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EDITOR'S NOTE

Is takotsubo syndrome a microvascular acute coronary syndrome? Towards a new definition

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Nomenclature

Acute coronary syndromes (ACS) remain the most important cause of morbidity and mortality in Europe,[1] the USA, and around the world. Initially termed myocardial infarction, the American College of Cardiology, the American Heart Association, and the European Society of Cardiology have agreed to introduce the term ACS for the various clinical presentations of acute myocardial infarction.[2] With this novel classification, patients with ST-segment elevation myocardial infarction (STEMI) are distinguished from those presenting with non-ST-segment myocardial infarction (non-STEMI) and those with unstable angina. The diagnosis of ACS therefore relies on (i) typical symptoms of ischaemia (chest pain); and (ii) typical ECG changes and/or elevated levels of cardiac troponins or other biomarkers of myocardial necrosis (*Table 1*).

A new disease

Takotsubo syndrome (TTS) is a relatively novel disease entity first described by Sato *et al.*[3] in Japan in female patients with clinical presentation and ECG presentation of a STEMI, normal coronary arteries, and apical ballooning of the left cardiac chamber resembling the shape of a Japanese octopus trap (*Figure 1*). After the first description, the syndrome has been increasingly recognized, and with the introduction of primary percutaneous coronary intervention (pPCI),[4,5] it became obvious that TTS is much more common than previously anticipated. Indeed, recently we published results so far from the largest series of patients with TTS in the *New England Journal of Medicine*, describing the clinical characteristics, triggering factors, and outcomes of this syndrome.[6] It appears that patients with TTS do have a 'substrate', i.e. commonly a neurologic or psychiatric diagnosis, and in most cases a 'trigger', i.e. physical or emotional stress leading to the acute presentation in the emergency department.

What to call the new disease?

Takotsubo syndrome has several names in the literature as is common for a poorly understood disease.[7] The expression cardiomyopathy appears inappropriate as TTS is in general characterized by a transient left ventricular dysfunction; it is definitively not a chronic disease, although recurrence is reported to occur in ~1.8% per patient-year.[6] Also, the term 'apical ballooning' is misleading as ~20% of the patients present with a midventriular, basal, or focal form. However, in appreciation of the first description and recognition by the Japanese cardiologists we feel that *takotsubo syndrome* appears most appropriate and should be used accordingly.

Acute presentation

Upon arrival, patients with TTS are often indistinguishable from those presenting with ACS. Indeed, in most cases, namely those presenting with left ventricular dysfunction (i.e. those with the most common form of apical ballooning), patients present with acute chest pain and/or dyspnoea as well as typical ECG changes with ST-segment elevations in the pre-cordial leads as well as III, aVL, and aVR. In addition to slight increases in cardiac biomarkers such as troponins, marked elevations of brain natriuretic peptide (BNP) are a hallmark of TTS (Ref. 8). Such patients typically present with normal or non-obstructive coronary arteries at angiography. Indeed, although TTS may be suspected based on the ECG findings and biomarker pattern, diagnosis is confirmed by coronary angiography (*Figure 1*).

Is takotsubo syndrome an acute coronary syndrome?

Based on these findings, the question arises: is TTS a novel form of an ACS? Indeed, as mentioned above, clinically and based on the ECG it is often indistinguishable from ACS, be it a STEMI or non-STEMI.[9] Increases in cardiac biomarkers that are also common in ACS make the differential diagnosis even more difficult, although mild increases in troponin and marked increases in BNP must raise a suspicion of TTS.[8] Therefore, diagnosis can only be confirmed by angiography with the demonstration of marked wall motion abnormalities that do not correspond to the territory of a major coronary artery (except focal TTS type) as well as usually the absence of haemodynamically relevant coronary artery disease (*Figure 2*).

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Table 1 Characteristics of ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, Takotsubo syndrome, and Prinzmetal angina

	STEMI	Non-STEMI	Takotsubo syndrome	Prinzmetal angina (vasospastic angina)
Age	40–70 years	50–90 years	50–70 years	<50 years, more frequent in Asians
Gender	Preponderance of males	Males and females	Predominantly post-menopausal females	
Emergency presentation	Chest pain (angina), sudden death, dyspnoea, cardiogenic shock, syncope	Chest pain (angina), dyspnoea, cardiogenic shock	Chest pain (angina), dyspnoea, cardiogenic shock, syncope	Chest pain (angina) at rest, dyspnoea, spontaneous remission
Trigger	Inflammation, emotional or physical stress	Inflammation	Emotional, physical stress, or no evident trigger	Drugs[a]
ECG	ST-segment elevation	ST-segment depression, T-inversion	ST-segment elevation, T-inversion, normal ECG, QTc prolongation	Transient ST-segment elevation
Biomarkers	Troponin ↑↑↑ NT-proBNP ↑↑	Troponin ↑-↑↑ NT-proBNP ↑	Troponin ↑ NT-proBNP ↑↑↑	Troponin ↔-↑, NT-proBNP ↔-↑
LV ejection fraction	40–60%	50–60%	30–45%	45–60%
LV wall motion abnormalities	Hypo-/akinesia in the territory of a major coronary artery	Hypo-/akinesia in the territory of a major coronary artery	Apical ballooning, mid-ventricular, basal, focal hypo-, a- or dyskinesia	Hypo-/akinesia in the territory of a major coronary artery (focal spasm) or generalized hypokinesia (diffuse spasm)
Coronary angiogramm	Occlusion of major epicardial coronary artery	Tight stenosis of major epicardial coronary artery	Typically normal coronary arteries[b]	Normal, segmental or diffuse spasm (provocative testing)
Coronary thrombus	+++	+/++	–	–
In-hospital mortality	5–7%	2–4%	3–5%	0–2%

LV, left ventricular; NT-proBNP, N-terminal pro brain natriuretic peptide; STEMI, ST-segment elevation myocardial infarction.
[a]Drugs such as cocaine, amphetamine, marijuana, alcohol, butane, chemotherapy drugs, and different antibiotics.
[b]Around 15% of patients have concomitant coronary artery disease (stenosis ≥50%).[6]

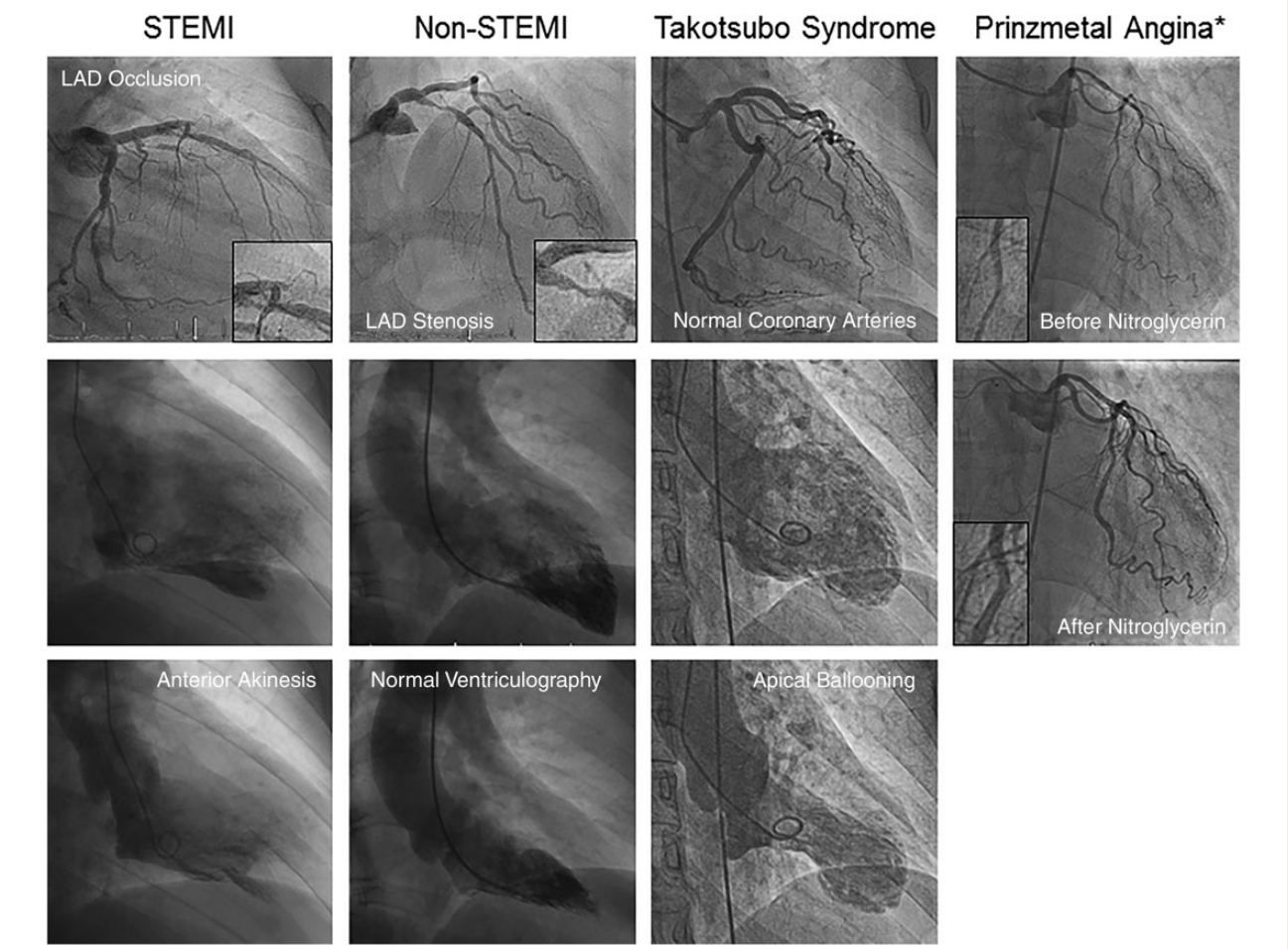

Figure 1 Typical angiographic presentation of ST-segment elevation myocardial infarction (STEMI), non-STEMI, Takotsubo syndrome, and Prinzmetal angina. The figure of Prinzmetal angina are from Ghadri JR *et al.*[14] and with permission of Oxford University Press.

While coronary arteries are in the majority of cases normal in contrast to typical ACS, patients do suffer from severe myocardial ischaemia, as reflected by chest pain, ECG changes, cardiac biomarkers, as well as left and, in some also, right ventricular dysfunction. However, in contrast to ACS, ischaemia is not related to a structural and/or functional occlusion of a major epicardial coronary artery due to plaque rupture or erosion or spasm, but most probably rather due to severe and prolonged microvascular constriction (*Figure 3*).

The mechanisms of this profound and prolonged microvascular constriction are unclear, but appear related to sympathetic activation with release of catecholamines[10] and endothelin.[11] Indeed, both catechoamines and endothelin levels are elevated in these patients and are known to produce profound and prolonged vasoconstriction. In this regard, it is of note that endothelin preferentially constricts the microcirculation.[12] Another related and rare form of ACS due to functional coronary vasoconstriction is Prinzmetal angina affecting, however, mainly large epicardial arteries[13,14] (*Table 1*).

Takotsubo syndrome is not harmless

Another initially unrecognized feature of TTS which is comparable with the currently known ACS is the fact that it is associated with a considerable mortality.[6] Indeed, 1 in 25 patients die during their hospitalization, a frequency that is comparable with that observed in patients with ACS receiving current state-of-the-art management including pPCI according to guidelines. This further confirms that TTS is a novel form of an ACS leading to left ventricular ischaemia and in turn potentially to lethal arrhythmias, cardiogenic shock, and death. Therefore, it has to be seriously considered in any patient presenting with chest pain, dyspnoea, or cardiogenic shock.

Conclusion

In summary, TTS fulfils all criteria of an ACS, specifically a microvascular form of it with similar symptoms on admission, ECG

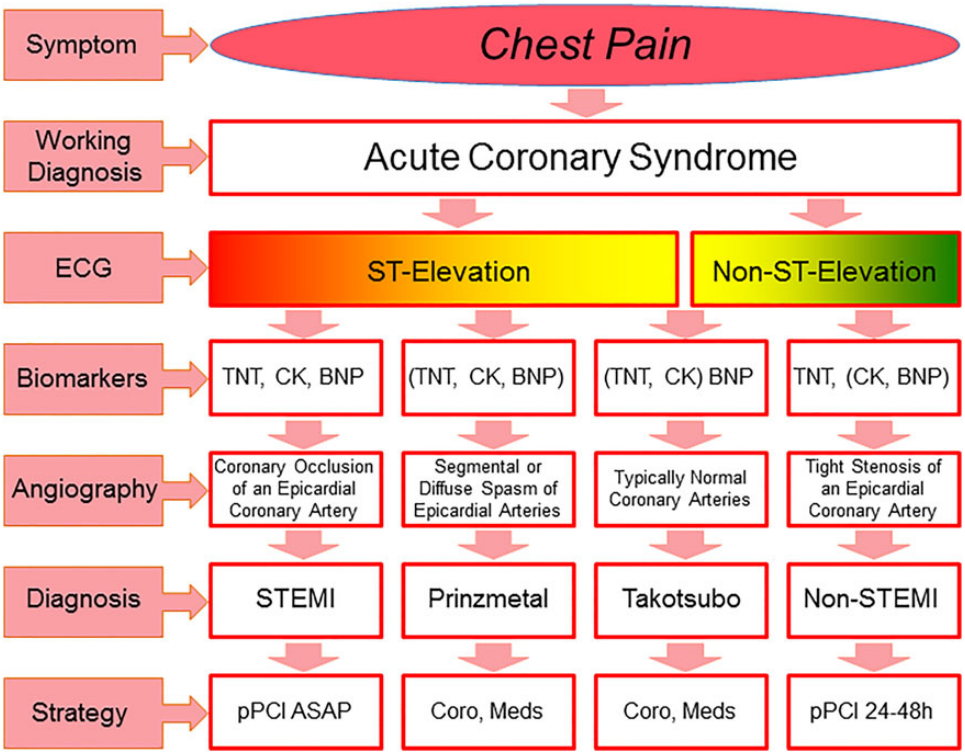

Figure 2 Differential diagnosis of acute coronary syndromes. BNP, brain natriuretic peptide; CK, creatine kinase; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TNT, troponin T.

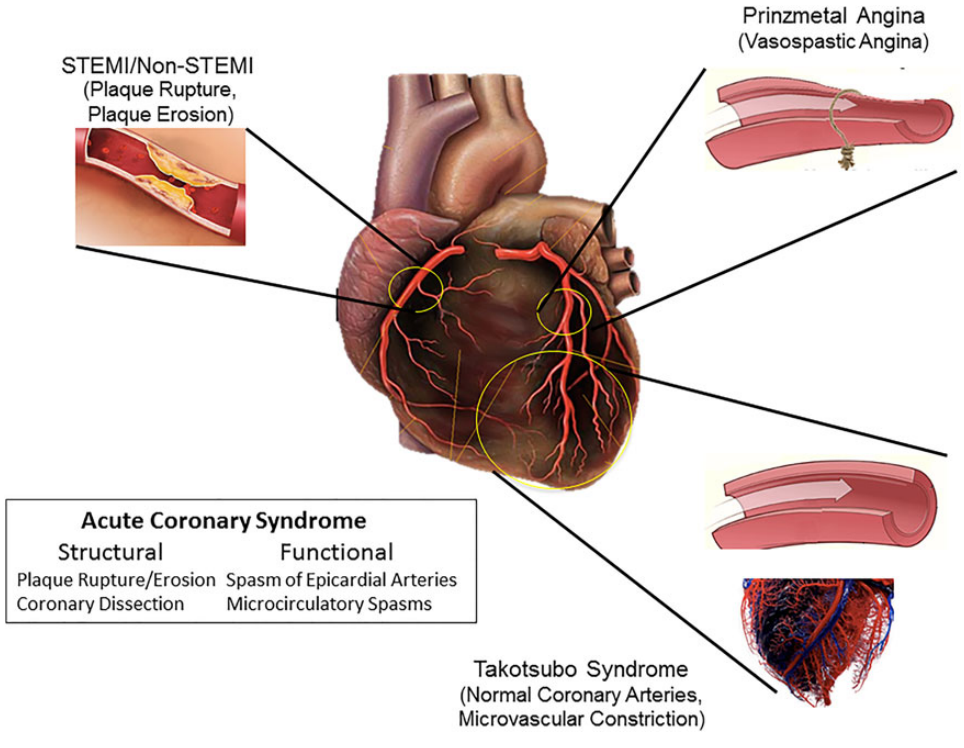

Figure 3 Macrovascular and microvascular ischaemia in patients with ST-segment elevation myocardial infarction (STEMI), non-STEMI, Takotsubo syndrome and Prinzmetal angina, respectively.

changes, and elevation of cardiac biomarkers, as well as comparabel mortality to STEMI and Non-STEMI, and should therefore be considered as such. Since the major cause is not a structural or functional occlusion of a major coronary artery, but—as suggested by current evidence—rather profound and prolonged vasoconstriction of the coronary microcirculation, its optimal management has yet to be defined by appropriate trials.

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