can also be found in other diseases, often found as comorbidities of CKD such as diabetes, arterial hypertension, obesity and metabolic syndrome[19]. Thus, multitopically enhanced activity and elevated levels of catecholamines in patients with CKD, or "catecholamine storm", play a significant role in the development of TCM, representing a pathophysiological link[20].

CASE REPORT

We report the case of a 83 year-old woman with an end stage renal disease on chronic hemodialysis program (HD), who was hospitalized due to a gram-negative sepsis, which was confirmed with blood culture (*Pseudomonas aeruginosa*) and laboratory findings (leukocytes 22.86 x 10^9/L, CRP 148.4 mg/L, procalcitonin >100 ng/ml). The catheter-related bacteremia was excluded due to negative culture findings. Of the other diseases, the patient suffered from type 2 diabetes (insulin-dependent), arterial hypertension, and paroxysmal atrial fibrillation with a contraindication for the use of anticoagulant therapy due to hemoptysis and suspected bronchial neoplasm. On the 7th day of hospital treatment, the patient complained of chest pain and shortness of breath. The chest pain traveled up to the neck, into the jaw, and then radiated to the back, with no vomiting or sweating. An electrocardiogram showed sinus tachycardia with left electric axis. An ST elevation was observed of 1,5 mm in anteroseptal leads, not previously described. Laboratory findings showed a significant increase in cardioselective enzymes – troponin hsI 523,2 ng/L (upper limit of normal less than 15,7 ng/L) and TEFP was 14.9. Departmend of cardiology was consulted, and the patient was transferred to Coronary care unit (CCU). Cardiac catheterisation laboratory (Cath lab) was activated and patient underwent coronary angiography which showed normal findings and no signs of obstructive coronary artery disease. Furthermore, transthoracic echocardiography was performed which verified left ventricular akinesis, predominantly apical (left ventricle inner diameter in diastole 4.6 cm, interventricular septum in diastole 0.8 cm) with large apical thrombus (thrombus size 2.4 x 1.4 cm). The ejection fraction by Teichholz formula was 35%, without significant valvular disease and with no pericardial effusion or signs of pulmonary hypertension. Follow-up electrocariogram showed atrial fibrilation, wirh resolution of the ST elevation. Patient was treated with warfarin anticoagulant therapy with prothrobin time control, combined parenteral antibiotic therapy (meropenem and vancomycin) and other symptomatic therapy. After 20 days of hospital treatment, the patient was discharged and continued with chronic HD treatment.

Insight into the hospital information system BIS (croatian *Bolnički informacijski sustav*), three months after the hospital treatment, the patient stopped attending the HD program with a suspicion of death of unknown cause.

DISCUSSION

The pathophysiological link between the influence of catecholamines on the development of

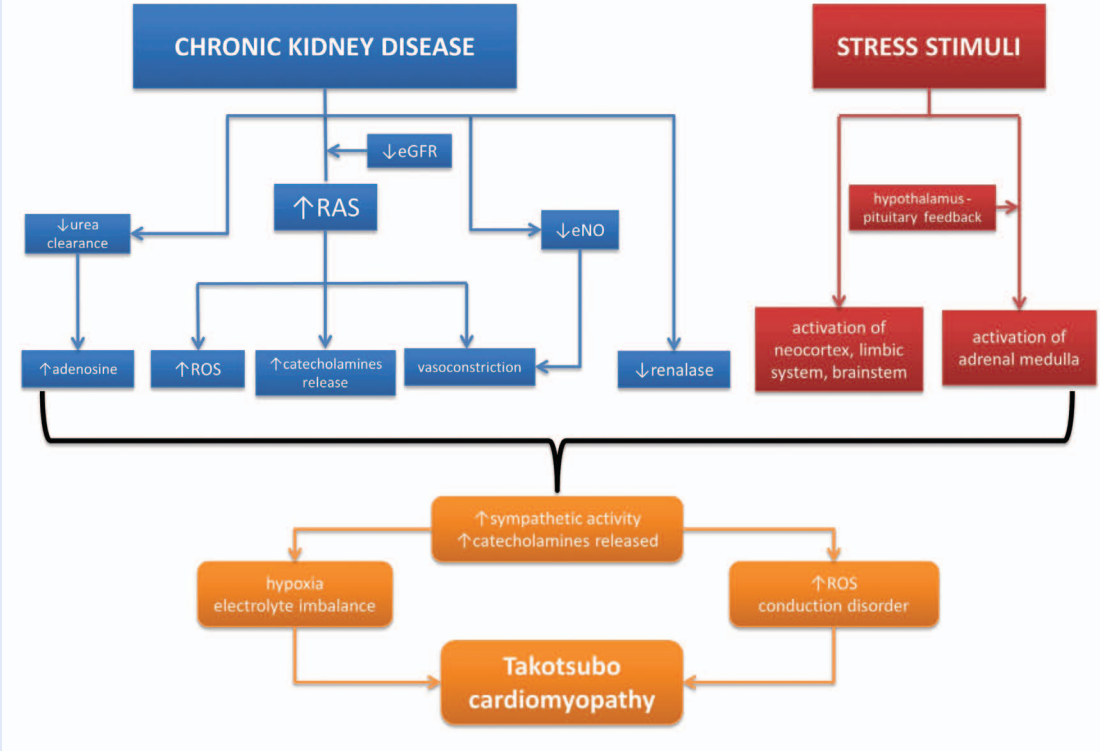

Figure 1. Pathophysiological association of chronic renal failure and stress stimuli for the development of Takotsubo cardiomyopathy.

↑ – increasing, ↓ – decreasing, eGFR – estimated glomerular filtration rate, RAS – renin angiotensin system, eNO – endothelial nitric oxide, ROS – reactive oxygen species.

TCM in patients with CKD is multitopic, resulting from the increased sympathetic activity in the context of renal disease and stressor response. Increased sympathetic activity is a known feature of CKD that occurs for several reasons. The activation of the renin-angiotensin system due to the reduced glomerular filtration leads to a series of cascade reactions with the formation of an end product – angiotensin II, which causes vasoconstriction and which also has an effect on the peripheral sympathetic nervous system by emphasizing the release of catecholamines from neuronal terminals[21]. Also, increased levels of angiotensin II in plasma contributes to excessive production of reactive oxygen species (ROS) and increased central sympathetic outflow[22]. Another important component of increased sympathetic activity in CKD is decreased synthesis or reduced bioavailability of endothelial nitric oxide (eNO). The reasons for this are endothelial dysfunction and/or the unavailability of L-arginine (by binding with the oxygen molecule creates two products; NO and L-citrulline)[23,24]. The central effect of reduced NO levels, demonstrated in an animal in vivo model using NO synthetase inhibitors (NOS), showed increased sympathetic activation with vasoconstrictor activity[25,26]. An additional effect of the kidney on increased activation of the central sympathetic system is the activation of renal baroreceptors and chemoreceptors due to decreased urea clearance and increased production of adenosine in CKD[27,28]. Less than 2 decades ago, a kidney protein encoded by the RNLS gene, renalase, was discovered with an essential role in catecholamine degradation and regulation of sympathetic function. The very mechanism of the opposite action of renalase against catecholamines is still ambiguous[29,30]. Therefore, patients with CKD lose the protective effect of renalase, a defense mechanism against increased catecholamine levels[30,31].

In TCM, the processing of a stress stimulus that the body recognizes as threatening leads to the activation of a number of brain structures that in-

clude the neocortex, limbic system, brainstem, and adrenal medulla with the consequent secretion of catecholamines. The association of the amygdala, hypothalamus, and cingulate gyrus with the locus coeruleus, the major site of secretion and release of catecholamines in the central nervous system (and innervating large segments of the neuroaxis), allows the influence of stress stimuli on the sympathetic response[32]. Connection between the sympathetic nervous system and the adrenal medulla, sympathoadrenal system, sends signals over preganglionic nerve fibers and with the consequent activation of the adrenal glands through acetylcholine. Thus, catecholamines released from the central and autonomic nervous system and from the adrenal glands, reach the heart through the circulation, binding to heart's adrenoceptors and inducing catecholamine toxicity in myocytes[20,33].

The influence of elevated levels of catecholamines, arising through various pathophysiological circuits, on the development of transient LV myocardial dysfunction still remains incompletely elucidated with several proposed hypotheses (figure 1). Increased adrenergic activation of the heart caused by catecholamines, leads to an imbalance in demand and availability of blood supply, the development of hypoxia, an increase in ROS, disturbances in the conduction of electrical potential and consequent imbalance of sodium, potassium and calcium ions. Which of the above mechanisms has dominance over the others or whether it is a completely unknown mechanism of origin remains to be considered[34-36].

Available data on the incidence of TCM in patients with CKD are scarce, counting about 30 reported cases in a review paper by Kariyanna et al in 2018[37].

CONCLUSIONS

Takotsubo cardiomyopathy is often similarly presented to acute coronary syndrome, but with known differences which may serve to differentiate the working diagnosis. The role of catecholamines in the pathogenesis of the disease is unquestionable, but the exact pathophysiological process is still hypothesized. Main aim of this case report was to supplement the scarce literature data on the incidence of Takotsubo cardiomyopathy in patients with chronic kidney disease with reference to the unexplained pathophysiological role of catecholamines.

Disclosures

The abstract of this case report was presented in the form of a poster presentation at the 2nd International Translational Medicine Congress of Students and Young Physicians – OSCON 2020, 13-14th of February 2020. – Osijek, Croatia.

An increased incidence of Takotsubo cardiomyopathy in patients with chronic kidney disease is to be expected due to similar pathophysiological processes leading to catecholamine stress, although a significant number of cases have not been reported in the literature.

Our report is in accordance with the CARE guideline available through the EQUATOR network (http://www.equatornetwork.org/) and COPE guidelines (http://publicationethics.org/).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The informed consent was not obtained due to death of the patient outside the hospital, of unknown cause.

Conflict of interest: Authors declare no conflicts of interest.

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