

Review Article

Takotsubo Syndrome and the Devil's Advocate

John E. Madias*

MD, FACC, FAHA, Icahn School of Medicine at Mount Sinai, New York, NY, and the
Cardiology Department, Elmhurst Hospital Center, Elmhurst, NY, USA

*Corresponding author

John E. Madias, MD, FACC, FAHA, Icahn School
of Medicine at Mount Sinai, New York, NY, and
the Cardiology Department, Elmhurst Hospital
Center, Elmhurst, NY, USA

Received: 22-07-2026, **Accepted:** 23-08-2026,
Published: 28-08-2026

Copyright: © 2026 John E. Madias. Distributed
under Creative Commons CC-BY 4.0

Citation: Madias JE. Takotsubo Syndrome and the
Devil's Advocate. J Clin Res Cardiol Cardiovascul
Med. 2026 August 23; 1(1): 11.

Abstract

Aim: The objective of this piece is to stir rethinking about what we all have considered as established, possible, impossible, probable and improbable, about TTS and its pathophysiology and management.

Review: This communication is based on two currently published articles on takotsubo syndrome (TTS), and all its relevant literature, deliberately adopting the skeptic/critical approach of “devil's advocate” in response to their content, exercising a self-free association mode of thinking about many of the particulars of this still elusive malady, as discussed in the two articles and also currently reflected in the literature.

Result: Many, but not all of the particulars of this still elusive malady are explored in free-associating about all aspects of TTS.

Conclusion: What we all have considered as established, possible, impossible, probable and improbable, about TTS and its pathophysiology may need re-exploration. New, “in-box” and “out-of box” ideas may need to be pursued. To this end the present communication may be of value, by prompting us all, clinicians and investigators, to self-brainstorm examining as many as possible associations about the demographic, genetic, familial, and comorbid underpinnings, pathophysiology, diagnosis, and therapy of TTS.

Keywords: Takotsubo syndrome; diagnosis of takotsubo syndrome; pathophysiology of takotsubo syndrome; management of takotsubo syndrome

Abbreviations and Acronyms: ACS: Acute Coronary Syndromes; AF: Atrial Fibrillation; AMI: Acute Myocardial Infarction); ASNS: Autonomic Sympathetic Nervous System; BNP: Brain Natriuretic Peptides; BP: Blood Pressure; CAD: Coronary Artery Disease); CANG: Coronary Angiography; CMD: Coronary Microvascular Dysfunction; cMRI: cardiac Magnetic Resonance Imaging; ECG: Electrocardiogram; ECHO: Transthoracic Echocardiogram; CO: Cardiac Output; HCM: Hypertrophic Cardiomyopathy; CS: Cardiogenic Shock; HF: Heart Failure; LGE: Late Gadolinium Enhancement; HR: Heart Rate; LV: Left Ventricle; LVGram: Left Ventricular Angiography; LVEDP: Left Ventricular End Diastolic Pressure; LVOTO: Left Ventricular Outflow Tract Obstruction; MINOCA: Myocardial Infarction with Nonobstructive Coronary Arteries); MR: Mitral Regurgitation; POCUS: Point of Care Ultrasound; RV: Right Ventricle; RWMA: Regional Wall Motion Abnormalities); SCAD: Spontaneous Coronary Artery Dissection; SVR: Systemic Vascular Resistance; TTS: Takotsubo Syndrome; VAC: Ventricular-Arterial Coupling

Preamble

This constitutes an introductory statement explaining the aims and the justification of attempting to “free associate” on the positions taken by a recent publication [1] on all the particulars of takotsubo syndrome (TTS); indeed, the positions taken reflect the composite of statements and elaborations contained in the literature on TTS, a large fraction of which as of 8/27/26, consists of 8,025 reports in PubMed, accessed in response to the MeSH search term “takotsubo” [2]. As an example, it has almost become a cliché to refer to a big list of plausible pathogenetic mechanisms of TTS, which in isolation or in concert are responsible for its causation. Similarly, the position often taken by all authors on the management of TTS is that our approach as treating physicians

should be to implement supportive therapy, while awaiting specially-designed randomized controlled trials (some of them concluded, or currently ongoing and recruiting patients) [1], to provide the necessary scientific justification for our therapeutic actions. Another stimulus for this composition has been spurred by the reviewing the literature in preparation for a recently published opinion paper [3], on the “ventricular-arterial coupling” characteristics of TTS. Of course, one cannot claim that the following associative self-brainstorming exercise, resulting in arguments and counterarguments about TTS, is all inclusive. It should be stressed in the outset that this is not a comprehensive narrative review of TTS, in the mold of prior such works [1]. Nevertheless, the objective of this communication is to stir exploratory thinking among clinicians and researchers, engaged in the recognition and management of TTS and elucidation of its pathophysiology.

Methodology

The approach used in the writing of this communication was based on the author's a self-brainstorming or "free association" in response to the content of the aforementioned two papers [1,3] and the literature [2], expressing random thoughts in the form of arguments and counterarguments, presented as "bullet-like" numbered (for easy reference) unassociated statements, thus drastically deviating from the sequential logical and scientific reporting format, employed in conventional publications. The reason that these free-standing statements were not grouped under subheadings (e.g. "Diagnosis of TTS", "Therapy of TTS", "Pathophysiology of TTS", etc), is that it was meant to enumerate them in sequence as they occurred to the author, while he was reading the above cited recently published comprehensive review paper on all aspects of TTS [1]; the reader is also prompted to engage in free-association about the content of the present communication, so that his/her experience retains the format of self-brainstorm. Such an exercise is characterized by "jumping" on issues pertaining to therapy while reading about diagnosis, or diverting from diagnosis to the pathophysiology of a disease entity. Finally, for maximal benefit the reader is encouraged to study the 2 referenced papers [1,3], before reading what follows.

A non-all-inclusive list of arguments and counterarguments about TTS

- 1] Although it is stated that TTS accounts for ~2-3% of suspected acute coronary syndromes (ACS), association of the former with myriads of comorbidities and consideration of milder "focal" morphological variants at imaging, TTS is a highly underdiagnosed illness.
- 2] The belief that ~90% of patients with TTS are women is currently challenged by the frequent encounter of male patients, particularly in association with a large variety of medical and surgical comorbidities, and other physical stresses.
- 3] Pediatric cases of TTS are being frequently reported in the literature; this reality has been obscured by the recruiting of patients ≥ 18 years old with TTS in the leading registries.
- 4] Diagnostic criteria of TTS have initially excluded patients with coronary artery disease (CAD) at coronary angiography (CANG), acute myocardial infarction (AMI), pheochromocytoma/paraganglioma, and spontaneous coronary artery dissection (SCAD), subsequently partially corrected in the revised criteria; along this line one wonders why we cannot also accept myocarditis, as a comorbidity of TTS.
- 5] The currently prevailing notion is that we need controlled randomized trials, specifically designed for the management of TTS, which nowadays consists of supportive therapies designed for patients with CAD, ACS, and heart failure (HF). It is conceivable that TTS is a form of segmental myocardial stunning, not unlike the one seen in ACS, AMI, following a relatively brief episode of variant (i.e., Prinzmetal's) angina, and/or catecholamine-induced cardiomyocyte toxicity. Accordingly, our contemporary pharmacological and device-based armamentarium may be adequate for the management of patients with TTS.
- 6] It may be of value to consider that the diagnosis of TTS is often made with considerable delay (particularly in "secondary TTS"), and thus by the time TTS is the established diagnosis, the innate healing process is already underway.
- 7] The issue of "stress" in TTS should be viewed in the context of the ideas of Hans Selye, the Father of stress field, who emphasized the concept of "nonspecificity" and thus a stereotyped body stress response to the emotional/physical/negative/positive stresses of life. Along this line of thought the differentiation of physical vs. emotional stresses may be meaningless, because none of the above is devoid of the other. Also, the notion that for 30% of the patients with TTS no stress triggers can be identified may not be correct, considering that "stress" is a very subjective/personal matter, often not communicated to others by the sufferer.
- 8] Work by Hans Selye revealed that stress in general has a profound effect on the gastrointestinal system, the thymus gland, and the spleen, expressed as shrinkage of these organs, and an increase in the volume of adrenals. Along this line of thought it may be of value to evaluate by imaging, changes in the volumes of thymus, spleen, and adrenals, as indices of the intensity of the stress that led to TTS.
- 9] Although TTS is associated with older and/or postmenopausal women, younger women are often afflicted in the setting of pregnancy, perinatal period comorbidities, malignancies, chemotherapy, SCAD, and gynecological/neurological/psychiatric maladies.
- 10] Microvascular dysfunction, nitrosative stress, metabolic dysregulation, catecholamine-induced lipotoxicity, myocardial and systemic inflammation, oxidative stress, among others, are often cited as triggers/pathogenetic mechanisms of TTS. It is conceivable that many of the above may constitute epiphenomena, following TTS' emergence. An indication of this is the occurrence of TTS in some otherwise healthy individuals and even adolescents and very young children, not expected to harbor these predisposing traits. Also, C-reactive protein (an index of systemic inflammation) is normal/mildly elevated in patients with TTS at admission, and its subsequent elevation suggests that it represents a consequence of TTS. Finally, something needing evaluation is whether all these purported triggers of TTS are/are not also present in patients with ACS and AMI, and to what degree.
- 11] It has been theorized that TTS is either a protective cardiocirculatory phenomenon [1] to avert fatal ventricular arrhythmias or a maladaptive response to stress; however, it could be both to varying degrees in different patients.
- 12] The abrupt onset of TTS may imply that it may be due to a transient segmental coronary vasospasm of some epicardial vessels, or rather their corresponding coronary microvasculature and/or regional cardiomyocyte catecholamine toxicity due to an unbridled autonomic sympathetic nervous system (ASNS) seethe with norepinephrine spillover, and induced outpouring of epinephrine by the adrenals [1,3].
- 13] In spite of TTS' reputed formal description in 1990, as

a transient segmental myocardial mechanical systolic hypokinesis/akinesis/dyskinesis, in the absence of obstructive CAD, it has always been with us and the animal kingdom, shown in experimental laboratory work and in the clinical domain before 1990, and connected to high adrenergic states or infusion of catecholamines.

- 14] One wonders whether a large proportion of what is currently called AMI with nonobstructive CAD (MINOCA) are not cases of TTS, particularly in MINOCA without detectable persisting regional wall motion abnormalities (RWMA) or late gadolinium enhancement (LGE), in follow-up testing with cardiac magnetic resonance imaging (cMRI).
- 15] Persisting RWMA, evidence of regional myocardial necrosis, and ventricular aneurysm, should not be considered incompatible with TTS. Indeed, such occurrences may point to unusually persisting pathogenetic actions of what has precipitated TTS, which may/may not represent anything different from the state of stunned myocardium seen in ACS or AMI.
- 16] Persisting LGE should not be considered incompatible with TTS. Indeed, there are reported cases of TTS with persisting electrocardiogram (ECG) ST-segment elevation, akinetic/dyskinetic myocardial regions, full left ventricular (LV) transmural scars, associated with interventricular and left ventricular (LV) free wall rupture, and death.
- 7] Considering the association with emotional stress (both negative and positive), physicians may consider proactively prescribing anxiolytics and β -blockers for patients both experiencing, or possibly expected to experience, emotional stress (i.e., bereavement, reunions).
- 18] The occasional emergence of TTS in the setting of anesthesia, surgery, and invasive procedures (e.g. ablation of atrial fibrillation [AF]), should prompt physicians to consider proactively initiating intravenous infusions of short half-life β -blockers for patients suffering hypertension, angina, ventricular arrhythmias or AF. Such infusions could be terminated in response to HF, bradycardia or heart blocks with impunity, due to the short half life (i.e., 3-9 min) of the employed β -blockers.
- 19] Recurrence of TTS is underdiagnosed if one considers that many patients evaluated for their index TTS episodes, have already suffered previously TTS with clinical episodes erroneously attributed to AMI, ACS, or CAD, or at follow-up many years after an index TTS episode.
- 20] The recent seemingly increasing rate of TTS triggered by physical stress may be due to the increasing recognition of TTS associated with other comorbidities (i.e., “secondary TTS”).
- 21] The recent seemingly increasing age of patients suffering TTS may be a reflection of the increasing human lifespan.
- 22] Changes in the incidence/prevalence of TTS as reflected in the reported literature is partially influenced by publication biases (i.e., “file drawer problem”), the nonpublication of many cases of TTS), that are continuously changing.
- 23] A seemingly increasing rate of the midventricular variant of TTS may be partially due to the “looseness” in including in reports of this variant the “apical/midventricular” combination phenotype.
- 24] Delving in the consequences of episodes of proven variant (Prinzmetal’s) angina (e.g., troponin release, RWMA at imaging, and their persistence), might be instrumental in deciphering the pathophysiology of TTS. I am referring herein to episodes lasting 20-30 min, and their clinical aftermath. There are reports of patients with angina/dyspnea episodes triggered by stress, who were asymptomatic by the time they reached the hospital, and who showed all the hallmarks of TTS. One wonders whether such episodes are due to diffuse coronary vasospasm or intense catecholamine toxicity, or both.
- 25] Serial uptrending vs. downtrending of high sensitivity troponin values may suggest a different stage of the clinical course (i.e., hyperacute vs. acute) of TTS.
- 26] Selective coronary epicardial and/or microvascular spasm based on ASNS/catecholamine-mediated stimulation of β_1 -, β_2 -, and α_1 -adrenergic receptors should be the subject of further contemplation, as viable pathogenetic hypotheses of TTS. Such mechanisms are not incompatible with the morphological TTS variants of reverse and midventricular TTS, if one assumes that spasm could be multi-site and selective, depending on the different types of adrenergic receptors, their topographic distribution, density, and sensitivity to various catecholamines.
- 27] Dynamic left ventricular outflow tract obstruction (LVOTO), particularly early in the clinical course of TTS, should be considered not as an occasional complication of the disease, but as a possible pathogenetic mechanism ushering the emergence of TTS. Indeed, it is advisable to evaluate for LVOTO, not via the initial formal transthoracic echocardiogram (ECHO) or CANG, but with early and frequent implementation of point of care ECHO (POCUS), using targeted portable or even hand-held ECHO devices, and auscultation for associated mitral regurgitation (MR), particularly in patients with hypotension, HF, and cardiogenic shock (CS).
- 28] Since estrogen deficiency and the post-menopausal state are associated with TTS, one wonders whether the use of reduced-dose estrogen supplementation may have a role in preventing TTS recurrence.
- 29] It is crucial that information is sought, recorded, and reported about the exact time of the onset of symptoms in patients with suspected/proven TTS.
- 30] During the early clinical stage of proven/suspected TTS, as assessed by the history and uptrending troponins, close monitored infusions of short-, or ultrasort β -blockers may be of value. This is imperative in the presence of LVOTO. Such infusions can easily be terminated without consequences, if bradycardia, heart blocks, or signs of HF arise.
- 31] It may be of value to resurrect measuring catecholamines (norepinephrine, epinephrine, and dopamine, and their

metabolites in plasma and urine), as was done early after the formal description of TTS. Uptrending or downtrending of catecholamine values may reflect the acuteness of the TTS clinical stage, and whether the process is acutely evolving or subsiding. In the first case one could advocate employing intravenous short-half-life β -blockers. Also, it is conceivable that there is an association between the rise of specific catecholamines and the TTS morphological variants.

- 32] Although one could evaluate once the peripheral ASNS state in the setting of TTS during hospitalization with electroneuromyography, it may be advantageous to adopt a monitoring technique of evaluating continuously or serially, the ASNS's cardiac input via thoracic electrical signals (i.e., a surrogate of stellate ganglia's neural input to the heart) by subjecting the routine electrocardiogram (ECG)-acquired signals to a 500-1,000 Hz analysis, a technique pioneered by Dr. Peng-Sheng Chen.
- 33] Heart rate variability, even deriving from short ECG recordings, should be serially and systematically evaluated in patients admitted with TTS, during hospitalization and at follow-up, for its diagnostic and prognostic value.
- 34] Pheochromocytoma should be suspected in patients admitted with suggestive symptomatology and eventually diagnosed with TTS. Many such patients are diagnosed after repeated admissions, and even after recurrent TTS.
- 35] All physicians, other members of medical teams, dentists, rehabilitation and nursing home facilities, and the public at large, should be familiar about the nosogenic potential of both negative and positive ("happy heart syndrome") stress, in precipitating TTS.
- 36] The concepts of "stroke-heart syndrome", with resultant brain-heart axis dysregulations as potential precipitants of TTS should always be part of our diagnostic approach, when faced with patients with structural or functional brain morbidities, psychiatric afflictions, electroconvulsive therapy, or any evidence of underlying stress.
- 37] Could epinephrine be administered for the management of anaphylaxis in half of the current recommended dose, with the second half administered, while the patients are monitored in terms of their anaphylactic attack and the response to epinephrine?
- 38] Occasionally patient case reports appear in the literature in which the authors vacillate whether the patients had suffered myocarditis or TTS; in light of frequent other various comorbidities of patients with TTS, one wonders whether it is conceivable that myocarditis and TTS can occasionally be present simultaneously.
- 39] RWMA in patients with myocarditis, and their evolution, along with the corresponding tissue characterization at cMRI can be used to distinguish among myocarditis, TTS, or myocarditis with TTS.
- 40] Although TTS with LVOTO is associated with MR, the latter can also be present in the absence of LVOTO, particularly with the apical or apical/mid-ventricular TTS phenotypes resulting from a dilated LV and mitral valve "tenting".
- 41] Presence of LVOTO should be correlated with ECG changes (either ST-segment elevation or T-wave inversion), which provide insights as to the timing of this hemodynamic complication, since ST-segment elevation occurs early in the clinical course, followed by T-wave inversion.
- 42] Time interval between inception of illness in TTS and subsequent performance of CANG, LVAngio, ECHO, and other imaging tests should be secured and recorded in the patients' records.
- 43] The interplay among "sigmoid septum", other LV segmental hypertrophies, probable or definite diagnosis of hypertrophic cardiomyopathy (HCM), LV "pseudohypertrophy", eventually dissipating, LV hypertrophy from long-standing hypertension, mitral valve leaflet elongation, papillary muscle abnormalities, along with transient MR, LVOTO, in serial ECHO or cMRI, should be explored in patients with TTS.
- 44] In terms of the pathophysiology of TTS, it may be of value to explore whether LVOTO was associated with ST-segment elevation, bespeaking of an early appearing LVOTO subsequently dissipating, a thought that has made some to theorize that LVOTO is the pathogenetic trigger of TTS.
- 45] In reference to brain natriuretic peptides (BNP) in TTS, one wonders whether these biomarkers are secreted in the absence of HF or CS, or are merely related to LV chamber dilatation. Does BNP have any arterial or venous vasodilating effect in TTS? Is BNP's level related to the associated catecholamine outpouring or hyperactivation of the ASNS? Is the BNP's rise partially independent of the underlying LV function in TTS?
- 46] Is troponin release in TTS due to cardiomyocyte injury, necrosis, or both? Is there a component of myocardial necrosis in TTS? Are some cardiomyocytes necrosed and some have undergone stunning with eventual recovery? Histological evaluation of tissue from endomyocardial biopsies or autopsies should provide the contrast between patients with TTS and AMI, particularly of the stunned (i.e., not necrosed), myocardial component in the latter. Can we possibly expect some correlation between the peak troponin release and the drop of LVEF, or the extent of LV RWMA, to grossly estimate the proportion of cardiomyocyte necrosis in patients with TTS?
- 47] Should we consider serotonin as one, additional to catecholamines, triggering factor for TTS, considering that some patients suffer TTS in the setting of drug uptitration of selective serotonin reuptake inhibitors?
- 48] Employment of β -blockers in periprocedural settings (e.g., catheter ablation for AF), or post-anesthesia and at peri-operative state to prevent emergence of TTS, or manage complicated early TTS, has been advocated by some. The use of short half-life (e.g., esmolol) or ultrashort-half-life (e.g., landiolol) could be employed, since they can be abruptly terminated with impunity, if HF, hypotension, or bradycardia emerge.
- 49] POCUS early and repeatedly implemented by many members

of the caring team, in addition to the referral for a subsequent formal ECHO testing is necessary for an earlier diagnosis and appropriate management of patients with TTS. Particularly important goals should be the detection of LVOTO, MR, worsening or improvement of LVEF, estimation of cardiac output (CO), and changing in the TTS morphological phenotypes.

- 50] Left ventricular end diastolic pressure (LVEDP), is frequently either not measured or reported, and this needs to be corrected. There is controversy in the literature whether LVEDP is or is not elevated in patients with TTS. In addition estimation of LVEDP by ECHO-based established methods needs to become routine, along with ECHO-based estimation of right atrial (RA) pressure, and CO. A calculation of LV ventricular-arterial coupling should become routine and evaluated serially [3], since it is different in TTS, that in patients with ACS, AMI, HF, and CS. Such measurements are useful in the management of patients with TTS and they may provide significant insights towards the elucidation of its pathophysiology.
- 51] There is a wide range of blood catecholamine levels in patients with TTS, partially due to the time of measurement in connection with the onset of the illness, the degree of catecholamine spillover resulting from the overstimulation of ASNS and/or the secretion from the adrenal glands. Also, there is a large variation of the kind of catecholamines (i.e., epinephrine, norepinephrine, dopamine) released in the bloodstream. Whether other blood elevated substances like neuropeptide Y, have a role in the pathogenesis of TTS is not clear. Variation in the levels of blood catecholamines may also be influenced by the variation of catecholamine reuptake; this is supported by the triggering of TTS in patients treated for depression, in whom starting or upgrading their therapy, employing norepinephrine, and dopamine reuptake inhibitors, triggers the disease. We should restart measuring catecholamines in patients with TTS; one of the benefits of such action might be the earlier diagnosis of patients with pheochromocytoma/paraganglioma, who often are being diagnosed with great delays and after multiple hospital admissions.
- 52] Triggering of TTS, its severity, and the variation in the morphological phenotypes, may be a function of the topography of the autonomic sympathetic and parasympathetic innervation, the density and sensitivity of β_1 -, β_2 -, α_1 - and other receptors to catecholamines, which also may be subject to continuous neuromodulation within the brain-heart axis.
- 53] TTS may be highly underdiagnosed outside and within hospitals, particularly in its mild and forme fruste forms, and with symptoms not so alarming for patient to seek medical attention. Also, it is conceivable that a difficult to detect “TTS component” may be present in patients with many other serious comorbidities.
- 54] It is conceivable that some patients with unspecified non-ischemic cardiomyopathy have a “chronic form of TTS”, resulting from many recurrent attacks of TTS; this hypothesis is supported by the occurrence of chronic LV dysfunction in some patients with pheochromocytoma/paraganglioma, with recurrent symptoms and multiple hospital admissions, eventually diagnosed, sometimes retrospectively with TTS.
- 55] The mean age of patients suffering TTS may stay the same, because we diagnose progressively more younger patients, particularly male with TTS in the setting of comorbidities, balancing the aged female victims suffering the illness; also, this is counteracted by the increasing longevity of the population, resulting in having octogenarians and nonagenarians presenting with TTS.
- 56] Atypical (i.e., nonapical) morphological variants of TTS will be identified progressively more frequently as imaging is improving and performed serially. Although the diagnosis of TTS is based on the identification of LV and RV RWMA, literature has appeared reporting patients with TTS diagnosed on the basis of ECHO systolic and/or diastolic dysfunction, with normal LVEF, no RWMA, and abnormal systolic and/or diastolic ECHO strain findings.
- 57] TTS may be a component of pathology in patients admitted with a hypertensive emergency/urgency or tachycardia-induced cardiomyopathies, when LV dysfunction is not associated with the global hypokinetic phenotype, but with LV and/or RV RWMA.
- 58] Is it possible that high sensitivity troponin I and T provide different insights about TTS, ACS, AMI, and thus their levels and dynamics warrant scrutiny? Is it possible that troponin I rather than T, in patients with TTS reflects changes in the cardiac musculature (i.e., injury/stunning vs. necrosis) due to ASNS surge?
- 59] What is the mechanistic nature of catecholamine cardiomyocyte toxicity in TTS? Is it due to overstimulation? Could this be explored in simulated animal experiments and cardiomyocyte cultures, comparing electrical stimulation of the peripheral ASNS (e.g., stellate ganglia) or exposure to graded blood catecholamine concentrations?
- 60] It has been stated that LVOTO constitutes a compensatory response to the LV ballooning in patients with TTS; of course, it is conceivable that LVOTO is due to a primary, catecholamine-induced increase in contractility. Some have theorized that LVOTO is a trigger for the emergence of TTS; along this line, there are reports proposing an evaluation in animals of the consequences of a protracted increase in the afterload on the LV response. It is relevant that patients admitted with hypertensive emergencies, sometimes reveal transient reduction of their LVEF; such patients should be evaluated serially with sophisticated ECHO testing for RWMA.
- 61] It is conceivable that there is one or many different pathogenetic mechanisms leading to TTS in general, or in its morphological variants, in particular.
- 62] One wonders whether measurements of coronary flow reserve will be useful in the better pathophysiological characterization and management of TTS; this may be the case only if such measurements are analyzed in connection with the time

interval between the measurements and the inception of the illness, and are coupled with parallel measurements in patients with ACS and AMI.

- 63] It has been proposed that therapies (current, or expected to be available in the future) for microvascular dysfunction may be of value in patients with TTS; of course, such therapies should be implemented for all patients with underlying stunned myocardium (i.e., ACS and AMI).
- 64] Irrespective of the adaptive or maladaptive nature of the mechanism(s) leading to TTS, what is important is to protect the myocardial segments displaying systolic hypokinesis/akinesis/dyskinesis/asynergy. Also, it is imperative that we maintain an adequate perfusion of vital organs, while simultaneously decreasing the ASNS surge and/or the catecholamine spillover, which exerts further stimulation of the cardiomyocytes and exacerbates the coronary microvascular dysfunction (CMD).
- 65] In addition to the guideline-directed medical pharmacological therapies for patients with TTS, we should consider intravenous short/ultrashort half-life β -blockers, fluid infusions, phenylephrine, sodium nitroprusside, pacemakers, cardiac circulatory support devices, extracorporeal membrane oxygenators, with constant switching from one to the other therapy(ies). This will require very close monitoring of blood pressure (BP), heart rate (HR), pulse oximetry, skin temperature, with frequent auscultation, and frequent serial POCUS.
- 66] When referring to multiple plausible pathogenetic mechanisms of TTS, consideration should be given to the possibility that some may be consequences of others.
- 67] The fact that different stress triggers lead to different stress responses in different individuals is well known, it is still puzzling as to the reasons for such varying inter-individual susceptibility.
- 68] Alterations and differences from ACS, AMI, HF, and CS in the LV ventricular-arterial coupling (VAC) in patients with TTS [3] may explain the relatively benign clinical course of patients with TTS than in patients with AMI, in the presence of worse LVEF and widespread RWMA.
- 69] In TTS literature reference is made about BP, HR, LVEF, and RWMA; however we should start measuring serially and reporting CO, RA, LA, RV systolic, and LV diastolic pressures, as derived from high quality ECHO, with calculations of VAC, systemic vascular resistance (SVR), and pulmonary vascular resistance.
- 70] Literature reports on TTS include patients with normal, mildly, moderately, and severely elevated left ventricular end-diastolic pressures (LVEDP). Work by the Japanese investigators, early after the formal description of TTS, revealed normal LVEDP, in patients with TTS evaluated in the catheterization laboratory a few hours after onset of the illness. The range of LVEDP measurements in patients reported from large patient cohorts or registries is wide, due to the inclusion of many patients with normal LVEDP. There is controversy whether LVEDP is elevated in patients with TTS.
- It is conceivable that LVEDP is normal or even lower than normal early in the clinical course, with LVEDP subsequently rising as a result of the evolution of the clinical course, complications, or administered therapies. LVEDP frequently either is not measured, or not reported, particularly when it is normal (publication biases). One of the reasons that LVEDP is not available in published reports, is that LVGram does not routinely follow CANG, since LV function assessment by ECHO has already been carried out. When right heart catheterization has been performed, pulmonary capillary wedge pressure measurement may be useful as a surrogate of LVEDP, although this should be considered with reservation, because the LV and RV VAC, are affected to different degrees in TTS.
- 71] TTS is often considered in isolation as a cardiac, instead of a cardiovascular/cardiocirculatory, affliction. TTS is a “total-body” illness with secondary body organs/systems dysfunction due to blood hypoperfusion (“secondary” illness component), and direct effects of hyperfunctioning ASNS and catecholamine outpouring on the body organs/systems (“primary” illness component). Accordingly, various body organs/systems’ pathologies might have triggered TTS, or have been caused by TTS. Neurogenic pulmonary edema in TTS is not necessarily due to secondary HF or CS, but due to primary nosogenic effects of the ASNS surge, norepinephrine spillover, and adrenal epinephrine hypersecretion, imparted to the lungs. Also, a peripheral arterial “vascular TTS” is probably a reality, which needs confirmation, and could be explored by serial evaluation of LV VAC in patients with TTS.
- 72] Neurocardiology is an emerging cardiology subspecialty, analogous to cardio-oncology; this discipline examines the amphidromic pathogenetic influences of the brain-heart axis. Notable such examples are various brain, heart, total body illnesses, emerging in the context of what is currently dubbed “the stroke-heart” syndrome.
- 73] Our index of suspicion for an underlying TTS comorbidity should be high when evaluating patients with all kinds of somatic (particularly neurological) and psychiatric illnesses, in order that ECG, biomarkers’ measurements, and ECHO are employed earlier, via a specially-designed routinely implemented protocol.
- 74] Not only chest pain and dyspnea are the presenting symptoms of TTS; patients are occasionally presenting with other than cardiac symptoms and signs (e.g., gastrointestinal manifestations), or in association with a serious comorbidity, with its expected symptoms and signs.
- 75] The issue of “pseudohypertrophy” due to myocardial edema in the setting of TTS needs careful consideration; along this line of thought, repeat imaging, particularly based on cMRI is indicated. In addition to the phenotypes of upper septal hypertrophy (i.e., “sigmoid septum”), possible underlying HCM (including the apical HCM variant), should be kept in mind, to avoid false diagnoses of TTS.
- 76] In evaluating hemodynamics and considering management of patients with TTS, one should keep in mind the complexity of its pathology with varying degrees of impaired contractility

of myocardial segments, composing a 2-compartment model, consisting of akinetic/dyskinetic and hyperkinetic components in the apical morphological phenotype, or 3-compartment model, with apical and basal hyperkinesis and mid-ventricular akinesis/dyskinesis, in the mid-ventricular variant.

- 77] A decreased tone of the peripheral ASNS via neurography noted in patients with TTS in a limited experience [1], is a counterintuitive finding, in a pathophysiological setting of a disease with a purported enhanced ASNS, with intense norepinephrine spillover, and stimulated adrenal epinephrine hypersecretion.
- 78] Stimulation of the α_1 -adrenergic receptors from the ASNS/ catecholamine surge is expected to increase peripheral vasoconstriction in patients with TTS; however the decreased SVR suggests that counteracting vasodilating effects must be at play; such influences may include the associated β_2 -adrenergic stimulation, nitric oxide, endothelium-derived hyperpolarizing factor, potassium ions, adenosine, prostacyclin PGI₂, abnormal parasympathetic influences, and the outpouring of brain natriuretic peptides. An added complexity is that all above peripheral innate vasodilators may be orchestrated by the ASNS and elevated catecholamines, with their varying composition, leading to different vasodilating properties.
- 79] It may be of value to scrutinize the peripheral vasoreactive consequences of the administered different catecholamines used in animal (usually murine) TTS models; in addition serial sampling for the innate vasodilating molecules in such experiments may be revealing in terms of the emerging different LV VAC phenotypes (i.e., vasoconstriction, vasodilation, unchanged from the baseline vascular tone).
- 80] Some inconsistencies have surfaced in the literature regarding LV VAC in patients with TTS, in the sense that although initially it was felt that TTS was different from ACS/AMI, more recent studies have observed similar hemodynamic and peripheral systemic circulatory responses [1].
- 81] Since different phenotypes of pheochromocytoma/ paraganglioma exist, in terms of the specific catecholamine hypersecretion in such patients hospitalized with or without diagnosed TTS, it should be scrutinized as to what is the stability or change in the LV VAC during the course of single episodes and cases or recurrent hospitalizations.
- 82] Sepsis is characterized by an induced global LV dysfunction, and TTS with a global LV dysfunction has rarely been encountered; accordingly, one could consider that all cases of sepsis-induced transient cardiomyopathy represent a TTS phenotype.
- 83] A proactive approach based on specific investigating protocols aiming to the diagnosis/management of many medical/ surgical conditions, frequently encountered as comorbidities (e.g, cancer) in patients with TTS, may be of value.
- 84] The diversity in the severity of TTS cases may be due to the complex interplay of TTS and the associated comorbidities.
- 85] The employment of timed Doppler/ECHO and thoracic bioimpedance technologies serially in patients with TTS, could provide all that is necessary for their hemodynamic characterization and its perturbations, resulting from the underlying healing process, the consequences of complications, the interactions with comorbidities, and the effects of therapies.
- 86] The hemodynamic consequences of administered therapies, viewed as inappropriate in the hindsight after a delayed diagnosis of TTS, have not been yet appreciated.
- 87] A protocol in the form of a list of timed hemodynamic parameters' measurement needs to be established, that should be implemented in all patients with TTS, and not only for the purposes of research.
- 88] Different "hemodynamic phenotypes" can be noted in patients with TTS, on the basis of serial assessment of BP, HR, CO, SV, SVR, systemic vascular compliance, LVEF, LV RWMA (qualitative and quantitative) and brain natriuretic peptides.
- 89] Six hemodynamic phenotypes appear to be present in patients with TTS (i.e., minor symptoms/no complications, hypertension and/or tachycardia, HF with normal BP, HF with low BP or CS, LVOTO without HF or CS, and LVOTO with HF or CS).
- 90] Management of the different hemodynamic TTS phenotypes should be different, and should include, supportive therapy and implementation of "primum non nocere" = "first do no harm", fluids infusion/diuretics, β -blockers, levosimendan/ milrinone, phenylephrine, inotropes/vasopressors, intra-aortic balloon pump, LV/RV cardiac circulatory support devices (e.g., Impella), and extra-corporeal membrane oxygenators.
- 91] Physicians should be quick in employing temporary electronic pacing after a brief trial of atropine, in patients with severe bradycardia, heart block, prolonged corrected QTc interval (particularly in patients with polymorphic ventricular tachycardia), and LVOTO.
- 92] The rise of creatine kinase and troponins and their ratio may be different in TTS and AMI; one could contemplate that released creatine kinase reflects more cardiomyocyte necrosis, while blood troponins suggest mixed underlying cardiomyocyte stunning and necrosis; accordingly this may be worth exploring. However, the recent trend of checking or reporting only on troponins, may render such an undertaking impossible.
- 93] The time interval between conversion of the ST-segment elevation to T-wave inversion may be shorter in patients with TTS than in patients with an ST-segment elevation AMI; thus, persistent ST-segment elevation in patients with TTS may imply that one is dealing more than a case of stunned myocardium, destined to recover completely, and thus partial myocardial necrosis; however, underlying pericarditis needs also to be factored in.
- 94] The low rate of emotional triggers in men shown to have

suffered TTS may be because fewer men than women admit such problems.

- 95] A brain scan (e.g., cMRI or functional MRI), after electroconvulsive therapy leading to TTS may be useful in showing which brain areas were responsible for the ASNS activation leading to TTS.
- 96] The mechanism of bradycardia at the onset of some cases of TTS, may reflect autonomic nervous system stimulation of brain loci from which the vagus nerve emanates.
- 97] We should stop referring to emotional or physical stress or its absence; there is no emotional stress without physical stressful consequences and the other way around. Also, patients appearing not to be under stress, need to be repeatedly and more intensely questioned. Finally, we should start relying more on objective evidence of stress, based on appropriate testing and relevant measurements (e.g., heart rate variability, administration of specific established stress testing methods, during hospitalization, and at follow-up).
- 98] Although TTS occurs before and after permanent pacemaker implantation for complete heart block, the pathogenetic mechanism of TTS in the latter cases may be due to an ASNS hyperactivation triggered by the resulting bradycardia or asystole, and the change in the interventricular/intraventricular conduction, engendered by the electronic pacing. Of course, TTS could also be related to the stress imparted by the procedure, for which this author has recommended standby short-acting β -blocker infusions, for some patients undergoing electrophysiological procedures.
- 99] Like patients with HCM, patients with TTS are not immune to other cardiac (e.g., AMI) and noncardiac (e.g., diabetes) illnesses.
- 100] It is conceivable that some patients with TTS could reveal normal heart function at imaging, due to a rapid recovery; indeed, such cases have been reported in the literature.
- 101] It is possible that some encountered cases of nonischemic cardiomyopathy may be due to many recurrent episodes of TTS, with some being mild, atypical, and self-limited.
- 102] Shifting morphological LV and RV variants during the same TTS admission or at TTS recurrence may be associated with alterations in the topography, density, type, number, and sensitivity of β -adrenergic receptors to the released different catecholamines, and their proportional blood composition.
- 103] The rapid resolution of the ECG ST-segment elevation and the transition to the T-wave inversion unlike what happens in the setting of ST-segment elevation AMI, suggest that the pathogenetic mechanism of TTS is a non ischemic condition, or due to a short phase of segmental coronary vasospasm (thus ischemic), which has dissipated by the time the patients are under our evaluation.
- 104] Scrutiny should be exercised at CANG and LVAng to differentiate AMI, TTS, SCAD, and AMI/TTS, and SCAD/TTS phenotypic combinations.
- 105] It is conceivable that the pathogenetic mechanism(s) of TTS is(are) exerted on the myocardium over the course of 30 to 60 min, and thus its(their) detection by the time we see the patients may remain problematic.
- 106] We should probably employ aggressive antithrombotic management in patients with TTS, similar to the ones used in ACS, AMI, or MINOCA, because of the underlying ASNS/hyperactivation/catecholamine-induced hypercoagulability, and the LV and RV severe RWMA. Also, vigilance should be exercised since LV thrombi may appear at different points of hospitalization, and even after hospital discharge.
- 107] Whether TTS is due to one or multiple pathogenetic mechanisms has not been as yet determined. This author favors the 1st scenario, differentiating TTS from ACS, AMI, MINOCA, and Prinzmetal's (variant) angina.
- 108] The variation in the clinical presentation of patients with TTS, and the associated outcomes, may be due to the time interval between onset of the illness and clinical presentation, associated drugs taken before admission or started after admission, with some of them being inappropriate for patients with TTS, and the variation of the intensity of ASNS surge and types and amounts of outpouring catecholamines.
- 109] While CMD is attributed to coronary vasospasm, inflammation, or endothelial dysfunction, the role of myocardial edema is often not mentioned, although it is conceivable that CMD may be totally or partially due to external to the vessel pressure, compromising the coronary microvessels' caliber.
- 110] To evaluate the pathogenetic role of inflammation in TTS, the rise of neutrophils and C-reactive protein could be followed to evaluate whether inflammation is a pathogenetic influence, or an epiphenomenon.
- 111] Of interest is that both normal and compromised coronary blood flow have been found in experimental murine models of TTS. One wonders whether the timing of observations or the experimental variation is at the roots of this discrepancies. It is possible that coronary blood flow reduction in the affected regions in TTS is an epiphenomenon, it is transit, and its of varying duration.
- 112] The role of inflammation cascade in TTS needs further exploration, it should be characterized in more detail, and studied in terms of its course in different patients. Also, various anti-inflammatory regimens administered as early as possible in patients with TTS may proven influential in preventing the early worsening or shortening of the clinical course.
- 113] In evaluating the role of neurological and psychiatric pathologies in patients with TTS, emphasis should be placed on their frequency and severity prior to the emergence of TTS, and not after.
- 114] Genetic polymorphisms of the ADRB1 and ADRB2 genes encoding β_1 and β_2 receptors respectively based on large genomic databases and patients with TTS need to be carried out to resolve whether the disease is due to a genetic predisposition. However, it is conceivable that the individual

predisposition to TTS is polygenic, and multifactorial (i.e., not only related to adrenergic receptors' polymorphism), in terms of its genetic underpinnings.

- 115] The proteomics and microRNA signatures of patients with TTS need to be explored in large databases, preferably in different TTS registries.
- 116] The tolerance of patients with TTS to their severe LV dysfunction may be partially explained by an altered LV-arterial coupling [3], which is determined not only by the cardiac decompensation, but by the total body alterations imparted by whatever causes TTS.
- 117] The possible attribution of TTS to an estrogen deficiency should be complemented by a study of other gender-based differences as contributors to the disease.
- 118] We should evaluate whether the rapid recovery of LV function is different to the one observed in patients with ACS, undergoing percutaneous coronary interventions/stenting.
- 119] The persistence of clinical problems in patients who have suffered TTS is currently unexplainable; partially one wonders whether such persistent affliction may be due to the possibility that unlike AMI affecting only the heart, TTS is a total- body illness.
- 120] Are some patients with unexplainable HF, decreased LVEF, or cardiomyopathy of unknown variety harbor a condition due to multiple episodes of TTS, some of them subclinical?
- 121] The circumferential LV involvement in patients with TTS does not preclude an ischemic etiology, since one could envisage ASNS-based hyperstimulation of the coronary microvasculature, leading to transient coronary vasospasm affecting selectively many epicardial coronary vessels and their branches.
- 122] Cardiomyocyte adrenergic stimulation and/or microvascular spasm is regional, and probably territorially shifting in the hyperacute and acute phases of TTS; perhaps the adrenergic receptors' functionality and even density may be dynamic, changing over time.
- 123] Exclusively RV or combined LV/RV TTS involvement may be related to the topography (i.e., regionality) of ASNS cardiac nerve distribution, adrenergic receptor density, and adrenergic receptor expression (i.e., sensitivity).
- 124] The dominance of stunning in TTS, in contrast to a combination of necrosis and stunning in AMI, may be due to the emergence of protective mechanisms, or the short time duration, of the noxious operating influences, causing TTS.
- 125] The current *modus operandi* in examining and monitoring patients with TTS is unlikely to provide answers about its pathogenesis; patients satisfying the InterTAK criteria of TTS in the Emergency Department should be subject to frequent auscultation and POCUS, implemented early and frequently, by many members of the team, and not only by the consulting cardiologists.
- 126] ECHO evaluation should be extended to systolic (and diastolic) strain regional characterization; some mild cases of TTS may be associated with normal LVEF and only presence of diastolic dysfunction.
- 127] Concern about applying different therapies designed for the management of chest pain, HF, CS, atrial and ventricular arrhythmias in patients with TTS seems to be unwarranted; indeed they should be implemented under close monitoring to ensure that they are effective. Also, such therapies could be terminated if they are found to be ineffective, or result in complications.
- 128] It should be kept in mind that cardiac assist devices should be implemented more frequently and much earlier in the management of TTS, than it is currently practiced.
- 129] In patients with TTS who have a history of previous episodes of pain or dyspnea, which have not been evaluated, and who did not experience full recovery of their LV function at follow-up imaging, it is conceivable that the underlying HF or cardiomyopathy may be due to recurrent episodes of mild or even subclinical episodes of TTS.
- 130] The available risk stratification algorithms, implemented in patients with TTS need to be revised, considering the observed change in demographics and other clinical attributes of currently evaluated TTS cohorts and registries.
- 131] Perhaps the choice of different β -blockers, in terms of their β_1 and β_2 adrenergic receptors' affinity may need to be explored regarding their therapeutic effectiveness; catecholamine blood levels may provide some guidance regarding which β -blocker should be preferred.
- 132] Since RV/LV thrombi in patients with TTS occur at different time points of hospitalization and even after discharge, the threshold for implementing anticoagulation should be low, and imaging should be repetitive and frequent.
- 133] It is advisable to use frequent manual measurements from printed recordings of the hospital ECG monitors to detect possible QTc prolongation, even if a single ECG lead is available from such recordings.
- 134] The issue of which RV/LV cardiac circulatory device(s) should be used and in what combination for patients with TTS and CS, and their associated complications, as well as their therapeutic effectiveness, according to the patients' age and gender needs further research, and should involve very large numbers of patients.
- 135] The diagnostic and prognostic particulars of patients with cardiac interventricular or free wall rupture need intense research scrutiny.
- 136] TTS registries should start prospectively to include detailed information pertaining to the short-term and long-term follow-up of patients after their discharge; this should include detailed data on all the drugs taken and their dosages.
- 137] Regarding the 6 therapeutic randomized trials under way [1], one hopes that detailed information will be secured about the time duration between the exact onset of the illness and the start of the administered therapy; also, laboratory information may be of value to estimate the clinical stage

of the TTS of the individual patients (e.g., ECG ST-segment elevation vs. T-wave inversion).

- 138] Adenosine may not have a therapeutic effect in patients with TTS if the CMD is not due to vasospasm but due to external compression of the coronary microvasculature due to myocardial edema, resulting from catecholamine-induced cardiomyocyte toxicity.
- 139] Formal assessment of CMD in a systematic fashion following CANG may be of value; if the technology or the expertise is lacking, employment of the simultaneously recorded ECG during and immediately following CANG may be considered (i.e., the time duration in ms of the recovery of ECG repolarization abnormalities resulting from coronary injections of the contrast medium or saline may be a reflection of the functional status of the coronary vasculature), based on work by this author.
- 140] Although investigated before, the therapeutic effect of antiplatelet agents in TTS needs to be reexplored more systematically and in large patient cohorts.
- 141] There is a possibility that the CMD associated with TTS is very early established, and thus by the time we diagnose or manage the patients it is very late to effectively intervene; perhaps awaiting the natural recovery, while we are supporting the patient hemodynamically, may be the way to act.
- 142] The effect of cyclosporine A (a calcineurin anti-inflammatory inhibitor) as an agent counteracting myocardial injury and inflammation in patients with TTS is undergoing evaluation [1]; also, colchicine may be considered for such an anti-inflammatory therapeutic role, considering that it is currently recommended in the management of ACS, AMI, and AF; it is conceivable that such interventions are implemented late in the clinical course, and they may be proven ineffective (vide supra about adenosine).
- 143] The hemodynamic consequences of all the currently investigated drugs (e.g. cyclosporine A) need to be closely investigated, while their therapeutic effects are evaluated.
- 144] The systematic employment of contrast ECHO in a serial manner for the evaluation of the status of CMD needs to be tried and become routine.
- 145] Serial high sensitivity troponin values may be useful in gauging the therapeutic response of various currently explored drug interventions.
- 146] Systematic evaluation of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, starting immediately after the diagnosis of TTS, should be evaluated.
- 147] N-acetylcysteine infusion to counteract the oxidative and nitrosative stress and inflammation in patients with TTS deserves an evaluation.
- 148] A problem not yet discussed regarding the currently proposed and/or evaluated drug therapies for patients with TTS [1] is the standardization of what is called “usual care”, against which the pharmacological interventions will be compared. Accordingly, it may be of value to compare the various drug

interventions against different types of “usual care”, as per carefully designed management protocols. The same applies to the different conventional drugs, administered in addition to the experimental drug therapies, which should be viewed as exerting possible synergistic, additive, or counteracting effects.

- 149] Attention should be directed to the nature of new cardiac and noncardiac diseases which, patients with an index episode of TTS, suffer at their short-term and long-term follow-up.
- 150] The implementation of permanent pacemaker and/or implantable cardioverter defibrillators, in response to various possible, present, or suspected electrophysiologic pathologies, need to be individualized, and orchestrated by multi-disciplinary teams.
- 151] The same caution should be exerted for patients with a TTS and prolonged QTc, which should also include clinical and laboratory exploration for many possible present or suspected underlying congenital and acquired electrophysiologic pathologies.
- 152] The familial and genetic risk of TTS needs to become explored in depth and in large databases of patients with TTS; accordingly, such evaluations should become an integral part of the data collected by TTS registries, for all recruited patients.
- 153] Comparison of what is reported in various types of articles in the World literature with periodic reports from established TTS registries may be of value, in obtaining a more complete and global picture of the apparent or real evolution of the TTS pathology.
- 154] The notion that TTS is associated with a reduced peripheral sympathetic tone (involving the heart and/or other body organs and systems needs scrutiny, and if found to be the case, has implications for the therapeutic application of β -blockers in patients with TTS.
- 155] There is no doubt that elucidation of the pathogenetic mechanism(s) leading to TTS and the emergence of proven effective therapies for its management will be extrapolated to the diagnosis and management of all other cardiovascular pathologies.

Conclusions

The above free-standing arguments and counterarguments about TTS are meant to engage our community of professionals, caring for patients with TTS and delving in its still elusive pathophysiology. Reading the present communication along with the 2 referenced articles [1,3], which have acted as the impetus for its composition, may be of some value. Understanding should be sought about the redundancy present in these individual statements, but redundancy is an inherent component of brain-storming or free- association. The thesis being explored in the current piece is whether the study of the 2 referenced sources and the repeated contemplation of the above 155 “bullet-like” statements, will increase the knowledge and the insights that caring physicians and researchers have about this puzzling disease. Also, it should be realized that these statements could have been infinite in number, even when emanating from a

single individual. Thus, it is in this spirit that the concluded remarks of this piece are deliberately short, and non referential of its content.

References

1. Omerovic E, Redfors B. Takotsubo syndrome: pathophysiological insights and innovations in patient care. *Nat Rev Cardiol*. 2026;23(4):239-254.. Available from: doi:10.1038/s41569-025-01211-5
2. PubMed. Takotsubo [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2026 Aug 27]. Available from: <https://pubmed.ncbi.nlm.nih.gov/?term=takotsubo>
3. Madias JE. Ventricular-arterial coupling in Takotsubo syndrome: controversies and opportunities. *J Cardiovasc Dev Dis*. 2026;13(5):175. Available from: doi:10.3390/jcdd13050175