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Editorial Open Access

Tako-Tsubo Stress Cardiomyopathy-A Quantum Event of the Heart?

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Editorial

Like quantum physics:

Two spaces,

One time,

Two times,

One place.

Finite and infinite mime

As light spread

From a prism,

Intellectual chasm,

Simple spasm,

Tsunamic schism,

A rare phantasm.

A quantum event,

Spread and spent

In time and space,

A lethal race,

A question

Of time.

(Alexandra Lucas-2015)

Tako-tsubo cardiomyopathy, named for a Japanese fisherman's octopus trap, is an extraordinary event wherein a so-called stress event induces a large area of myocardial stunning. A Japanese physician Dr. Sato first described Tako-tsubo cardiomyopathy at the Hiroshima City Hospital in 1990 [1-4]. In its classic form, there is aneurysmal dysfunction of the apical myocardium with dyskinesis and bulging of the ventricular wall, but with preserved function of the base of the heart. As might be predicted, there are also other atypical variants, including one which is reported to affect selectively the mid-portion of the left ventricle [5]. Tako-tsubo's cardiomyopathy is now considered to represent a group of acute onset cardiomyopathies, which are also named stress-induced cardiomyopathies.

We would like to open a discussion around the prevailing opinions and the available evidence that this cardiomyopathy is the result of an adrenaline surge, with stress causing microvascular dysfunction on a wide scale [6-8]. Atherosclerotic plaque rupture or erosion with *in situ* thrombosis resulting in ST elevation myocardial infarction (STEMI or acute heart attack) has been considered a distinct event, unrelated to Tako-tsubo cardiomyopathy. However, many of the measurements demonstrating a catecholamine excess and abnormal vasoreactivity, signs of microvascular dysfunction, have been recorded after the inciting event is complete. Thus, only a snapshot of the devastation is seen. Just as when a photographer captures the after effects of a tidal wave, the initial seismic event that results in a tsunami is not recorded. We would like to suggest that plaque erosion and thrombosis with distal emboli causing downstream or distal microvascular occlusions may be, like a tidal wave that wreaks havoc on the shoreline, the initiating events for a cardiomyopathy such as Tako-tsubo [8-10]. It is certainly well understood that the coagulation serine protease system, the inflammatory and also the hemodynamic vascular systems that regulate arterial pressure and tone have very close interactions. This editorial is intended to open up a discussion on the potential inciting events for this cardiomyopathy.

Our understanding of the pathophysiology of Tako-tsubo cardiomyopathy is, as mentioned above, based upon studies performed after the event has occurred. There is evidence for increased adrenergic activity with microvascular spasm and subsequent reduced or sluggish blood flow [6-8]. Reduced or impaired microvascular vasoreactivity has been measured in clinical studies where measurements are generally recorded in patients after the heart is already damaged. Evidence for unstable or ruptured plaque has been variable [9,10]. Thrombotic [11] as well as inflammatory [12] reactants have not been significantly increased in Tako-tsubo patients when compared to acute unstable coronary syndromes or STEMI. However, endothelial dysfunction, vasospasm and stasis of blood flow are all associated with increased thrombosis. Conversely, elements in the thrombotic and thrombolytic protease cascades or indeed with the prostacyclin and thromboxane pathways can induce both changes in local vasoreactivity as well as thrombosis [13,14].

Tako-tsubo often presents as an anterior infarction on EKG and on echocardiogram with attendant elevation of cardiac enzymes, initially indistinguishable from a STEMI. Thus patients with Tako-tsubo often have EKG changes, regional LV systolic dysfunction on echocardiography, and abnormal cardiac biomarkers suggestive of acute myocardial infarction on presentation, much like a patient with a

STEMI. However, when the patient is taken to the cardiac catheterization lab for urgent coronary angiography, the coronaries are noted to be patent with excellent TIMI III flow. There is occasional note made of luminal irregularities on non-obstructive (less than 50-70%) narrowing in the major left coronary branches. This cardiomyopathy is then diagnosed as an acute onset cardiomyopathy of unknown etiology often referred to as a stress cardiomyopathy.

Intravascular ultrasound was unable to detect ruptured plaque in one study on a series of patients admitted with Tako-tsubo cardiomyopathy [9], while a second study detected unstable plaque, with rupture or erosions, in a high percentage of patients [10]. Ultrasound can be misleading, as thrombus or plaque rupture may not always be accurately identified. While 70% of unstable plaques in acute infarction are indeed produced by plaque rupture, 30% are caused by simple plaque erosion or calcified nodules that protrude through the plaque, causing local plaque disruption and thrombosis [15]. These reports would suggest that we do not as yet have sufficient evidence to determine whether unstable plaque and thrombosis with distal embolization can or cannot cause Tako-tsubo cardiomyopathic changes. Nonetheless, the consensus has been that a diffuse vasospastic event with a catecholamine gradient causes this acute event. Analysis of myocardial blush in prior studies certainly has indicated impaired distal myocardial perfusion [16,17]. Whether this is due to vasospasm or microemboli remains ambiguous, and is not readily determined by conventional coronary angiography.

Noninvasive imaging studies demonstrate findings consistent with myocardial inflammation, sympathetic denervation, and microcirculatory dysfunction occurring in regions of dysfunction, but they still do not reveal the inciting event or why there is a predilection for certain regions of the heart. Similarly we cannot rule out microvascular plaque rupture and thrombosis. Positron emission tomography studies using FDG show myocardial stunning in Tako-tsubo patients, demonstrating transient reductions in glucose metabolism in regions of abnormal systolic function despite relatively intact myocardial perfusion [18]. Similarly, in regions of dysfunction, cardiac MRI demonstrates findings consistent with edema likely due to myocardial inflammation in the acute phases of the disease that resolve with ventricular functional improvement. Late gadolinium enhancement findings at the time of presentation can vary; they are either absent or patchy, and when present they tend to resolve [19]. It is unclear if the variability in such findings invokes different mechanisms or merely varying degrees of severity.

Tako-tsubo patients often do well and ventricular function improves with time and with current treatments for both STEMI and congestive heart failure. Although the prognosis is generally favorable, acute complications are reported due to arrhythmogenic cardiac arrest, acute decompensation with severe heart failure or cardiogenic shock, as well as ventricular thrombosis and cerebrovascular accidents (stroke). As the patient is often suspected to have an acute ischemic event, with coronary thrombosis, treatment is generally initiated in the emergency room with aspirin and heparin, anti-platelet and anti-thrombotic agents, respectively. This treatment will reduce thrombotic burden and embolism. Subsequent treatment will generally include angiotensin converting enzyme inhibitors and beta blockers for the heart failure and/or arrhythmias, both of which treatments improve outcomes after myocardial infarction and also in heart failure.

We would thus like to initiate further discussion about the concept that some subsets or all of Tako-tsubo cardiomyopathic events may result from a singular event with plaque erosion or rupture. An event wherein a proximal ulcerated coronary plaque ruptures and forms a clot that, instead of causing local thrombus, spontaneously embolizes distally, and occludes numerous small arterial branches and capillaries. This embolic shower can thus spread and block blood flow, with local arterial plaque thrombosis and distal embolization occurring simultaneously, an event occurring at two places and at one time, causing acute stress induced damage to the ventricular wall. According to Davies's work on the pathogenesis of unstable plaques [15], we now know that ulceration or rupture of an atherosclerotic plaque in a coronary artery forms the basis for many myocardial infarctions. The local plaque ulceration exposes the highly pro-thrombotic and pro-inflammatory plaque components, fat and connective tissue (collagen), that in turn activates platelets and initiate the thrombotic cascade with local arterial thrombosis and occlusion preventing normal blood flow. These plaques are typically no more than 50-60% stenosed prior to rupture, erosion, and/or acute occlusion with thrombosis. There are in fact reports that these non-hemodynamically significant plaques in coronaries cause the majority of infarctions. Other pathological investigations have reported that in the setting of one acute arterial thrombotic event there are frequently multiple other sites with microthrombi, i.e., the clot formation is often widespread throughout the coronary vasculature and is not limited to a single site.

These same events may lead to local thrombosis, but it is well known that clots can propagate, i.e., thrombus induces more thrombus. Once formed, a clot can also break off and embolize downstream to distal small arterial branches. We have all seen a clot in an artery during primary PCI for STEMI that migrates distally, occluding smaller branches, as in the 'no reflow' phenomenon where there is a lack of restoration of distal blood flow. In some cases of Tako-tsubo cardiomyopathy a proximal hazy narrowing is seen in the left anterior descending artery (LAD), which might be considered a source for thromboembolic spread [9]. Stressful events have also been correlated with the triggering of acute more common ST elevation MI (STEMI), induced by plaque rupture and local occlusive thrombosis.

We would therefore query whether these snapshots that clinicians see when caring for patients with Tako-tsubo cardiomyopathy accurately depict its underlying process. We should question whether the moment of plaque rupture, thrombosis, and microvascular embolization has already occurred. Perhaps our photograph sees only the postlude when the damaged or ruptured plaque lumen surface has sealed. As a photographer might state, we may have missed the actual event and taken only a late and inaccurate picture after the actual event has occurred. In Tako-tsubo, we may perhaps be witnessing an event occurring in two places simultaneously, e.g., local thrombosis with distal embolization causing small vessel occlusions, rather than an etiology limited to the distal arterial branches of the coronary stress. Or there may be two events, with thromboemboli as well as vasospasm and possibly local microvascular plaque instability and thrombosis. The good outcomes in patients with patent coronary arteries in Tako-tsubo cardiomyopathy would also argue for an acute event where sudden arterial occlusion and subsequent reperfusion can lead to successful recovery, much as when an early PCI and stent in STEMI causes improved morbidity and mortality together with improved left ventricular function.

We thus would suggest that for Tako-tsubo cardiomyopathy we have approached the pathophysiology using linear logic, but in reality, we are witnessing a quantum event. We are witnessing an event where thrombus at a site of eroded or ruptured plaque forms but does not remain *in situ*. Instead this clot propagates and then spreads,

embolizing downstream to distal small vessels. This embolism would induce local microvascular spasm as well as thrombotic occlusion and sudden damage to the myocardium. Only further extensive investigations will demonstrate whether both diffuse vasospasm with secondary thrombosis or disseminated thromboembolic showers with secondary vasospasm cause the profound heart damage seen with Tako-tsubo cardiomyopathy.

In Tako-tsubo we would suggest that we have witnessed events that occur at two places caused at one time by one event, a true quantum event of the heart.

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