"Reverse McConnell's Sign": Interpreting Interventricular Hemodynamic Dependency and Guiding the Management of Acute Heart Failure during Takotsubo Cardiomyopathy

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ABSTRACT: Although most patients with Takotsubo cardiomyopathy (TTC) have benign clinical course and prognosis, TTC can induce acute heart failure and hemodynamic instability. TTC mimics the clinical features of acute anterior wall myocardial infarction (AMI). Bedside clinicians often have a diagnostic dilemma when cardiac catheterization and angiography are either contraindicated or can cause potential adverse consequences. Misdiagnosing TTC as AMI will lead to initiation of harmful pharmacological or device-based treatment, which worsens hemodynamic compromise. Therefore, understanding and interpreting the unique pathophysiological and hemodynamic features of TTC in a better manner becomes crucial to guide effective clinical management of acute heart failure/cardiogenic shock during TTC. We review recent advances in echocardiographic diagnosis of TTC and its role in guiding bedside management of acute heart failure and cardiogenic shock, with specific focus on the interpretation of discrepant, but reciprocally dependent, left and right ventricular hemodynamics during acute stages of TTC.

KEYWORDS: Takotsubo cardiomyopathy, acute heart failure, cardiogenic shock, interventricular dependency, reverse McConnell's sign

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Introduction

Among patients undergoing emergent coronary angiography for suspected acute coronary syndrome, approximately 2%–4% are found to have Takotsubo cardiomyopathy (TTC). Most of these patients are postmenopausal elderly women. TTC often mimics the clinical features of acute anterior wall myocardial infarction (AMI).[1] Both AMI and TTC can cause cardiac pump failure and hemodynamic instability, resulting in poor clinical outcome.[2] To avoid missing AMI, current guidelines advocate using diagnostic coronary angiography to guide first-line diagnosis and therapy.[3] However, bedside clinicians often have a dilemma when cardiac catheterization and thrombolytic therapy are either relatively contraindicated or can cause potential adverse consequences. Meanwhile, in patients with cardiac pump failure and hemodynamic instability, misdiagnosing TTC as AMI will lead to initiation of harmful pharmacological or device-based treatment, which worsens hemodynamic compromise.[4] Thus, understanding and interpreting the unique pathophysiological and hemodynamic features of TTC in a better manner becomes crucial to guide effective clinical management of acute heart failure/cardiogenic shock during TTC. We review recent advances[5–12] in echocardiographic diagnosis of TTC and its role in guiding appropriate management of heart failure and cardiogenic shock, with specific focus on interpreting the unique pathophysiology underlying the discrepant, but reciprocally dependent, left ventricular (LV) and right ventricular (RV) hemodynamics during TTC.

LV Functional Changes

Compared with patients with AMI, those with TTC usually have higher LV volumes (both systolic and diastolic) and worse systolic function (lower LV ejection fraction). Quantitative wall motion abnormalities in those with TTC, measured by the wall motion score index, are more prominent than those with AMI.[13] With two-dimensional (2D) echocardiography, although similar "apical ballooning" is sometimes observed in both AMI (Fig. 1A: in diastole; Fig. 1B: in systole) and TTC (Fig. 1E: in diastole; Fig. 1F: in systole), the distinctive segmental wall motion patterns can help us differentiate between TTC and AMI. In contrast with AMI, TTC typically results in a hypocontractile (or akinetic) apical wall, but hypercontractile basilar walls, and its abnormal anatomic distribution is not confined to any single coronary artery

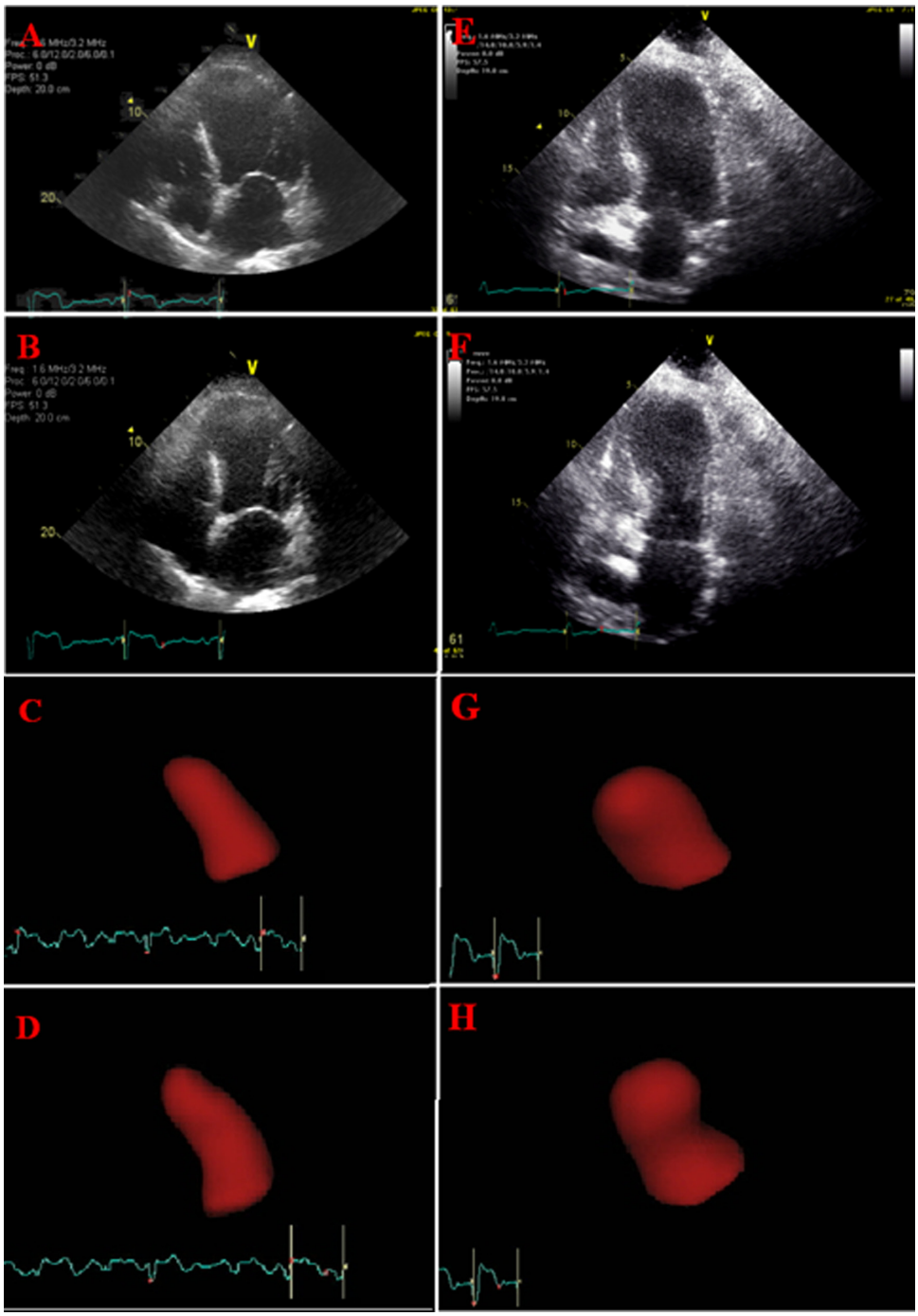

Figure 1. Distinctive distribution patterns of left ventricular (LV) wall motion abnormality in two-dimensional (2D) (**A, B, E,** and **F**) and three-dimensional (3D) (**C, D, G,** and **H**) echocardiography images in patients with anterior ST segment elevation myocardial infarction (AMI) and Takotsubo cardiomyopathy (TTC).
Notes: Left panels: AMI; right panels: TTC.

territory (Movie Clips 1 and 2). These imaging features can be better characterized with three-dimensional (3D) and strain echocardiography techniques.

In contrast with 2D techniques, 3D reconstruction[14] reduces anatomic assumption and estimation errors in the assessment of the segmental wall motion. With this technique, distinctive segmental wall motion pattern can be characterized and distinguished between AMI (Fig. 1C: in diastole; Fig. 1D: in systole) and TTC (Fig. 1G: in diastole; Fig. 1H: in systole). AMI is usually caused by the culprit lesion within the left anterior descending (LAD) artery, and its regional wall motion abnormality is confined to the LAD territory.[15,16] In contrast, the contractile abnormalities in TTC are "circular," involving multiple coronary artery territories. After 3D reconstruction, the topography of LV segmental myocardial dysfunction in TTC is characterized by symmetrical wall motion abnormality extending equally into the anterior, inferior, and lateral walls. Meanwhile, the motion of

the basilar LV segments is hyperkinetic, showing significant discrepancy in myocardial contractile status between apical and basal walls.

Interestingly, the abnormal electrocardiographic (EKG) changes in TTC have also been previously identified beyond a single coronary artery territory[15–17]: TTC is more frequently associated with ST segment elevation in leads III, aVF, II, –aVR, and I, especially lead –aVR, and is less frequently associated with ST segment elevation in leads aVL and V_1–V_4, especially lead V_1.[15] In addition, although "ST segment elevation" EKG change in the anterior precordial leads can occur in patients with either AMI or TTC, different ST segment changes in the inferior leads often provide the hint for distinguishing TTC from AMI. In AMI, ST depression in the inferior leads usually presents as a reciprocal change (Fig. 2A). However, this reciprocal change is often absent in TTC. Instead, coexisting ST segment elevation in the inferior leads is commonly identified, particularly with ST segment elevation in lead II being more prominent than that in lead III (Fig. 2B).

Strain/strain rate echocardiography can add more diagnostic value to the differentiation of AMI and TTC. Strain/strain rate analysis assesses myocardial deformation directly, which is independent of not only volume but also myocardial tethering or translational effects. Thus, 2D strain with speckle-tracking analysis automatically tracks myocardial motion throughout the cardiac cycle and allows the rapid generation of regional myocardial strain curves that are site specific and angle independent.[18] This technique quantifies ventricular radial, circumferential, and longitudinal strains. Systolic peak longitudinal strain has been proven to deliver reproducible and quantitative ventricular segmental and global assessments, resulting in incremental increase in sensitivity, specificity, and diagnostic accuracy during the evaluation of abnormal subclinical myocardial contractility.[19,20] An automated function imaging (AFI) based on 2D strain with speckle-tracking

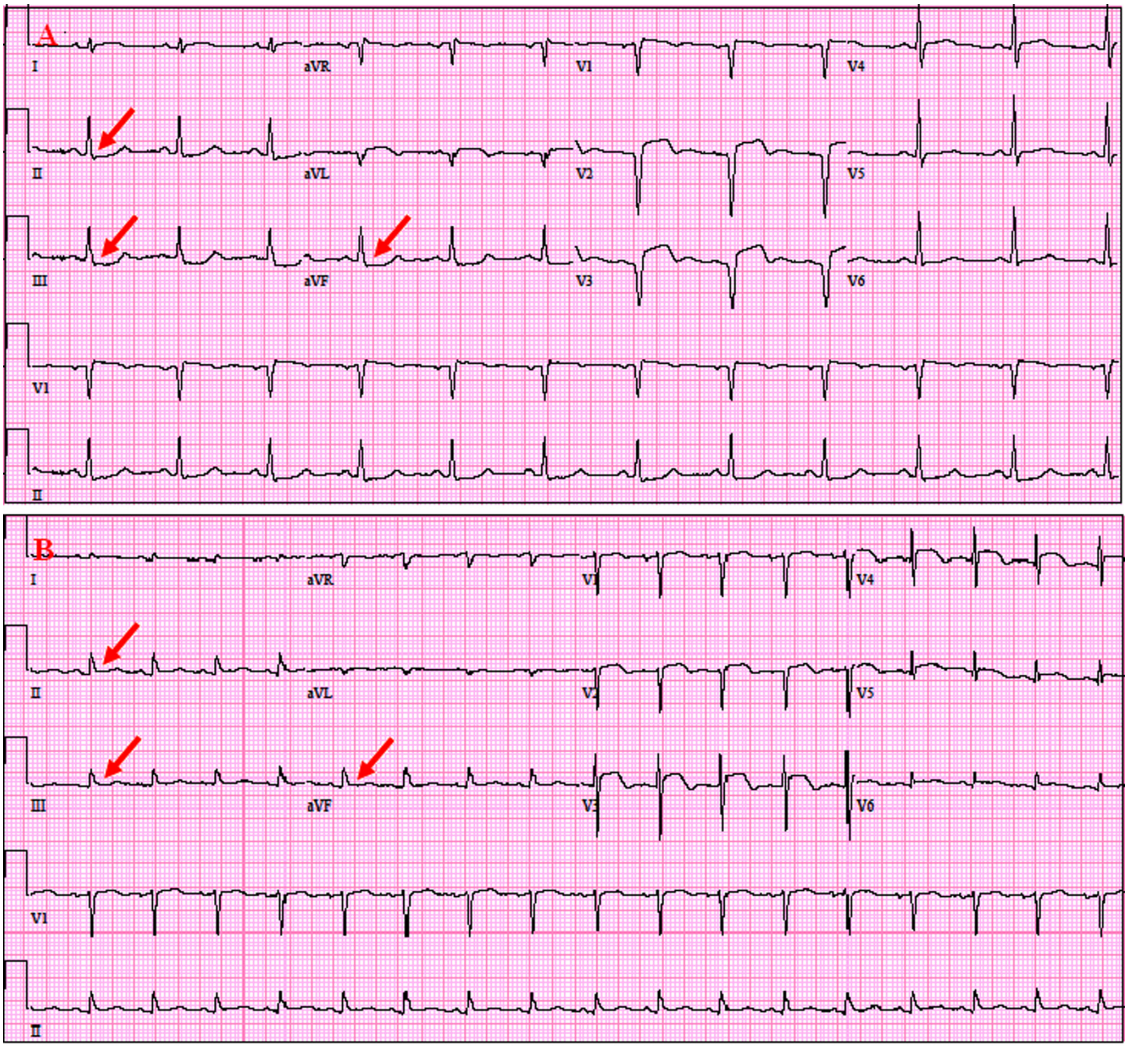

Figure 2. Distinctive "ST segment elevation" electrocardiographic (EKG) patterns in patients with anterior ST segment elevation myocardial infarction (AMI) and Takotsubo cardiomyopathy (TTC) (left panels: AMI; right panels: TTC). In AMI, ST depression in the inferior leads usually presents as a reciprocal change in patients with anterior myocardial infarction (**A**). Coexisting ST segment elevation in the inferior leads is commonly identified, particularly with ST segment elevation in lead II being more prominent than that in lead III (**B**).

analysis can integrate LV peak systolic longitudinal strain into a "bulls-eye" figure in a standard 17-segment LV model, thus being especially useful in the identification of different patterns of regional contractile abnormality between AMI and TTC (Fig. 3A and C[10,21]). The recently developed four-dimensional (4D) strain technique uses a robust postprocessing tool to track myocardial contractility from frame to frame in three dimensions over time and further improves the diagnostic accuracy of strain techniques (Fig. 3B and D). Using the new-generation echocardiography machines, bedside physicians are able to rapidly perform area strain analysis and process AFI maps, either online or offline, to establish the "real" distinctive myocardial deformation curves through the entire cardiac cycle in both TTC and AMI.

LV Hemodynamic Changes

LV filling pressure. Interestingly, although both 2D and 3D images reveal that patients with TTC have worse systolic dysfunction than those with AMI, Doppler studies suggest that their LV filling pressures appear to be lower.[22] The ratio of early diastolic mitral valve inflow velocity (*E*) to mitral annulus velocity (*E*a), *E*/*E*a ratio, is a well-established noninvasive method to estimate LV filling pressure. Both *E* and *E*/*E*a ratio are usually lower in most TTC patients than in those with AMI.[22] Indeed, the combination of Doppler and tissue Doppler measurement often gives us important clues that enable differentiation between TTC and AMI during cardiac shock.

Dynamic LV outflow tract obstruction. Myocardial stunning is usually the reason for pump failure and cardiogenic shock in AMI. In contrast, dynamic LV outflow tract (LVOT) obstruction may play an important role in the low cardiac output in TTC patients,[9,11] particularly when they receive inappropriate treatment (positive inotropic agents or insufficient fluid repletion). Both significantly decreased ejection time and increased gradient across LVOT can be detected in TTC.[9] This is likely contributed by both hyperdynamic motion of the basilar walls and systolic anterior motion (SAM) of the anterior leaflets of the mitral valve. The LVOT obstruction in TTC is likely more severe if there is preexisting hypertrophy of the basal septal wall.[23]

Functional mitral regurgitation. In contrast with acute ischemic mitral regurgitation (MR) in AMI, which is usually caused by mitral valve leaflet tethering with dysfunctional papillary muscle, MR in TTC is usually induced, or enhanced, by disrupted coaptation of the mitral valve produced by SAM.[9,11,24] Thus, the direction of MR jet is usually either

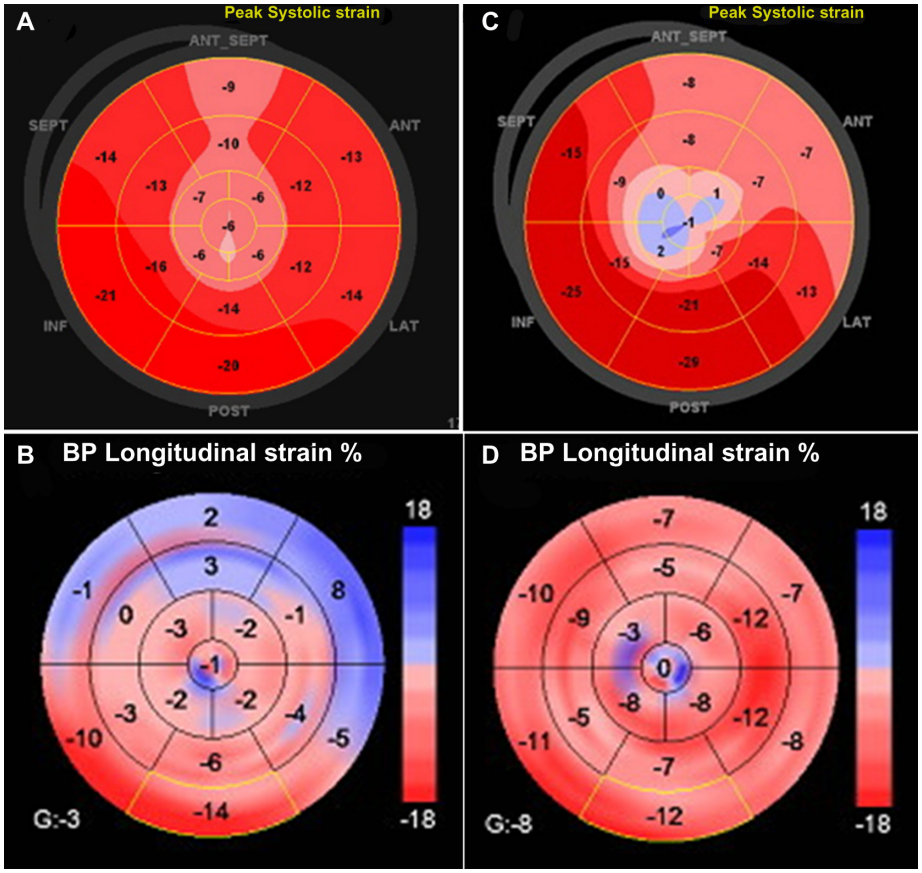

Figure 3. Different myocardial deformation/strain measurements in patients with AMI and TTC. Left panels: AMI; right panels: TTC. Two-dimensional (2D) strain and speckle-tracking analysis shows peak systolic longitudinal strain in a 17-segment LV model (**A** and **C**); four-dimensional (4D) strain technique shows the real-time area strain patterns in a 17-segment LV model (**B** and **D**). The walls with decreased peak systolic strain are highlighted by both digital and color codes.

centric or posterior in AMI but anterior in TTC.[9,11] The duration of MR is usually long (pansystolic) in AMI but short (late systolic) in TTC.[9]

Interestingly, as an MR jet-based assessment of LV systolic function, the isovolumic contractility index dP/dt is also significantly different between TTC and AMI during cardiogenic shock. The dP/dt index is measured by using the time interval between 1 and 3 m/sec of MR velocity (in continuous wave spectrum) during isovolumetric contraction (before the aortic valve opens, when there is no significant change in left atrial [LA] pressure). Moreover, dP/dt is usually lower in TTC than in AMI, probably due to worse systolic dysfunction in TTC.

RV Functional Changes: Reverse McConnell's Sign?

RV involvement in TTC has been previously described.[25,26] We recently identified a characteristic feature of RV morphology and function in TTC.[9,10] In AMI, the motion of the RV free wall is lack of characteristic feature. During TTC, the motion of basilar and middle segments of RV free wall appears to be hyperkinetic. In contrast, the motion of apical segment of RV free wall is hypokinetic in TTC, in the same manner as its LV apex motion[9,10] (Fig. 4A and B, Movie Clip 2). This discordant motion feature is exactly opposite to the classic echocardiographic appearance of acute massive pulmonary embolism, McConnell's sign. The hyperkinesis of RV likely, at least partially, represents an adaptive physiologic response to low LV preload, to maintain cardiac output. However, the tethering of RV apex to an akinetic LV apex in TTC accounts for reduced wall motion of its RV apex. Interestingly, this "reverse McConnell" phenomenon might be also found in some patients with severe and acute cardiogenic shock, which is not caused by TTC. Therefore, an interesting postulate was raised recently[7,8]: TTC might be a ubiquitous contingent self-protection system of the heart, to avoid adverse outcome when it is jeopardized.

In TTC with cardiogenic shock, the location of the hinge points (between hyperkinetic and hypokinetic segments) in RV free wall often approaches the same level as the hinge points in LV septal, lateral, and inferior wall.[9,10] Interestingly, this condition is often associated with worse RV failure symptoms,[10,25] "RV strain pattern" in EKG,[10] and higher levels of the heart failure biomarker brain natriuretic peptide (BNP).[27]

RV Hemodynamic Changes

Due to the lack of well-established methodologies to assess RV function and hemodynamics,[28] the data on RV hemodynamic change during TTC is very limited. We recently reported that reversible tricuspid regurgitation (TR) could be a unique imaging finding in TTC with cardiogenic shock.[11] In contrast to TR in AMI, the severity of TR often becomes worse with the onset of TTC and significantly improves after recovery from TTC.[11] Thus, if there are previous echoimaging data available, the changes in the severity (regurgitant volume) of TR from Doppler/color Doppler and quantitative measurements will be likely helpful for the differential diagnosis between TTC and AMI.

As discussed before,[11] during TTC, the hyperkinetic motion of RV possibly generates higher systolic pressure and increases the gradient between RV and right atrium during systole. Meanwhile, SAM-associated MR in LV increases pulmonary venous pressure and RV afterload. Both mechanisms can contribute to the dynamic increase of regurgitant volume of TR during TTC, despite unchanged effective tricuspid valve regurgitant orifice area.[11] This explains the worse symptoms and signs of right heart failure previously reported in patients with "severe TTC."[25]

Supporting Interventricular Dependency in Patients with Benign Clinical Course

The characteristic clinical features of TTC include the following: 1. In spite of its sometimes-grave presentation, TTC

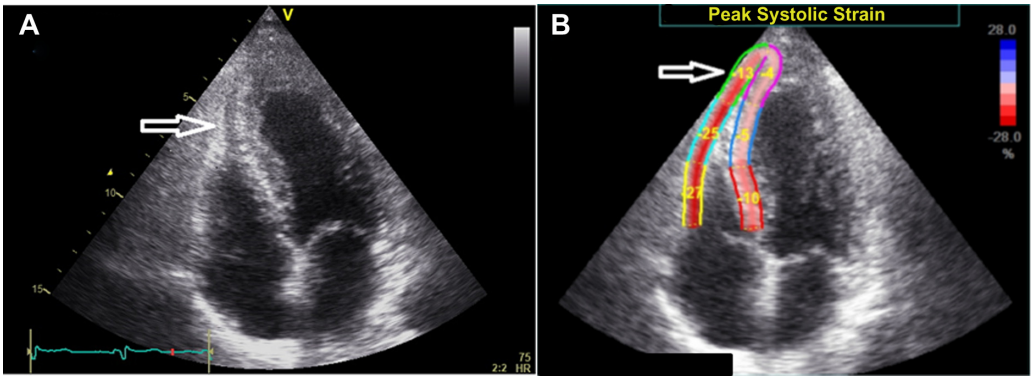

Figure 4. A unique right ventricular (RV) feature, "Reverse McConnell's Sign," shown in a two-dimensional image (**A**) and speckle-tracking analysis images (peak longitudinal peak systolic strain) (**B**).

Notes: Movie Clip 1 Distinctive left and right ventricular wall motion patterns in the apical four-chamber windows of two-dimensional echocardiography in patients with anterior ST segment elevation myocardial infarction (AMI). Movie Clip 2 Distinctive left and right ventricular wall motion patterns in the apical four-chamber windows of two-dimensional echocardiography in patients with Takotsubo cardiomyopathy with right ventricular "Reverse McConnell's Sign."

usually rapidly improves without residual cardiac impairment; 2. despite remarkable increase in the heart failure biomarker BNP, the increase in the myocardial injury biomarker (troponin) is often insignificant; 3. hypokinesis of LV (except for basilar walls) is concurrent with hyperkinesis of RV; 4. the increase of LV filling pressure is not proportional to the severity of LV systolic dysfunction. Unraveling the mechanism underlying these clinical discrepancies can virtually help us distinguish TTC from AMI in patients and guide appropriate management.

Excessive sympathetic stimulation has been found to play an essential role in the pathogenesis of TTC.[29] Recent studies further suggest that TTC is mediated by a switching of epinephrine signaling transduction through the pleiotropic β_2-adrenergic receptor (β_2AR) from canonical stimulatory G-protein–activated cardiostimulant (Gs) to inhibitory G-protein–activated cardiodepressant (Gi) pathways. The biased agonism of β_2AR-Gs and β_2AR Gi between cardiac apex and base underpins its characteristic apical ballooning feature.[30,31] β_2AR Gi signal transduction has been well studied and is known to be antiapoptotic and cardioprotective. Thus, this switching on of epinephrine signaling transduction during TTC might have likely evolved as a cardioprotective strategy to limit catecholamine-induced myocardial toxicity during acute stress.[32]

Clinic evidences also support the self-protective role of TTC. In response to a variety of stresses and excessive sympathetic stimulations, an acute LV dilatation likely represents an intrinsically active, instead of passive, reaction of the heart, to avoid irreversible damage of the vulnerable myocardial portions within the heart. Without concurrent increase in LV blood volume and preload, the LV filling pressure will not significantly increase accordingly. This not only avoids abrupt increase in pulmonary capillary wedge pressure and pulmonary edema but also reduces the harmful regional stress on LV walls. At the same time, activation of the less-vulnerable myocardium of basilar RV and LV walls can form a transiently alternative conduit, bypassing most of the apical and middle cardiac cavities and detouring blood flow through the base of the heart toward LVOT. This helps maintain reasonable cardiac output and fulfill the blood demand from rest of the body. In most TTC cases, this discrepant, but reciprocally dependent, interventricular functional status is able to protect the majority of the myocardium from irreversible injury and maintain TTC patients' hemodynamic stability, until the trigger factors and excessive catecholamine surge subside. Therefore, this well-coordinated machinery is able to keep up benign clinical courses in most (probably including clinically elusive or undiagnosed) TTC cases.

Therefore, the therapeutic strategies for most TTC patients with benign clinical manifestation and hemodynamic stability should involve mainly support, not disruption, of this intrinsic, and likely preprogrammed "rescue" mechanism by the heart, to avoid worsening hemodynamics.

Managing TTC Patients with Malignant Clinical Phenotypes (Acute Heart Failure and Cardiogenic Shock)

The causes of malignant clinical phenotypes of TTC, such as acute heart failure and cardiogenic shock, could be multifactorial, such as severe LV systolic dysfunction, severe MR, and dynamic LVOT obstruction.[33] Timely identification and addressing of the specific etiologies that interrupt the otherwise-harmonious interventricular dependent system is the key to guiding effective therapy for these "malignant TTCs" and avoiding or reducing adverse events.[9] When the sympathetic stimulation is too strong, or there are preexisting cardiac structural or functional abnormalities that impinge on this transiently functional "rescue" pathway within the base of the heart, acute heart failure and cardiogenic shock can possibly occur.

Myocardial hypercontractility in TTC mainly involves basal LV and RV walls. A preexisting structural abnormality, isolated basal septal hypertrophy (often found in elderly females and patients with long history of uncontrolled hypertension), can mechanically precipitate the development of dynamic LVOT obstruction.[34–36] The reflex tachycardia after LVOT obstruction will shorten the diastolic time, lower LV diastolic preload, and deteriorate this vicious cycle. Either preexisting RV dysfunction or uncoupling of LA to LV mechanics from atrial fibrillation can also prevent efficient LV preload refilling. Inappropriate utilization of diuretics and catecholamine pressors will significantly worsen this condition. Therefore, although LVOT obstruction is not commonly found in hemodynamically stable TTC patients, definitive or latent dynamic LVOT obstruction might play a much more important role in the development of heart failure and cardiogenic shock during TTC.[9] SAM of the anterior leaflet of the mitral valve not only worsens LVOT and reduces stroke volume but also disrupts coaptation of mitral valve and increases regurgitant volume. MR can simultaneously decrease cardiac output and increase pulmonary venous pressure. As a consequence, hemodynamic instability and pulmonary edema/worsened TR can occur.[25]

In TTC patients with clinical acute heart failure and hemodynamic instability, maintaining appropriate LV preload, to attenuate dynamic LVOT obstruction and secondary MR/TR, should be the major therapeutic target in the acute stage.[7] The therapeutic efficacy of beta-blockers[37] and alpha-antagonists on TTC-associated LVOT obstruction and cardiogenic shock warrants further investigation.[38] Due to its afterload reduction effect and potential to increase LVOT gradient, the application of intra-aortic balloon pump in patients with TTC and LVOT obstruction is likely harmful. Instead, extracorporeal membrane oxygenation or new-generation percutaneous Impella ventricular assist device can be considered as an alternative way to support TTC patients' hemodynamics during acute heart failure and cardiogenic shock.[39]

Summary

In the past decades, research effort has been continuously devoted to looking for differences in either morphological or functional properties between TTC and AMI. However, evidence is concurrently mounting that TTC and AMI might sometimes share intrinsic functional components.[40] Better interpretation and understanding of the unique pathophysiological features and the discrepant and interdependent ventricular hemodynamics during the acute stages of TTC comprise the most important steps to help us appropriately manage the malignant phenotypes of TTC and avoid adverse events/outcomes. Therapeutic strategies for most TTC patients with benign clinical manifestation should mainly involve the support, not disruption, of the intrinsic "rescue" mechanism of the heart. In TTC patients with acute heart failure and cardiogenic shock, maintaining appropriate LV preload, to attenuate dynamic LVOT obstruction and secondary MR/TR, should be the major therapeutic target during acute stages. The therapeutic efficacy of beta-blockers and alpha-antagonists warrants further investigation. Novel ventricular assist devices might be considered an efficient strategy if the intrinsic "rescue machinery" of the heart fails to support RV hemodynamics.

Author Contributions

Conceived the concepts: KL. Wrote the first draft of the manuscript: KL. Contributed to the writing of the manuscript: ZXS, TMW. Made critical revisions and approved final version: KL. All authors reviewed and approved the final manuscript.

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