McConnell’s Sign – an insight into the Pathogenesis of Takotsubo syndrome?

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Introduction

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy, is an acute cardiac syndrome. The unique characteristic of TTS is that one or more circumferential cardiac segments are stunned out of contraction in the absence of an explanatory coronary lesion\(^1\). Although the peculiar myocardial akinesia can affect any part of the ventricular wall, the common patterns of TTS are *apical akinesis* (the typical TTS) and *basal akinesis* (the inverted pattern)\(^2\). The pathogenesis underlying Takotsubo syndrome is incompletely understood. Several mechanisms have been proposed for the development of TTS, including overstimulation of the β2-adrenoceptor-Gi pathway\(^3\), acute coronary microvascular and endothelial dysfunction\(^4\), aborted myocardial infarction with spontaneous recanalisation\(^5\), acute metabolic stunning\(^6\), acute left ventricular outflow tract obstruction (LVOTO) and abnormal ventriculo-arterial coupling.

One critical shortcoming of some these proposed mechanisms is that they are not able to elucidate why myocardial akinesia in TTS is usually segmental and circumferential. Although the gradient distribution of β-adrenoceptors or sympathetic nerves in the heart may explain why catecholamine-induced myocardial akinesia can be apical or basal, such physiological properties, including genetic profiles, currently fail to explain why different anatomical variant of TTS can recur in one patient\(^7\).

McConnell’s sign associates with elevated afterload and mimics inverted Takotsubo

McConnell’s sign is an characteristic echocardiographic finding of the regional dysfunction of the right ventricle in pulmonary embolism (PE)\(^8\). Figure 1 shows the typical pattern of McConnell’s sign in a patient with acute PE: a distinct bulge
(indicating akinesia) in the mid-free wall of the right ventricle during a systole, while the apex is spared from dysfunction and contracts into a peak cone. The unique pattern of cardiac contractile dysfunction in PE has certain features which resemble inverted Takotsubo syndrome (Figure 1)?

Acute embolic occlusion of a large pulmonary artery causes an abrupt increase in pulmonary artery pressure, and thus an elevated afterload for the right ventricle. This may lead to increased wall-stress and akinesia in the basal myocardium, thus explaining McConnell’s sign. Similarly, in a preclinical model we identified that the inverted TTS variant was associated with high afterload. We were able to induce variant patterns of TTS by catecholamines, which have different effects on afterload. Low afterload seems to restrictively precipitate the development of typical TTS (apical akinesia), while high afterload leads to inverted TTS variant. Moreover, interfering with the effects of a catecholamine on blood pressure alters the pattern of TTS, which is supposed to be induced by the catecholamine. We hypothesise that the level of ventricular afterload may influence which cardiac segments are subjected to increased wall-stress and thus circumferential akinesia. However the interplay of afterload and internal LV cavity pressures with other factors including perfusion, adrenergic signalling and how these effect only a certain cardiac segments, but not the entire ventricular wall, is unclear.

**Sequential contraction may determine how the ventricular afterload affects wall-stress in a restricted segmental distribution**

The ventricular myocardium has been divided schematically into 16 segments, and these are sequentially stimulated in circumferential groups to contract and eject blood from the ventricular cavity. The myocardium of each segment is highly
organised in three layers. The endocardial layer goes in helix-strand ascending, while the epicardial myofibres are helix-strand descending. The middle layer is circular and parallel to the ventricular equator, and perpendicular to the apical-basal axis (Figure 2A)¹¹. The helical-strand muscles generate circumferential torsion forces that rotate the apex and basal myocardium in opposite directions (along the long axis), while contraction of the circular muscles contributes to radial contraction and ejection of blood from the cavity during systole. Contraction of these cardiac muscle layers produces different vectors of peak strain (see Figure 2B). Sequential electrical activation of these cardiac muscles is potentially important for the efficiency of ventricular systole. Based upon the anatomy of the bundle of His and Purkinje fibre system cardiac contraction usually starts at the apex and advances towards the base. During systole transmural pressure passively imposed on cardiac segments may be continuously changed during a systole. More specifically, during the isovolumetric contraction of a systole, wall-stress in the basal myocardium is progressively raised due to the earlier contractions of the apex and the mid-ventricular wall. For the purpose of the present discussion, wall-stress passively imposed on a cardiac segment is termed preload wall-stress. In the setting of PE, or stress with increased systemic vasoconstriction, where afterload is severely elevated, high intraventricular pressure is required to open the pulmonary/aortic valve. This will introduce increased transmural pressure and preload wall-stress to the basal myocardium. If the preload wall-stress exceeds the limitation that basal myofibres can afford, contraction of the myofibres is disrupted, possibly explaining basal akinesia in PE and inverted TTS. Perhaps contractile band rupture observed in the hearts of TTS patients is due to a cardiac segment contracting against such an extremely increased preload wall-stress that the myofibres get ruptured.
However, low afterload seems to distribute preload wall-stress differently from high afterload. Because the aortic valve opens when intraventricular pressure exceeds the pressure of the aortic artery, transmural pressure and preload wall-stress in the basal myocardium is unlikely to reach a high level in the condition of low afterload. This probably explains why the base can be spared from akinesia in typical Takotsubo, where the afterload is severely decreased. However, with a strong inotropic and chronotropic drive of catecholamines, intensive and rapid contraction of the base may precipitate outflow obstruction and cause an increase in wall-stress of the apical myocardium. Indeed, outflow obstruction has been recorded in 25% of patients with typical TTS\textsuperscript{12}. Perhaps outflow obstruction is one pivotal factor in determining how low-afterload introduces increased wall-stress only to the apical or apical-middle myocardium. However, because the apex usually contracts before the base, how the base is able to contract before the apex and obstructs the outflow is not clear. We hypothesise that the characteristic twisting and rotating contraction of the heart may be relatively delayed in the apex, compared with the circumferential contraction in the base, when heart frequency is significantly accelerated. In our experiment, delayed apical twisting contraction has been recorded in many rats before apical ballooning (apical akinesia) is fully developed (Video 1).

**Increased wall-stress triggers myocardial stunning, possibly by myocardial overstretch**

How increased wall-stress results in myocardial akinesia has not been completely determined. One mechanism proposed for McConnell’s cardiac dysfunction is localised ischemia as a result of increased wall-stress in the free wall of the right ventricle\textsuperscript{9}. Elevated wall-stress increases oxygen consumption\textsuperscript{13, 14} and perhaps results in a relative myocardial ischemia due to a demand-supply mismatch. We believe that
a similar demand-supply mismatch also occurs in the setting of TTS, where coronary
blood flow is not significantly decreased but energy demand is severely increased\textsuperscript{15}. However, ischemia may not be the major cause of the cardiac stunning in TTS, though it does cause cardiac dysfunction. Myofibres may become overstretched in the cardiac segments exposed to suddenly increased wall tension/stress, overstretch-induced contractile dysfunction\textsuperscript{16} may be the onset of myocardial stunning. Overdistention of myofibres reduces contractility, due to a series of stretch-induced abnormalities, e.g., sarcomere overstrain, fewer cross-bridges between myosin and actin, stretch-induced currents\textsuperscript{17}, cytoplasmic calcium alteration\textsuperscript{18}, and instability of membrane potential\textsuperscript{19}. In addition, repeated passive stretching of the myocardium in the affected cardiac zone tends to produce progressive lengthening of the myofibres – so-called stretch-induced ‘creep’ and ‘softening’\textsuperscript{16, 20}. These effects may contribute to explain the unique deformation of \textit{paradoxical spherical bulging} during systole in the akinetic cardiac area, which is observed in McConnell’s sign and TTS. We have hypothesise that TTS myocardial stunning occurs as the heart alters metabolism to preserve energy for basic non-contractile cellular survival during severe oxygen insufficiency, by shutting down mechanical cardiac activity\textsuperscript{15}. Overstretch may be one mechanism potentiating the myocardium to cease mechanical contraction.

In conclusion, McConnell’s sign describes the unique cardiac dysfunction observed in pulmonary embolism. The mechanism is associated with increased wall-stress of the mid-free right ventricular wall as a result of abruptly increased pulmonary artery pressure. A similar mechanism may be a factor in the development of inverted Takotsubo. The development of inverted TTS in a preclinical model is closely associated with a high afterload, while typical TTS (apical ballooning) was usually observed in the context of a low afterload in the same preclinical model.
Sequential contraction of cardiac muscles may be crucial in determining whether the base or apex is subjected to increased wall-stress (and thus akinesia) in the condition of high or low afterload. Increased wall-stress, resulting in myocardial akinesia, may lead to overstretch-triggered myocardial stunning. Ischemia-related myocardial dysfunction as a result of increased wall-stress may also interact with these and other mechanisms to promote the development of myocardial stunning.

7. From AM, Sandhu GS, Nkomo VT, Prasad A. Apical ballooning syndrome (Takotsubo syndrome) presenting with typical left ventricular morphology at initial presentation and mid-ventricular variant during a recurrence. *J Am Coll Cardiol*. 2011;58:e1


A similar pattern of myocardial dysfunction develops in pulmonary embolism (PE) and inverted Takotsubo syndrome. In both conditions, the apex contracts and forms a peak cone (yellow arrows), while the base and the mid-free wall are stunned out of contraction and paradoxically bulge out during systole (blue arrows). The left picture is an echocardiograph of the unique myocardial dysfunction in the right ventricle in the setting of PE (McConnell’s sign). The right picture is left ventricular endsystolic ventriculography in a subject with inverted Takotsubo syndrome.
Arrangement of the ventricular muscles and strength patterns after muscle contraction.

Cardiac muscles are highly organised in three layers. The epicardium is helix-descending and
the endocardium is helix-ascending. Contraction of these helix muscles generates strengths of helix-ascending (green arrows), strengths towards the base along the long axis (red arrows), and clockwise circumferential strengths (blue arrows). The mid-ventricular muscles are circular and are on the planes of the short axis. Contraction of the circular muscles produces strengths pointing to the centre on the plans of the short axis (purple arrows).