Takotsubo cardiomyopathy: Pathophysiology and role of cardiac biomarkers in differential diagnosis

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Abstract

Takotsubo cardiomyopathy (TC) is characterized by reversible ventricular dysfunction, not limited to the distribution of an epicardial coronary artery. A disease primarily afflicting post-menopausal women, it is frequently mistaken for acute anterior wall myocardial infarction. Alternatively called Stress Cardiomyopathy, physical or emotional triggers are identified in only three fourths of TC patients. Long considered a benign condition, recent findings suggest poor short term prognosis similar to acute coronary syndrome (ACS). Despite the widely recognized pathophysiological role of catecholamine excess, its diagnostic role is uncertain. TC is suspected based on typical wall motion abnormalities in ventriculogram or echocardiogram. Several additional electrocardiographic, laboratory and imaging parameters have been studied with the goal of clinical diagnosis of TC. While several clinical clues differentiate it from ACS, a clinical diagnosis is often elusive leading to avoidable cardiac catheterizations. Natriuretic peptides (NPs), a family of peptide hormones released primarily in response to myocardial stretch, play a significant role in pathophysiology, diagnosis as well as treatment of congestive heart failure. TC with its prominent ventricular dysfunction is associated with a significant elevation of NPs. NPs are elevated in ACS as well but the degree of elevation is typically lesser than in TC. Markers of myocardial injury such as troponin are usually elevated to a higher degree in ACS than in TC. This differential elevation of NPs and markers of myocardial injury may play a role in early clinical recognition of TC.

Key words: Takotsubo cardiomyopathy; Natriuretic peptide; Brain natriuretic peptide; N-terminal-pro brain natriuretic peptide; Troponin; Cardiac biomarkers; Acute myocardial infarction

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Core tip: Takotsubo cardiomyopathy (TC) characterized by reversible ventricular dysfunction is frequently mistaken for acute anterior wall myocardial infarction often leading to avoidable cardiac catheterizations. While several clinical clues differentiate TC and acute coronary syndrome...
the apical stunning. High level of epinephrine could trigger signal switching of β2AR and apical-basal gradient of β2-adrenergic receptor (β2AR) may explain the apical stunning. High level of epinephrine could trigger signal switching of β2AR from stimulatory G-protein to inhibitory G-protein. Apical myocardium with higher concentrations of β2AR may be more susceptible, compared to basal myocardium leading to apical stunning [9]. The histological changes of TC mirror catecholamine toxicity seen in pheochromocytoma. Loss of cardioprotective action of estrogen against catecholamine excess may explain higher incidence of TC in postmenopausal women. Positron emission tomography (PET) studies have suggested disturbances in glucose and fatty acid metabolism in TC patients [10]. Findings suggestive of coronary vasospasm as well as microcirculatory dysfunction have been described in coronary angiograms of TC patients.

DIFFERENTIAL DIAGNOSIS

ACS is the primary differential diagnosis as both disease states have significant overlap in their clinical presentation. TC is often mistook for acute anterior wall ST elevation myocardial infarction (occlusion of proximal left anterior descending artery). Other differential diagnoses include myocarditis, endogenous catecholamine excess to STEMI and NSTEMI [6].
pheochromocytoma), exogenous catecholamine excess (Cocaine, Amphetamine), peripartum cardiomyopathy and cerebrovascular disease (Japanese guidelines have cerebrovascular disease as exclusionary criteria unlike the commonly used Mayo criteria). Other differential diagnosis for chest pain such as aortic dissection, pulmonary embolism should be considered as well.

### DIAGNOSIS

Several diagnostic criteria including the Modified Mayo\textsuperscript{[11]} and Japanese\textsuperscript{[12]} criteria have been proposed underlining the difficulty in diagnosis of TC. As per the widely used Modified Mayo criteria, all of the following 4 criteria must be met for diagnosing TC: (1) transient hypokinesis, akinesis, or dyskinesis of the LV mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma and myocarditis. Several approaches have been proposed to facilitate differentiating TC from ACS. They include use of laboratory findings [catecholamine levels, cardiac biomarkers, lipid levels and investigational markers such as soluble lectin like oxidized LDL receptor-1 (sLOX-1), Copeptin, ischemic modified albumin (IMA), sST2 (soluble suppression of tumorigenicity-2), etc.], imaging modalities [echocardiography, computed tomography (CT) coronary angiogram, invasive coronary angiogram, cardiac magnetic resonance imaging (CMR), single photon emission computed tomography (SPECT) and PET], EKG findings and risk scores.

### LABORATORY FINDINGS

More studies have focused on laboratory findings due to their universal availability at the time of presentation as well as availability of repeat measurements. Several markers including Copeptin\textsuperscript{[13]}, lipid profile\textsuperscript{[14]}, sLOX-1\textsuperscript{[15]}, IMA\textsuperscript{[16]}, sST-2\textsuperscript{[17]} have been proposed for differentiating TC from ACS. High HDL-C and lower levels of LDL and triglycerides have been reported in TC compared to MI\textsuperscript{[14]}. Forty percent of TC pts had hyperalphalipoproteinemia or hypotriglyceridemia. sLOX-1 elevation has been found comparable to troponin rise in ACS and is lower in non-ACS patients including TC\textsuperscript{[15]}. Changes in level of sST2 have additional predictive value for TC in patients with normal Troponin I\textsuperscript{[17]}. The most studied laboratory findings though are natriuretic peptides (NP), markers of cardiomyonecrosis (troponin I and T, creatine kinase and myoglobin) and catecholamines.

### NP

NP belong to a family of peptide hormones with natriuretic and vasodilatory properties in addition to other pleotropic effects\textsuperscript{[18]}. Atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP) constitute the natriuretic peptide family. Under normal conditions
ANP is primarily released from atria, BNP from both atria and ventricles (ventricles more than atria) and CNP from nervous tissue and vascular endothelium\cite{19,20}. The NPs act via the natriuretic peptide receptors (NPR) NPR-A, NPR-B and NPR-C\cite{18}. ANP and BNP act primarily through NPR-A leading to natriuresis, vasodilation, inhibition of aldosterone synthesis, thirst suppression, sympatholysis and inhibition of release of vasopressin and adrenocorticotropic hormone\cite{18,20}. Additional effects on pulmonary vasculature and airway smooth muscle cells have been described\cite{20}. CNP which has less potent natriuretic effect, acts primarily via NPR-B and modulates vascular tone, cardiac remodeling and proliferation of vascular smooth muscle cells. Primary mechanism of NP clearance is by NPR-C mediated internalization and lysosomal degradation\cite{21}. While ANP was discovered earlier in the 1980s, BNP and amino terminal proBNP (NT-proBNP) - an inactive by-product of BNP formation, have been more widely studied for their role in pathophysiology, diagnosis as well as treatment of heart failure.

**BNP**

BNP is initially produced in the form of preproBNP a 134 amino acid (AA) peptide. Cleavage of the 26 AA signal peptide forms the proBNP which is further cleaved by enzyme Corin into active 32 AA BNP and inactive 76 AA amino terminal proBNP (NT-proBNP). BNP has a short half-life (about 20 min) and is cleared by neutral endopeptidase (Neprilysin) and by NPR-C mediated clearance. NT-proBNP has a longer half-life (120 min) and is cleared renally\cite{22}. Use of neprilysin inhibitor (sacubitril) increases BNP levels by inhibiting its clearance but does not affect clearance of NT-proBNP\cite{23}. Upper limit of normal in the non-acute setting is 35 pg/mL for BNP and 125 pg/mL for NT-proBNP\cite{24}. In acute setting, higher cut-off values are recommended (BNP < 100 pg/mL and NT-proBNP < 300 pg/mL)\cite{24}. In the Breathing Not Properly trial, BNP < 100 pg/mL had a high diagnostic accuracy of 83.4% to distinguish other causes of dyspnea from heart failure\cite{25}. The PRIDE (ProBNP Investigation of Dyspnea) study proposed an age based cut-off for NT-proBNP (> 450 pg/mL for age < 50, > 900 pg/mL for age > 50) for diagnosing HF and < 300 pg/mL for ruling out CHF\cite{26}. International Collaborative of NT-proBNP (ICON) study, a pooled analysis recommended a cut off of > 1800 pg/mL for age > 75\cite{27}. Asians and african americans have higher levels compared to caucasians and hispanics\cite{28}. Obese patients tend to have lower levels and heart failure with preserved ejection fraction (HfEF) patients have levels lower than heart failure with reduced ejection fraction (HFrEF) patients\cite{29,30}. Causes of BNP and NT-proBNP elevation include cardiac causes such as heart failure, ACS, valvular heart disease, pericardial diseases, atrial fibrillation, myocarditis, and cardioversion and non-cardiac causes such as advancing age, anemia, renal failure, pulmonary diseases, critical illness, sepsis, burns, etc\cite{31}.

**NP in TC**

Reversible LV dysfunction without significant myocardial ischemia and or necrosis is the hallmark of TC, leading to significant elevation of NP. Among TC patients, the classic form of TC with basal hyperkinesis and apical ballooning appears to have higher degree of NP elevation compared to the basal (inverted) variant\cite{8}. BNP has been correlated with the degree of basal hyperkinesis, measured by iBase (difference between end systolic and end diastolic dimension of the LV base measured 10 mm below aortic valve)\cite{31}. NT-proBNP levels rise within first 24 h after the onset of symptoms with slow and incomplete resolution during the 3 mo thereafter\cite{32}. NT-proBNP levels have been shown to correlate with plasma catecholamine levels and the severity of LV dysfunction, as measured by the wall motion score index and LV ejection fraction\cite{32}.

**Myonecrosis markers in TC**

With lack of significant myonecrosis, TC patients usually have lesser degree of elevation of cardiac myonecrosis markers such as myoglobin, creatine kinase and troponin when compared to ACS patients. Studies comparing TC with anterior ST elevation myocardial infarction (STEMI) showed significantly lower mean peak troponin T levels in TC patients\cite{33}. Some studies suggested threshold values for troponin to rule out TC while other studies contradicted it. Ramaraj et al\cite{34} found troponin T > 6 ng/mL or troponin I > 15 ng/mL were unlikely in TC but Song et al\cite{35} found about 20% of patients included in their study of TC patients had troponin I > 15 ng/mL. Among TC patients, inverted (basal) type TC patients tend to have higher elevation of myonecrosis markers\cite{36}.

**Relative elevation of NP and Myonecrosis markers in TC**

Comparing TC to STEMI, Madhavan et al\cite{37} found lower troponin (0.62 ng/mL vs 3.8 ng/mL), higher BNP (944 pg/mL vs 206 pg/mL) but no significant differences in plasma normetanephrine, metanephrine, cortisol or hs-CRP levels. Fröhlich et al\cite{38} found NT-proBNP (ng/L)/myoglobin (μg/L) ratio of 3.8, distinguished TC from STEMI, while a NT-proBNP (ng/L)/myoglobin (μg/L) ratio of 14, distinguished TC from NSTEMI. NT-proBNP (ng/L)/TnT (μg/L) ratio of 2889, distinguished TC from STEMI, while a NT-proBNP (ng/L)/TnT (μg/L) ratio of 5000 distinguished TC from NSTEMI. NT-proBNP levels usually peaked 22 to 26 h after a cardiac event, whereas TnT levels peaked 8 to 13 h after the first manifestation of chest pain. In a study of 52 patients with TC, Lahoti et al\cite{39} found higher NT-proBNP/troponin T in TC than in ACS patients (5154 vs 183). Peak BNP/peak troponin ratio > 2500 yielded a 90% sensitivity and specificity for TC.

Randhawa et al\cite{40} compared 58 patients and 97 acute myocardial infarction patients and found early
BNP/TnT and BNP/CKMB ratios help to differentiate TC from AMI with greater accuracy than BNP alone. Median BNP/TnT and BNP/CKMB ratios were, respectively, 1292 and 28.44 in the TC group and 226.9 and 3.63 in the AMI group. TC was distinguished from AMI with 95% specificity with the use of BNP/TnT ratio of $\geq 1272$ (sensitivity 52%) with area under the curve (AUC) of 0.822 and BNP/CKMB ratio $\geq 29.9$ (sensitivity 50%) with AUC of 0.862. When QT prolongation was combined with BNP/CKMB, the AUC was even higher (Figure 1). Doyen et al. found TnI elevations in TC comparable to anterior NSTEMI but lower than anterior STEMI, earlier peaking of troponin in TC than ACS (6 h vs 12 h) and higher BNP/TnI ratio (642) than anterior NSTEMI (184.5) or anterior STEMI (7.5). BNP/TnI ratio showed high area under the curve (AUC) in receiver operating characteristic (ROC) analysis. The AUC for TC vs STEMI was 0.98 (0.94 to 0.99) and TC vs NSTEMI was 0.81 (0.72 to 0.88) (Figure 2). The InterTAK registry study group compared matched cohorts of 455 TC (out of 1750 TC patients in InterTAK registry) and 455 ACS patients. Median troponin levels in TC were not significantly different from ACS but CK and BNP levels were significantly different.

InterTAK Diagnostic Score

InterTAK Diagnostic Score was developed using a derivation cohort with TC patients recruited from the International Takotsubo Registry and ACS patients from a Zurich hospital (TC, $n = 218$; ACS, $n = 436$). The score has seven variables each with an assigned score value: Female sex 25, emotional trigger 24, physical trigger 13, absence of ST-segment depression (except in lead aVR) 12, psychiatric disorders 11, neurologic disorders 9, and QTc prolongation 6 points. A cut-off value of 40 score points yielded a sensitivity of 89% and specificity 91%. With a score of $\geq 50$, nearly 95% of TC patients were correctly diagnosed and with a score $\leq 31$, approximately 95% of ACS patients were diagnosed correctly. The score was subsequently validated in an independent validation cohort (TTS, $n = 173$; ACS, $n = 226$).

While several studies have reported higher levels of NPs in TC and higher troponin in ACS, utilizing ratio of NP to troponin, CKMB or myoglobin to differentiate TC from ACS in clinical practice is more complicated. As discussed earlier the cut off values used in different studies varied widely (Table 2). In general the ratio is higher for TC than ACS and among ACS the ratio is higher for NSTEMI compared to STEMI. The use of different markers for myonecrosis - troponin I and T, CKMB or myoglobin as well as ventricular stretch - BNP or NT-proBNP in different studies affects the wider applicability. Also, most of the studies used peak troponin and or NP levels instead of levels at presentation, which limits the utility of this ratio in avoiding cardiac catheterizations in acute settings. In addition, all these studies were retrospective. The InterTAK score derived from a large cohort study did not include cardiac biomarkers. In the derivation cohort, while the CK was higher in ACS patients and BNP higher in TC patients, the troponin levels were surprisingly higher in TC patients (6.67 × ULN) compared to ACS.
patients (3.75).

**Catecholamines**

With catecholamine excess thought to underlie the pathogenesis of TC, several studies have looked at catecholamine measurements with mixed results. Nguyen et al.\(^{[37]}\) reported correlation of peak NT-proBNP levels in TC patients with simultaneous plasma normetanephrine levels as well as LV ejection fraction. On the contrary Madhavan et al.\(^{[36]}\) found significantly higher elevation of BNP in TC patients compared to STEMI patients but similar plasma normetanephrine, metanephrine and cortisol levels. In their study majority of TC patients had normal 24-h urine metanephrines, catecholamines and cortisol.

**IMAGING**

Echocardiographic findings in TC include reversible wall motion abnormalities extending beyond distribution of an epicardial coronary artery, basal hyperkinesis, LVOT obstruction, reversible MR and RV dysfunction. Reverse Mcconnell’s sign with RV basal hyperkinesis and hypokinesis of RV apex has been described in TC\(^{[41]}\). Common coronary angiogram findings include absence of ruptured plaque or obstructive coronary artery disease. Coronary vasospasm with provocative maneuvers as well as delayed filling has been reported in TC patients. Ventriculogram often demonstrates the typical takotsubo-like shape. Microcirculatory dysfunction has been demonstrated in TC using index of microvascular resistance\(^{[42]}\). CMR findings include enhancement in T2-weighted images representing myocardial edema in the hypocontractile segments during acute phase and absence of first-pass perfusion hypoenhancement\(^{[43]}\). Evidence of late gadolinium enhancement (LGE) findings in TC are conflicting. Some studies suggest absence of LGE differentiates TC from ACS and myocarditis while other studies have reported reversible LGE in TC, if CMR is done in acute phase (< 72 h)\(^{[44,45]}\). Reduction of fatty acid metabolism during acute phase has been reported using \(^{123}\text{I}\)-\(\beta\)-methyliodophenylpentadecanoic acid (BMIPP) imaging\(^{[46]}\). Reduced intramyocardial uptake during \(^{123}\text{I}\)-metaiodobenzylguanidine (MIBG) imaging suggests sympathetic denervation\(^{[46]}\). A reverse perfusion metabolism mismatch in PET with normal perfusion and reduced \(^{18}\text{F}\)-fluoro deoxyglucose (FDG) uptake has been described in TC patients\(^{[41]}\).

**ELECTROCARDIOGRAM**

Several EKG criteria have been proposed to help differentiate TC from ACS. These include lack or rarity of reciprocal ST depression, widespread T wave inversion, low QRS voltage on presentation, attenuation of QRS voltage in serial EKGs, QTc prolongation, frontal plane ST vector, ST segment elevation (STE) in aVR without STE in V1, lower rate of Q-waves, more frequent STE in the inferior leads, ratio of the sums of STEs in leads V4-V6 to the sums of STEs in leads in V1-V3, lower amplitude of STE (< 1.5 mm) and a summated amplitude of the S-wave in V1 plus the R-wave in V6 < 1.5 mV\(^{[47,48]}\). While these EKG findings could have additive value in diagnosis of TC, their diagnostic accuracy for TC diagnosis have been found wanting in some studies\(^{[49,50]}\).

**CONCLUSION**

TC presents a diagnostic challenge by virtue of its similarity in clinical presentation with anterior wall STEMI. The different pathophysiology underlying these two processes leads to a differential degree of elevation in NP and troponin with NP relatively higher in TC and troponin relatively higher in STEMI. While conceptually sound, the use of various assays (BNP vs NT-proBNP, Troponin I vs Troponin T) and wide range in elevation of NPs and Troponin with significant overlap in these two conditions, limits the diagnostic utility of ratio of NPs and troponin. Use of uniform assays for NP and myonecrosis markers and larger trials could pave the way for wider use of NP/troponin ratio in clinical decision making in future.

**REFERENCES**

1. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to...
multivessel spasm. In: Kodama K, Haze K, Hon M, editors. Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure. Tokyo: Kagakuyaoraryousha, 1990: 56-64.

2 Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of Takotsubo cardiomyopathy in the United States. Am Heart J 2012; 164: 66-71.e1 [PMID: 22795284 DOI: 10.1016/j.ahj.2012.03.020]

3 Khera R, Light-McGroary K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for takotsubo cardiomyopathy in the United States. Am Heart J 2016; 172: 53-63 [PMID: 26856216 DOI: 10.1016/j.ahj.2015.10.022]

4 Tempelin C, Ghahdi JR, Diekmann J, Nimmagadda KC, Nagrani T, Naqi M, Wetz RV, Weisbergs LF, McCord D, Ghavami F, Gala B, Lafferty JC. Serum lipoprotein levels in takotsubo cardiomyopathy vs. myocardial infarction. KF, McCord D, Ghavami F, Gala B, Lafferty JC. Serum lipoprotein levels in takotsubo cardiomyopathy vs. myocardial infarction. Int Arch Cardiol 2011; 4: 14 [DOI: 10.1186/1755-7682-4-14]

15 Kobayashi N, Hata N, Kume N, Shinada T, Tomita K, Shirakabe A, Kitamura M, Nozaki A, Inami T, Seino Y, Mizuno K. Soluble lectin-like oxidized LDL receptor-1 and high-sensitivity troponin T as diagnostic biomarkers for acute coronary syndrome. Improved values with combination usage in emergency rooms. Circ J 2011; 75: 2862-2871 [PMID: 21937834]

16 Zhong Y, Wang N. Other diagnostic methods with high sensitivity can be used to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. Int J Cardiol 2016; 222: 1068 [PMID: 26837863 DOI: 10.1016/j.ijcard.2015.10.024]

17 Yang IS, Kim HJ, Shin HJ, Kim SJ, Hur M, Di Somma S. GREAT Network. Soluble ST2 and troponin I combination: Useful biomarker for predicting development of stress cardiomyopathy in patients admitted to the medical intensive care unit. Heart Lung 2015; 44: 282-288 [PMID: 26077669 DOI: 10.1016/j.heur.2015.04.010]

18 Wilkins MR, Redondo J, Brown LA. The natriuretic peptide family. Lancet 1997; 349: 1307-1310 [PMID: 9142076 DOI: 10.1016/S0140-6736(06)9427-7]

19 Pucci A, Wharton J, Arbustini E, Grassos M, Dioglio M, Needleman P, Viganò M, Mosconi G, Polak JM. Localization of brain and atrial natriuretic peptide in human and porcine heart. Int J Cardiol 1992; 34: 237-247 [PMID: 1532953]

20 Calzetta L, Orlandi A, Page C, Rogliani P, Rinaldi B, Rosano G, Cazzola M, Matera MG. Brain natriuretic peptide: Much more than a biomarker. Int J Cardiol 2016; 221: 1031-1038 [PMID: 27447810 DOI: 10.1016/j.ijcard.2016.07.109]

21 Potter JR. Natriuretic peptide metabolism, clearance and degradation. FEBS J 2011; 278: 1808-1817 [DOI: 10.1111/j.1742-4658.2011.08082.x]

22 Woodard GE, Rosado JA. Recent advances in natriuretic peptide research. J Cell Mol Med 2007; 11: 1263-1271 [DOI: 10.1111/j.1749-4934.2007.00125.x]

23 Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL, Swedberg K, Desai AS, Gong J, Shi VC, Solomon SD. Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. J Am Coll Cardiol 2016; 68: 2425-2436 [PMID: 27908347 DOI: 10.1016/j.jacc.2016.09.931]

24 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-2200 [PMID: 27206819 DOI: 10.1093/eurheartj/ehw128]

25 Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollandier JE, Due P, Omland T, Storrow AB, Abraham WT, Wu AH, Cleopat P, Stegg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347: 161-167 [PMID: 12124404 DOI: 10.1056/NEJMoa020233]

26 Januzzi JL, Camargo CA, Anwaruddin S, Bagghis AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chau CE, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB. The N-terminal Pro-BNP investigation of dyspea in the emergency department (PRIDE) study. Am J Cardiol 2005; 95: 948-954 [PMID: 15820160 DOI: 10.1016/j.amjcard.2004.12.032]

27 Januzzi JL, van Kinmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalbo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006; 27: 330-337 [PMID: 16293638 DOI: 10.1093/eurheartj/eh6361]
Diagnostic utility of cardiac biomarkers in discriminating Takotsubo cardiomyopathy from acute myocardial infarction. *J Card Fail* 2014; 20: 377.e25-377.e31 [PMID: 25089311]

30 Deyoen D, Molceri P, Chiico O, Schwour E, Curboni P, Chaussee C, Mansencal N, Ferrari E. Cardiac biomarkers in Takotsubo cardiomyopathy. *Int J Cardiol* 2014; 174: 798-801 [PMID: 24794960 DOI: 10.1016/j.ijcard.2014.04.120]

31 Ghadri JR, Carmann VL, Jurisic S, Seifert B, Napp LC, Dieckmann J, Bataisoa DR, D’Asencio F, Ding KJ, Sarcon A, Kazemian E, Birri T, Ruschitzka F, Lüscher TF, Tempelin C; InterTAK co-investigators. A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry. *Eur J Heart Fail* 2016 [PMID: 27928880 DOI: 10.1002/ejhf.683]

32 Liu K, Carhart R. “Reverse McConnell’s sign”: a unique right ventricular feature of Takotsubo cardiomyopathy. *Am J Cardiol* 2013; 111: 1232-1235 [PMID: 23558000 DOI: 10.1016/j.amjcard.2012.12.007]

33 Warisawa T, Naganuma T, Nakamura S. Reversible Microvascular Dysfunction in Takotsubo Syndrome Shown Using Index of Microcirculatory Resistance. *Circ J* 2016; 80: 750-752 [PMID: 26794154 DOI: 10.1253/circj.CJ-15-1283]

34 Ono R, Falcão LM. Takotsubo cardiomyopathy systematic review: Pathophysiological process, clinical presentation and diagnostic approach to Takotsubo cardiomyopathy. *Int J Cardiol* 2016; 209: 196-205 [PMID: 26896623 DOI: 10.1016/j.ijcard.2016.02.012]

35 Larousbigoitza Zaldumbide E, Pérez-David E, Larena JA, Velasco del Castillo S, Rumoroso Cuevas JR, Onaindia JJ, Lekuona Goya I, Garcia-Fernandez MA. The value of cardiac magnetic resonance in patients with acute coronary syndrome and normal coronary arteries. *Rev Esp Cardiol* 2009; 62: 976-983 [PMID: 19712618]

36 Avgeliano G, Huguet M, Costabel JP, Ronderos R, Bjibens N, Kuschpin P, Thierer J, Tobón-Gómez C, Martínez GO, Frangi A. Morphologic pattern of late gadolinium enhancement in Takotsubo cardiomyopathy detected by early cardiovascular magnetic resonance. *Clin Cardiol* 2011; 34: 178-182 [PMID: 21400545 DOI: 10.1002/clc.20877]

37 Yoshikawa T. Takotsubo cardiomyopathy, a new concept of cardiomyopathy: clinical features and pathophysiology. *Int J Cardiol* 2015; 182: 297-303 [PMID: 25585367 DOI: 10.1016/j.ijcard.2014.12.116]

38 Looi JL, Wong CW, Lee M, Khan A, Webster M, Kerr AJ. Usefulness of ECG to differentiate Takotsubo cardiomyopathy from acute coronary syndrome. *Int J Cardiol* 2015; 199: 132-140 [PMID: 26188834 DOI: 10.1016/j.ijcard.2015.07.046]

39 Madias JE. Transient attenuation of the amplitude of the QRS complexes in the diagnosis of Takotsubo syndrome. *Eur Heart J Acute Cardiovasc Care* 2014; 3: 28-36 [PMID: 24562801 DOI: 10.1177/2048872613504311]

40 Vervaat FE, Christensen TE, Smeijers L, Holmvang L, Hashab P, Szabó BM, Widdershoven JW, Wagner GS, Bang LE, Gorgels AP. Is it possible to differentiate between Takotsubo cardiomyopathy and acute anterior ST-elevation myocardial infarction? *J Electrocardiol* 2015; 48: 512-519 [PMID: 25818746 DOI: 10.1016/j.jelectrocard.2015.02.008]

41 Johnson NP, Chavez JF, Mosley WJ, Flaherty JD, Fox JM. Performance of electrocardiographic criteria to differentiate Takotsubo cardiomyopathy from acute anterior ST elevation myocardial infarction. *Int J Cardiol* 2013; 164: 345-348 [PMID: 21802749 DOI: 10.1016/j.ijcard.2011.07.029]
