The Case for Takotsubo Cardiomyopathy (Syndrome) as a Variant of Acute Myocardial Infarction

Takotsubo cardiomyopathy (syndrome) has emerged as an important acute cardiac condition characterized by reversible left ventricular (LV) ballooning that is independent of epicardial coronary obstruction. Uncertainty about the mechanism of takotsubo events is reflected in diverse classifications for this entity, considered a cardiomyopathy (in the United States) and an acute heart failure syndrome (in Europe). Nonetheless, we believe that it is worthwhile to underscore here the consistent similarities between takotsubo events and acute myocardial infarction (AMI). The universal AMI definition requires evidence of myocardial necrosis together with myocardial ischemia (ie, chest pain, characteristic changes on the ECG, or new LV regional wall motion abnormality).

Because each of these elements is typically present during takotsubo events, we believe it reasonable to examine the available evidence for takotsubo as a novel variant of AMI, characterized by the combination of irreversibly damaged cells (necrosis), in addition to reversibly injured myocytes that demonstrate the phenomenon of ischemia/reperfusion stunning (Figure). This narrative may inform a clinically relevant classification and guide investigation into the pathophysiology of this enigmatic condition.

EVIDENCE FOR ISCHEMIA

At presentation, takotsubo events are characterized by anginal chest pain, ischemic electrocardiographic changes, and regional wall motion abnormality, a constellation of findings indistinguishable from AMI and consistent with acute myocardial ischemia. Ischemic chest pain is present in most patients during takotsubo events, often associated with ST-segment elevation, a marker of transmural ischemia and the most common electrocardiographic finding, present on admission in almost 50%. In patients without ST-segment elevation, findings consistent with subacute ischemia, including T-wave inversion and transient precordial Q waves, are frequent.

In takotsubo events, a variety of new regional wall motion abnormalities (“ballooning”) is a universal finding, immediately raising concern for acute ischemia and often leading to medical treatment with anticoagulant and antiplatelet agents for suspected acute coronary obstruction. Furthermore, transmural myocardial edema corresponding to the region of LV dysfunction, a hallmark of acute transmural ischemia, is a constant finding in takotsubo events.

Other evidence for ischemia includes reduced tissue blood flow with invasive methods (myocardial blush grade, coronary flow velocity reserve, index of microcirculatory resistance). Myocardial contrast echocardiography has documented reversible perfusion defects within abnormally contracting myocardium, similar to that observed in ST-segment–elevation AMI, whereas nuclear imaging has demonstrated circumferentially reduced perfusion matching regions of abnormal LV contraction.
EVIDENCE FOR EARLY REPERFUSION

A hallmark of takotsubo events is complete reversibility of regional LV akinesia or dyskinesia and normalization of ejection fraction, occurring over days to weeks, reminiscent of postischemic myocardial stunning, a process known to represent acute transmural ischemia interrupted by early reperfusion. The unusual electrocardiographic patterns that follow a takotsubo event, including progressive T-wave inversion and QT-interval lengthening, may also reflect early reperfusion. Electrocardiographic evolution in takotsubo cardiomyopathy generally parallels LV contractile recovery. Therefore, it resembles the dynamic repolarization changes that occur after transient anterior wall ischemia, in which progressive T-wave inversion is associated with normalization of LV wall motion, considered an electrophysiological footprint of an ischemia/reperfusion cascade.

EVIDENCE FOR MYOCARDIAL NECROSIS

Troponin elevation is virtually universal during takotsubo events, with a temporal release similar to that of AMI, generally considered biomarker evidence of necrosis. Notably, the degree of troponin elevation is often less than expected relative to the magnitude of LV systolic dysfunction, which suggests a process dominated by reversibly injured (stunned) cells associated with less irreversible injury (necrosis).

Direct histopathological evidence of necrosis can be found in myocardial biopsies showing foci of myocyte death, vacuolization with cellular debris, contractile protein disarray, and contraction bands (a unique pathological finding common to both ischemia/reperfusion AMI and catecholamine-mediated myocardial injury). Postmortem examinations in a few patients with takotsubo cardiomyopathy have identified areas of transmural injury with contraction bands or myocyte rupture. Examinations of myocardium from an experimental isoproterenol-induced takotsubo rat model revealed scattered foci of necrosis and mitochondrial edema and macrophages with cellular debris, consistent with ischemia-mediated myocardial injury. Late gadolinium enhancement has been reported in 40% of patients with takotsubo cardiomyopathy (with the use of a threshold of 2 SD above remote myocardium), associated with higher troponin levels. This observation suggests that the degree of myocardial necrosis present in most takotsubo events approaches the resolution of current cardiac magnetic resonance.

DISSIMILARITIES: TAKOTSUBO VERSUS AMI

Despite the many similarities detailed here, certain clinical differences distinguish takotsubo events from AMI.
First, the occurrence of ischemia in takotsubo events must be reconciled with the absence of acute epicardial obstruction, suggesting the possibility of a process with its genesis at the microvascular level. Second, the degree of LV systolic dysfunction in takotsubo events (ejection fraction, 30%-40%) typically exceeds that characteristic of AMI (ejection fraction, 40%-50%). In AMI, lower ejection fraction is associated with greater mortality, yet hospital mortality in takotsubo events is comparable to that of AMI despite a greater magnitude of LV systolic dysfunction, probably because ejection fraction usually recovers rapidly to normal after takotsubo events. Finally, treatment for AMI focuses on urgent revascularization, whereas in takotsubo cardiomyopathy, there currently is no effective therapy that can promote LV contractile recovery or prevent recurrence.

SUMMARY
In consideration of our critical analysis of a substantial body of evidence, we propose that takotsubo cardiomyopathy (syndrome) conforms closely to a variant of AMI characterized by acute transmural ischemia interrupted by spontaneous reperfusion, resulting in a unique condition for which dominant features are postischemic myocardial stunning and irreversible injury (necrosis). Evidence for acute myocardial ischemia includes typical presenting symptoms together with ischemic electrocardiographic changes, transmural myocardial edema, and regional wall motion abnormality. The presence of myocardial necrosis is supported by dynamic troponin release together with histopathology demonstrating contraction bands and other findings of cell death. Reperfusion and stunning are manifest by reversible regional LV wall motion abnormality and dynamic T-wave inversion with QT interval lengthening. Defining the mechanism responsible for myocardial ischemia and necrosis in takotsubo cardiomyopathy (syndrome) may lead to a better understanding of the pathophysiology of these events and ultimately to more effective management for this increasingly common condition.

REFERENCES

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Disclosures
None.