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Review

Pathophysiology of Takotsubo Cardiomyopathy: Reopened Debate

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Takotsubo cardiomyopathy (TTC), a persistently obscure dysfunctional condition of the left ventricle, is uniquely transient but nevertheless dangerous. It features variable ventricular patterns and is predominant in women. For 30 years, pathophysiologic investigations have progressed only slowly and with inadequate focus.

It was initially proposed that sudden-onset spastic obliteration of coronary flow induced myocardial ischemia with residual stunning and thus TTC. Later, it was generally accepted without proof that, in the presence of pain or emotional stress, the dominant mechanism for TTC onset was a catecholamine surge that had a direct, toxic myocardial effect.

We think that the manifestations of TTC are more dynamic and complex than can be assumed from catecholamine effects alone. In addition, after reviewing the recent medical literature and considering our own clinical observations, especially on spasm, we theorize that atherosclerotic coronary artery disease modulates and physically opposes obstruction during spasm. This phenomenon may explain the midventricular variant of TTC and the lower incidence of TTC in men. We continue to recommend and perform acetylcholine testing to reproduce TTC and to confirm our theory that coronary spasm is its initial pathophysiologic factor. An improved understanding of TTC is especially important because of the condition's markedly increased incidence during the ongoing COVID-19 pandemic.
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The authors of the earliest English-language−translated report on transient takotsubo cardiomyopathy (TTC) hypothesized that multivessel spasm most likely caused myocardial stunning and thus TTC.[1] Since then, alternative causes of TTC have been debated inconclusively. Most of the relevant literature during the past 30 years has consisted either of case reports describing associations between TTC and various clinical circumstances; or of retrospective, observational registry publications lacking progressive working hypotheses.[2-8] Even though clinicians administer catecholamine-based vasopressors or inotropic agents to 10% to 20% of TTC patients for associated hypotension or shock,[6,9] most authors typically state that TTC is probably caused by stress, catecholamine surge, or both. Thus, TTC is often called stress or catecholamine cardiomyopathy. Nevertheless, serum catecholamine levels do not seem to be regarded as clinically useful and are almost never obtained and reported.[9,10] Experimentation in animal models has concentrated on administering high-dose catecholamines in small animals until death occurs (in 30%−50% of instances) or cardiomyopathy develops. These studies represent catecholamine cardiomyopathy, not TTC. Credible animal models of TTC should probably start with inducing endothelial dysfunction before administering catecholamines.

Women are 9 times more likely than men to have TTC. As both sexes age, coronary artery disease (CAD) becomes relatively more prevalent and TTC cases less prevalent in men than in women.[6,7,9]

We present a novel theory regarding the effects of CAD in the presence of TTC, and we emphasize the value of using acetylcholine (ACh) to test for spontaneous spasm and cardiac endothelial dysfunction in patients who have TTC.

Determining the Cause of Diseases

In 1882, Koch proposed how to identify the cause of infectious disease,[11,12] then the most frequently studied pathologic condition. In brief, a microorganism must be found in diseased but not in healthy individuals, it must be cultured from a diseased

individual, it must cause the disease when administered to healthy individuals, and it must match the original microorganism when isolated from newly infected individuals. We have recently applied these postulates to patients who have TTC.

To document unusual spastic tendencies (the starting point for our theory), we have used ACh to test cardiac endothelial dysfunction in patients recovering from TTC, and we have used positive test results (>80% spastic, diffuse narrowing) to investigate the mechanism of TTC and to evaluate its spontaneous reproducibility after an episode. The use of nitroglycerin to counteract the coronary spastic effects of ACh makes the test safe and confirms cause and effect. Our theory includes the idea that spasm leads to left ventricular (LV) dysfunction by ischemic stunning.

Inadequacies of the Catecholamine Stress Theory

The theory that catecholamine stress itself can cause TTC has not yet been adequately tested. It may help to determine whether a substantial rise in serum catecholamine levels at TTC onset identifies a potential predisposing or precipitating factor, but not in healthy people.[10] In addition, the frequent clinical use of dobutamine testing only rarely causes TTC.[13] In a cohort registry study of 1,016 patients with TTC, the mean heart rate of 86 ± 20.8 beats/min and systolic blood pressure of 131.8 ± 28 mmHg at clinical presentation did not suggest a credible catecholamine-surge state,[6] and Y-Hassan[14] proved that we cannot currently substantiate the presence of a catecholamine surge in TTC. Adequately designed animal experiments might apply to human cardiac endothelial dysfunction only if a preliminary endothelial dysfunctional state were added to the catecholamine model, for example by applying cardiac radiation.[10,14]

Prolonged spasm has long been known to lead to the myocardial stunning that is presumably the essential mechanism for TTC.[1,10] For all these reasons, ACh testing of endothelial dysfunction may credibly identify the cause of stunning in TTC in specific circumstances.[13,15]

Coronary Artery Disease in Association with Takotsubo Cardiomyopathy

A prevailing rule, empirically introduced in the 1990s but unsupported by hard evidence, is that diagnosis of TTC initially needs to exclude the presence of significant CAD[6,9] or any CAD.[2] Indeed, LV dysfunction on the basis of CAD alone (such as in acute-onset thrombotic occlusion) may explain morphologic myocardial patterns similar to those in TTC. Clinically, emergency coronary angiography has routinely been demanded to establish the diagnosis of TTC, after CAD has been excluded. As a consequence, the incidence and relevance of CAD in TTC were unclear until the angiographic findings of the International Takotsubo Registry (InterTAK) investigators were carefully analyzed.[9] In this retrospective study of 1,016 patients who had strictly defined TTC, the presence of CAD was reported and studied consistently. Only 35.7% of the 1,016 patients had no CAD. In the cohort, 923 (90.8%) were women, 575 (64%) of whom had mild and moderate CAD or CAD necessitating coronary angioplasty.[9] Only 20% of the men with TTC had normal coronary arteries.

Coronary artery disease typically manifests itself 10 years earlier in men than in women[16] and may explain the different observed patterns of TTC and its differential incidence by sex and age (Fig. 1).[6] We think that if even nonobstructive CAD is present during spastic episodes, a stenting type of effect would result from intimal thickening and annexed calcific deposits. Of note, for centuries the traditional term for CAD was "hardening of the arteries" because stenotic coronary arteries could not be easily depressed by applying external compression at autopsy. Although luminal narrowing is the usual and most recognized consequence of CAD, this hardening of the arteries may indeed impede coronary narrowing during superimposed spasm. During ACh testing of endothelial dysfunction in patients recovering from TTC, angiograms have revealed a spastic effect on apparently CAD-free small distal vessels or on arteries in women, but no or only slight effect on epicardial proximal arteries with CAD, especially in men (Figs. 2–6).[13,17]
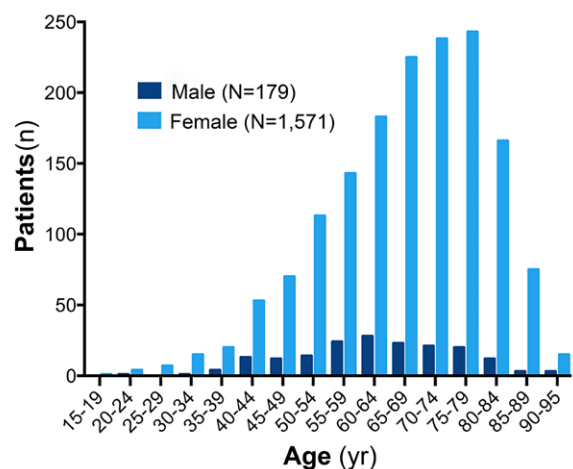

Fig. 1 International Takotsubo Registry data show accumulated incidence of takotsubo cardiomyopathy by age and sex in 1,750 patients. Relative incidence peaks at age 60 to 64 years in men and at 75 to 79 years in women.

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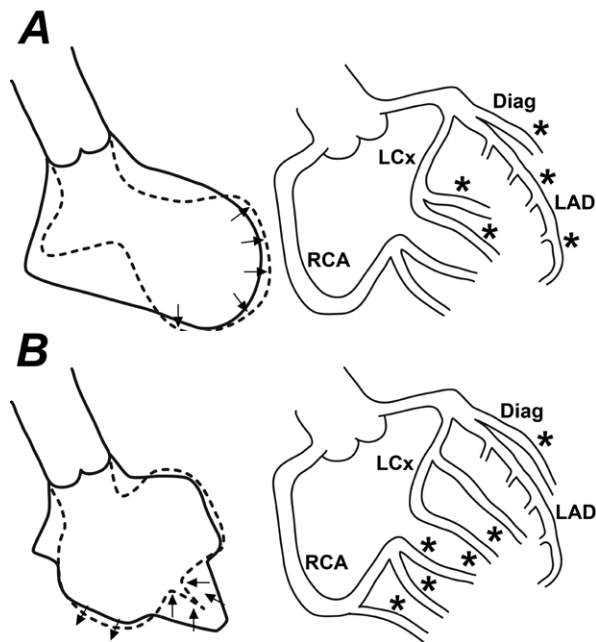
Fig. 2 Drawings (left panels) show **A**) apical and **B**) mid left ventricular locations of akinesia in takotsubo cardiomyopathies. The different arterial spastic behavior during acetylcholine testing (right panels) is probably related to atherosclerotic intimal disease, assumed present in the epicardial left anterior descending coronary artery (LAD) in **B**). The intramural septal branches (free of coronary artery disease) become severely obstructed from spasm (asterisks). Arrows indicate phasic left ventricular systolic motion, assuming similar end-diastolic volumes in all cases (continuous line).

Diag = diagonal coronary branch; LCx = left circumflex coronary artery; RCA = right coronary artery

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The relationship between TTC and CAD may also explain the sex paradox: if spasm underlies TTC, and if CAD interferes with spasm, men who have CAD would be protected from TTC manifestation in comparison with women who do not have CAD.

If spasm is the initial mechanism of TTC, then cardiac endothelial dysfunction may be the only known precondition that explains the peculiar related features.[13,18] The stages are as follows. First, TTC onset is typically sudden and unexpected, usually in a previously hemodynamically stable patient and without clinical evidence of an exceptional catecholamine surge.[14] Second, TTC is usually accompanied by early anginal pain and ST-segment changes, along with relatively milder cardiac troponin elevation but a higher brain natriuretic peptide (BNP) level than in acute myocardial infarction of similar extent. The mild troponin elevation accompanies brief occlusion, whereas the elevated BNP level accompanies persistent, extensive LV stunning.[3,6-9,19] This behavior by itself suggests transient occlusion with secondary stunning but without complete myocardial necrosis. Third, only spasm can cause the sudden-onset, rapidly disappearing severe LV dysfunction shown on emergency coronary angiograms at a patient's hospital admission; catecholamine toxicity with its direct myocardial damage would not act as abruptly or reversibly. As is well known, ACh causes vasodilation in patients who have normal coronary arteries, whereas the severe, diffuse vasoconstriction frequently observed in TTC is otherwise unprecedented in human beings.[20] Fourth, if endogenous catecholamines were the essential cause, one would expect a gradual onset with persistent ischemic spasm and stunning at least until angiography was completed. Only in exceptional cases, typically in resuscitated victims of sudden cardiac arrest, can spasm be detected during emergency angiography. Fifth, stunning usually resolves spontaneously within a few days in the absence of recurrent sustained spasm. Sixth, at the end of stunning, spasm inducibility through ACh testing is negative unless the patient remains at risk of recurrent TTC.

Support for Acetylcholine Testing to Explain Midventricular Takotsubo Cardiomyopathy

We now propose that if ACh testing is performed at an appropriate time after TTC occurs, it may confirm the spasm theory in most cases of TTC (Figs. 2–6).[13,17] In the apical variant, the proximal, mid, and distal LV segments (probably only away from CAD-affected arteries) react to ACh-induced spasm, with diffuse narrowing down to the smaller intramural branches that usually have no substantial CAD. Conversely, in midventricular TTC, the apical LV maintains normal systolic function (possibly because of existing CAD in the epicardial left anterior descending coronary artery) and adequate apical runoff (Fig. 3). Large prospective studies that include the use of computed tomographic angiography (CTA) or intravascular ultrasound are needed to correlate TTC territory size with CAD location and LV dysfunction.

An alternative theory is that different existing locations of LV β-receptor adrenergic subtypes protect the LV inlet. This mechanism is unlikely because TTC is transient, no similar congenital dysfunction has been reported, and patients with recurrence can have different TTC patterns at different times.[3,7,8,19,21]

In regard to the spasm theory, some concern persists that ACh testing is not reliable; however, this objection may be attributable to improper timing of testing.[3-5,8,19] We think that ACh-test positivity follows a consistent pattern (Fig. 5)[13] that implies several dynamic stages after TTC events. Either existing cardiac endothelial dysfunction (most likely related to inadequate production of nitric oxide, a primary vasodilator) must critically worsen
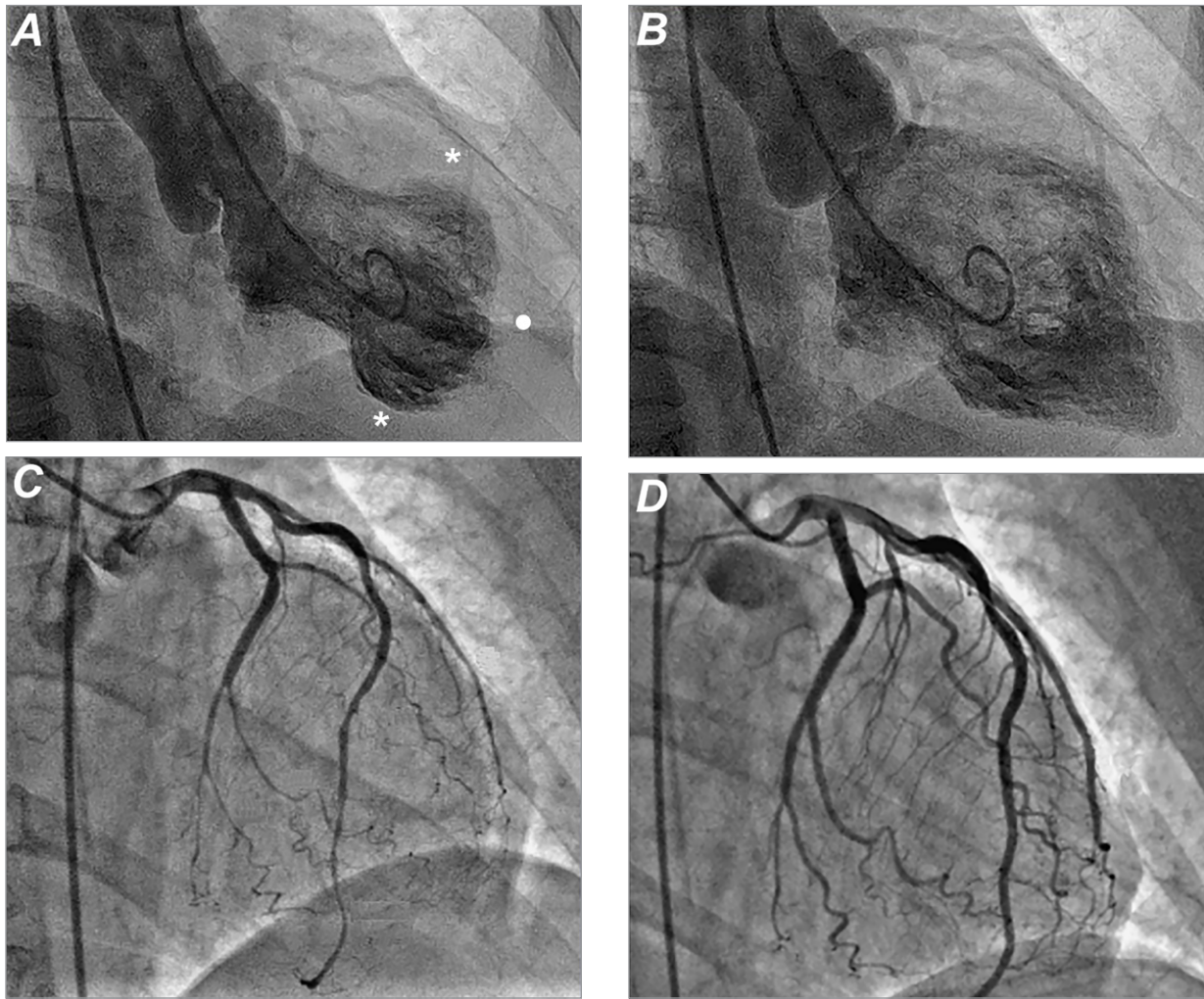
Fig. 3 *In a 70-year-old woman, left ventricular angiograms at **A**) end-systole and **B**) end-diastole show a hypercontractile apex (bullet) and akinetic midventricular ballooning (asterisks) during end-systole, a case of midventricular takotsubo cardiomyopathy. Subsequent left coronary artery angiograms show the same mechanism when **C**) acetylcholine reproduces critical spastic narrowing of the LCx–OM1, LCx–OM2, diagonal, and septal branches amid preserved apical flow, and **D**) nitroglycerin enlarges the vessels, exposing minimal residual irregularities in the left anterior descending coronary artery that are likely evidence of nonobstructive coronary artery disease not properly quantifiable on angiograms.*

LCx = left circumflex coronary artery; OM = obtuse marginal branch

before TTC onset, or precipitating factors beyond life-event stress must be unusually severe. Examples are cancer chemotherapy, radiotherapy to the mediastinum, or cardiac viral infection.[13,22-24] The histologic and metabolic features of cardiac endothelial dysfunction still need to be better defined and quantified.

When endothelial dysfunction is high, the TTC episode is frequently precipitated by simple, common stress that initiates spontaneous, severe, diffuse coronary narrowing with consequent acute transient ischemia in territories supplied by CAD-free coronary arteries (Figs. 4, 5, and 7).[13,25] Some catecholamine elevation may also contribute to spastic episodes, but only by acting on arteries that have endothelial dysfunction, we think.[8,15]

Acetylcholine testing enables firm diagnosis within 7 days after TTC onset. This tool is therefore highly useful in guiding treatment and preventing recurrence, and it reduces dependence on nondefinitive and delayed criteria for defining TTC (Fig. 7).[25]

Uncomplicated, nonrecurring TTC usually lasts 7 days, after which LV systolic function recovers to nearly normal. Electrocardiographic changes after TTC are evidence of a recovery that may include QTc prolongation for several weeks.

The apical and midventricular variants constitute 95% of all TTC cases.[7] Our reviews of registry data and experience with the ACh test suggest that different TTC variants occur only because of CAD modulation in the myocardial areas of dysfunction[6,9]; however, we think that the initial spastic stimulus is probably uniform across the variants. Large prospective studies are needed to correlate the territory size and location of LV
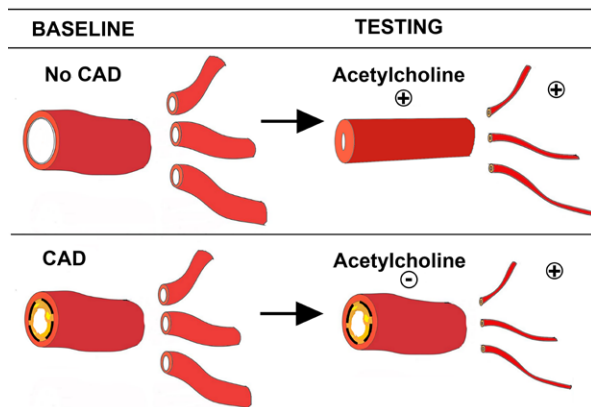
Fig. 4 Diagram illustrates the interrelationship between coronary artery disease (CAD) and takotsubo cardiomyopathy (TTC). When CAD is absent (upper panel), occasional spasm can induce luminal narrowing followed by dependent myocardial TTC; conversely, substantial CAD (lower panel) resists severe arterial spasm, preventing luminal narrowing and TTC by means of a stenting effect. Because all-vessel CAD occurs earlier in life and more frequently in men than in women, men would be comparatively more protected from TTC.
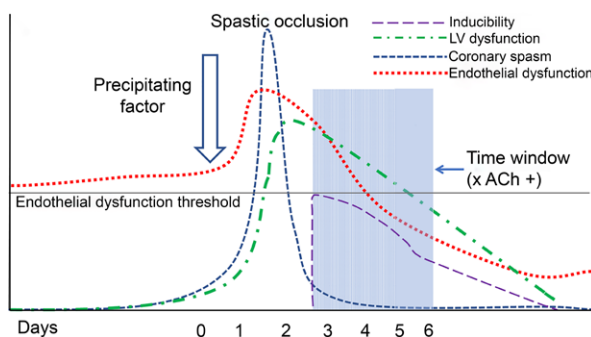

Fig. 5 Diagram shows dynamic mechanisms during an episode of takotsubo cardiomyopathy: the degree of endothelial dysfunction (dotted red line) and its threshold for spasm inducibility (gray line), the time courses of spontaneous spasm (dashed blue line), left ventricular (LV) dysfunction (broken green line), and the inducibility window for reproducing spasm with use of acetylcholine (ACh) (dashed purple line and shaded area).

Adapted and reprinted with permission from Angelini P, Uribe C. Is transient takotsubo syndrome associated with cancer? Why, and with what implications for oncocardiology? J Am Heart Assoc 2019;8(15):e013201.[13]
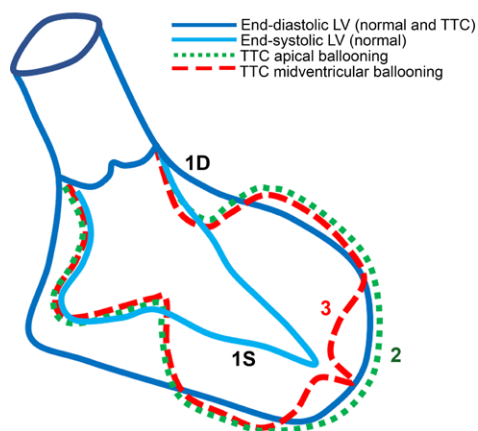

Fig. 6 Diagram shows different left ventricular (LV) conditions: normal, apical takotsubo cardiomyopathy (TTC), and midventricular TTC. At end-systole, the normal heart is shown (light blue, **1S**); apical TTC corresponds with diffuse coronary spasm (dotted green line, **2**); and midventricular TTC (intermittent red line, **3**) has preserved apical contraction because left anterior descending coronary artery disease prevents apical akinesia. For simplicity, the end-diastolic outline is shown as identical in the 3 conditions (dark blue line, **1D**).

Fig. 7 The International Takotsubo Registry (InterTAK) Diagnostic Score, a point system, relies on clinical factors for diagnosing takotsubo cardiomyopathy (TTC) at varying levels of certainty. The variables are not well quantifiable; also, for example, no male could be diagnosed to have TTC without exhibiting emotional stress: male sex + stress = 49 of the required 71 points.

Adapted and reprinted with permission from Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. Eur Heart J 2018;39(22):2047-62.[25]

dysfunction with CAD in apical compared with midventricular TTC, in men compared with women, and at different ages.

In addition, the difficult-to-explain generalized spontaneous resolution of spasm early after TTC onset seems to lead to a phenomenon called autovaccination, which not only interrupts spasm but also tends to prevent recurrence.[13,26] Autovaccination is especially surprising because it occurs in spite of concomitant, persistent endothelial dysfunction and frequently also emotional or physical stress.[13,26]

The true mortality rate of TTC is unknown, especially because out-of-hospital events are underreported and diagnosis at autopsy is problematic.[13] The typically reported mortality rate of 1% to 5% pertains chiefly to in-hospital complications such as shock, congestive heart failure, ventricular fibrillation, cerebral embolism, and LV rupture.[6,7,27] We have come to assume that coronary spastic occlusion lasting longer than 45 to 60 minutes after a TTC episode would lead to coronary

thrombosis, which is rarely recognized on angiograms or at autopsy. The spontaneous resolution of spasm may be caused by vascular smooth-muscle fatigue, ischemic dysfunction, or both.

Clinical Diagnostic Value of Acetylcholine Testing

Coronary patency and LV shape do not define TTC by themselves,[13,15] which is why we strongly recommend ACh testing to diagnose and characterize TTC by re-enacting the initial pathology either before or after LV functional recovery. In our experience, an early ACh challenge enables the capture of relevant angiographic data by merely ruling out fixed obstructive CAD. Of importance, studying the mechanism of myocardial stunning must wait until the LV wall spontaneously recovers 2 to 6 days after TTC onset (Fig. 5).[13] Nitrate therapy prevents early recurrence but does not speed myocardial recovery.

The time window for ACh test positivity varies by patient. False-negative results usually appear when testing is performed >7 days after TTC onset. We prefer to test 2 to 4 days after onset. A late-positive ACh result strongly suggests a high risk of recurrent TTC.[15,18] Still to be clarified is whether ACh release acts at the central neural system level or at the vagal nerve endings before TTC episodes; this will need to be done through large, well-designed prospective trials, possibly including molecular biology and gene-activation testing.[3,8]

Some clinical cardiologists may hesitate to undertake ACh testing in cases of suspected TTC. The procedure is not new but it may not be well taught, and it is rarely performed outside specialized centers. Secondary referral to specialized centers would cause disadvantageous delay at the critical early stage. Practitioners may lack experience in evaluating coronary spasm or may perceive an associated unjustifiable risk to the patient. Finally, reports of the test's frequently false-negative results may have dampened opinion about its value and led to unfamiliarity with newer testing techniques, appropriate dosing, and especially optimal timing.[13,15]

An uncomplicated ACh challenge takes 20 to 30 minutes to perform. Progressive intracoronary doses (25, 50, 75, and 100 μg) of ACh are usually administered during 30- to 120-second intervals, followed by coronary angiography.[28,29] Alternatively, we have recently begun performing the test with a single, slowly administered dose of ACh of up to 100 μg, because infused intracoronary nitroglycerin rapidly reverses spasm if it occurs. This practice substantially shortens procedure time, reduces the amount of contrast medium necessary, and enables a single coronary angiographic examination. The only significant side effects that we have encountered are transient atrioventricular block, which a temporary pacemaker easily controls (recommended when testing the atrioventricular node artery); and paroxysmal atrial fibrillation, reported in approximately 5% to 15% of cases.[20] An ACh challenge for TTC or for chest pain with negative coronary angiographic results is indicated only in qualified, selected patients.

If operators do not wish to clarify TTC pathophysiology by means of early ACh testing, or if patients decline it, 50% to 75% of patients with a TTC-like presentation will not need emergency catheterization; emergency CTA can be used to rule out severe CAD.[8,9] It should be understood that delaying catheterization (after early stand-alone diagnostic echocardiography) would help only to study the probability of recurrent coronary spasm, not TTC pathophysiology.[15]

Early reports of an increased incidence of TTC during the ongoing COVID-19 pandemic[23] (4–5 times that of acute coronary syndromes before the pandemic) increase the urgency to complete pathophysiologic studies and to confirm a documented, supportable treatment protocol. Of note, COVID-19 patients have been found to have severe, diffuse endothelial damage at autopsy.[30] Now may be an opportune time to plan prospective and controlled studies to reveal ways to reduce the morbidity and death associated with some COVID-19 cardiac conditions. In addition, new forms of COVID-19 may appear in the future.

Limitations

This paper's limitations are intrinsic to discussing a rare and unique disease entity that has a complex, dynamic, and largely unknown pathophysiology. The main implication of our spasm-based theory, consequent to our substantial pilot experience, is that expanding and focusing ACh testing is crucial for broadening the understanding of TTC pathophysiology.

Our group has performed approximately 100 ACh tests after TTC. At first, we selected patients referred too late after TTC onset. However, we have published only a few results in mostly unusual cases because the testing has been empirical, not part of a large prospective controlled study.

Conclusion

Spontaneous, increased spasticity is most likely the dominant mechanism of TTC onset, and existing endothelial dysfunction is its fundamental predisposing functional anomaly. Catecholamine administration or its natural release is potentially a nonessential precipitant of TTC, typically in the presence of triggers such as pain, emotional stress, or central neural system pathology. Acetylcholine testing to confirm transient spastic behavior is crucial for defining effective treatment and prevention. Coexistent CAD seems to affect the different observed incidence and pattern expressions of TTC in the sexes. Instead of simple high-dose catecholamine administration, we think that preliminary induction of

endothelial dysfunction in animals may lead to a more credible experimental model of TTC. We recommend multicenter, coordinated, prospective clinical investigations into the potential pathophysiologic mechanisms of this complex, dynamic, transient cardiac phenomenon.

Acknowledgment

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