

## REVIEW ARTICLE—DISEASE DISCOVERED IN JAPAN AND THE ROLE OF NUCLEAR CARDIOLOGY

### Nuclear Cardiology Approach in Takotsubo Syndrome

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#### Abstract

**Takotsubo syndrome is an acute clinical condition mimicking acute myocardial infarction. Nuclear cardiology imaging obtains information that is close to the pathology of Takotsubo syndrome and is widely used in clinical practice to accumulate evidence. Regional semi-quantitative analysis revealed that the metabolic abnormalities were exclusively in the apical area, which was one of the features of Takotsubo syndrome.  $^{123}\text{I}$ -MIBG has the ability to reveal apical sympathetic nerve abnormalities, which often are prolonged. This article describes both the latest findings of Takotsubo syndrome as well as the characteristics of the disease condition and the practical use of a nuclear cardiology technique.**

**Keywords:** BMIPP, Ischemia, Metabolic imaging, MIBG, Sympathetic nerve function, Takotsubo  
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**T**akotsubo syndrome is an acute clinical condition mimicking acute myocardial infarction. Initially described in 1991 by Sato et al. in Japan (1), the typical angiographic appearance with apical ballooning and hypercontractility of the basal segments of the left ventricle has been given the name Takotsubo syndrome. Takotsubo syndrome is more likely to occur in elderly women and is characterized by wide reversible constriction disorders centered on the apex of the left ventricle (1-3).

The cause of Takotsubo syndrome has been suggested to be microcirculatory disorder, catecholamine myocardial disorder, localized myocarditis transient plaque rupture, coronary spasm and the like. Although it is also called Takotsubo cardiomyopathy, it is not suitable to call it cardiomyopathy, as it merges with various diseases, so it would be appropriate to refer it as Takotsubo syndrome. Nuclear cardiology imaging obtains information that is close to the pathology of Takotsubo syndrome and is widely used in clinical practice to accumulate evidence (3-6). This article describes both the latest findings of Takotsubo syndrome as well as the characteristics of the

disease condition and the practical use of the nuclear cardiology technique.

#### Myocardial blood flow imaging

Decreased apical uptake at an early stage of Takotsubo syndrome, after its onset, reflects myocardial perfusion abnormalities in the apex. Abnormal myocardial perfusion in the apex occurs 3-5 days after the onset of Takotsubo syndrome, and its abnormality gradually improves in the subacute phase and chronic phase (7). Thallium chloride ( $^{201}\text{Tl}$ ) or  $^{99\text{m}}\text{Tc}$ -labeled sestamibi (MIBI) or tetrofosmin is used as a tracer (radiopharmaceutical) for performing myocardial blood flow. It is mainly used for evaluating the site of myocardial injury and myocardial viability. Resting myocardial perfusion scintigraphy with  $^{99\text{m}}\text{Tc}$ -labeled MIBI or tetrofosmin is a lipophilic cation preparation, and ingestion and retention of myocardium depends on cell membrane potential of the myocardium and mitochondrial membrane potential. The defect in the resting imaging indicates damaged myocardium. An early image after one hour of injection and a late image

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after 4 hours may be obtained, and in the myocardial injury lesion, the decreased uptake in the delayed image may become prominent. A method to evaluate the prognosis of patients with dilated cardiomyopathy by the measurement of  $^{99m}\text{Tc}$ -MIBI-washing out has been reported (8). The mitochondrial dysfunction is closely related to the region where the washout of  $^{99m}\text{Tc}$ -MIBI is enhanced. It is possible to evaluate the abnormality of mitochondrial membrane potential with higher sensitivity in comparison to detecting perfusion abnormalities (8).

A positron emission tomography (PET) examination has been used to evaluate myocardial perfusion. A decrease in the coronary flow reserve (CFR) of the apex in patients with Takotsubo syndrome was reported by a  $^{13}\text{N}$ -ammonia PET study (9-11). Even after normalized left ventricular wall motion, the decrease in CFR of the apex remains to be observed. The CFR in the acute phase of Takotsubo syndrome was reportedly slightly declined in the left anterior descending coronary artery, the left circumflex, and the right coronary artery. In the chronic phase, coronary blood flow reserve was fully normalized with PET.

A previous clinical report showed that Takotsubo cardiomyopathy often resembled acute coronary syndromes such as acute myocardial infarction and unstable angina (3). It is known that about 1% of all patients who have been diagnosed with acute myocardial infarction have a feature of Takotsubo syndrome. An electrocardiogram cannot provide sufficient information on the extent or area of myocardial damage, but myocardial perfusion imaging makes it possible to obtain information on the severity of myocardial damage and myocardial viability to infer prognosis.

#### LV functional measurements using electrocardiogram-gated SPECT

Left ventricular functional information such as the apical contraction, systolic and diastolic function of the left ventricle, and left ventricular dyssynchrony, can be obtained together with myocardial perfusion by evaluating electrocardiogram (ECG)-gated SPECT (QGS) (Fig.1). The RR interval of the electrocardiogram can be divided into 8 or 16 intervals after the acquisition. Functional parameters can be quantified from QGS (Fig.1).

Furthermore, with the advances in analytical techniques, a phase analysis to evaluate the timing of left ventricular contraction has become possible. Currently, bandwidth, phase SD, and entropy are known to be the index of left ventricular synchronous evaluation using various kinds of analysis software (12). The apical wall motion abnormality in Takotsubo syndrome is often transient in many cases and it is difficult to evaluate the apical wall motion with echocardiography in clinical practice. Acute phase and subacute

morphological abnormalities can be diagnosed by perfusion imaging with QGS without performing left ventriculography.

#### Fatty acid metabolism imaging

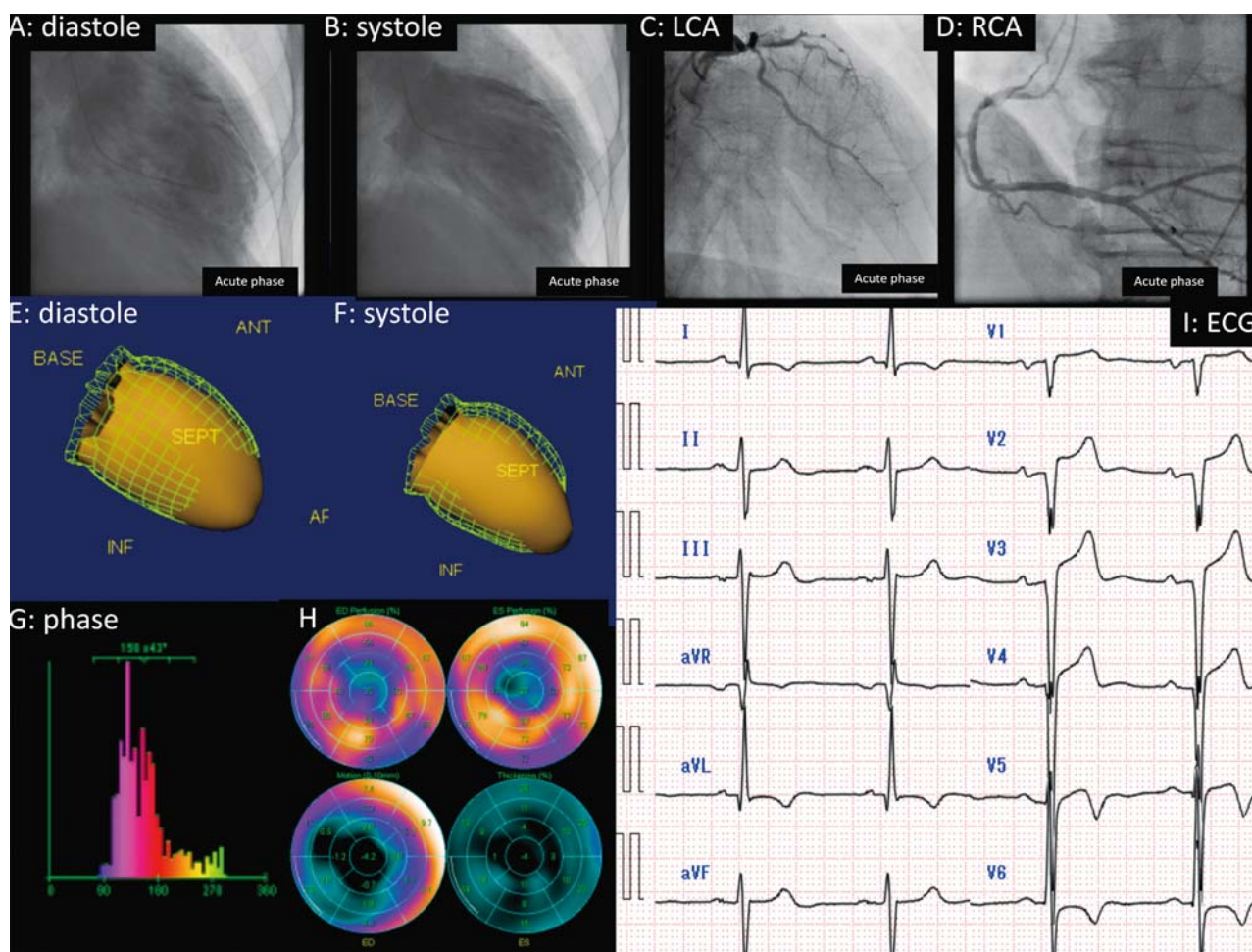
$^{123}\text{I}$ -beta-methy-iodophenyl pentadecanoic acid (BMIPP) shows the same pharmacokinetics as a fatty acid in vivo, and it is taken into cardiomyocytes and then is transferred into lipid pools and mitochondria. Because the methyl group exists in the  $\beta$  position as a side chain, it is less susceptible to  $\beta$  oxidation and remains a long time in myocardial cells.

Myocardial ischemia is known to cause a decrease in fatty acid utilization in myocardium and shifts from fatty acid metabolism to glucose metabolism.  $^{123}\text{I}$ -BMIPP imaging can detect a microcirculation abnormality at the cell level by evaluating myocardial fatty acid metabolic abnormality. Perfusion and metabolism are mismatched with less uptake of  $^{123}\text{I}$ -BMIPP than thallium uptake, and this has been reported among myocardial infarction or angina patients, indicating ischemic myocardium. Recent studies have shown that perfusion and metabolic information may improve risk stratification of patients with coronary artery disease (13).

$^{123}\text{I}$ -BMIPP imaging is used as an adjunctive diagnosis of acute coronary syndromes to differentiate patients with chest pain. When performed within 3 days of the onset, the diagnostic sensitivity of  $^{123}\text{I}$ -BMIPP imaging is considered to be high (74%) (13), as it is possible to detect ischemia due to obstructive coronary stenosis or coronary artery spasm (13, 14). This noninvasive scintigraphy method is widely applied to the diagnosis of acute coronary syndrome, and there is little risk of the examination itself, which is considered to be the most suitable method to investigate early cardiac metabolism during hospitalization (15-17). It is most important to distinguish whether patients with chest pain have Takotsubo syndrome or acute coronary syndrome. Takotsubo syndrome has unique characteristics of the reduced apical uptake in the myocardium (15). Regional semiquantitative analysis revealed that the metabolic abnormalities were exclusively in the apical area, which are one of the features of Takotsubo syndrome (15). If the diagnosis of Takotsubo syndrome can be confirmed by imaging, a watchful and waiting approach may be possible and no coronary angiography is needed. but when acute coronary syndrome cannot be denied, coronary angiography should be performed without hesitation (15).

#### Cardiac sympathetic nerve imaging of Takotsubo syndrome

$^{123}\text{I}$ -MIBG scintigraphy is a kind of imaging often used for prognostic evaluation of heart failure because it can visualize cardiac sympathetic nerve (18, 19). The sympathetic nervous function can be accurately evaluated by the heart-to-mediastinum ratio (HMR) using the planar image of the heart and measuring the global sympathetic abnormalities in the



**Fig. 1** 66-year-old patient with Takotsubo syndrome.

Apical ballooning of left ventriculogram at diastolic phase (A) and at systolic phase (B). Coronary angiography revealed no stenosis at acute phase in left coronary artery (C) and right coronary artery (D). Quantitative gated-SPECT showed apical ballooning at sub-acute phase (E: diastole, F: systole). G: Left ventricular contractile dyssynchrony was observed in the phase analysis. H: Decrease of apical blood flow, wall motion and wall thickening in the polar map display. I: initial ECG from first admission.

whole heart. Akashi and colleagues observed that the HMR in  $^{123}\text{I}$ -MIBG decreased, and washout rate increased in the acute phase of Takotsubo syndrome (20-23). While the HMR evaluates cardiac sympathetic dysfunction abnormality of the whole heart, local evaluation can be made by using SPECT image. SPECT imaging can accurately depict the abnormal regions of sympathetic nerve function in Takotsubo syndrome. Sympathetic dysfunction often occurs in the apex and is often more extensive than in the region of metabolic abnormality.  $^{123}\text{I}$ -MIBG often shows prolonged and extensive abnormalities centered on the apex. A follow-up observation with  $^{201}\text{Tl}$ ,  $^{123}\text{I}$ -BMIPP,  $^{123}\text{I}$ -MIBG showed that  $^{201}\text{Tl}$  abnormalities tended to recover soon, and  $^{123}\text{I}$ -MIBG defects lasted longer. Recovery of the decreased uptake mostly occurred in the order of  $^{201}\text{Tl}$ ,  $^{123}\text{I}$ -BMIPP, and  $^{123}\text{I}$ -MIBG. The abnormality of  $^{123}\text{I}$ -MIBG might be fixed irreversibly. Diagnosis by  $^{123}\text{I}$ -MIBG imaging can be used supplementarily in subacute or chronic phase. The fusion image between SPECT and computed tomography angiography may offer better diagnostic informa-

tion on the anatomy and function in Takotsubo syndrome (Fig. 2) (24-26).

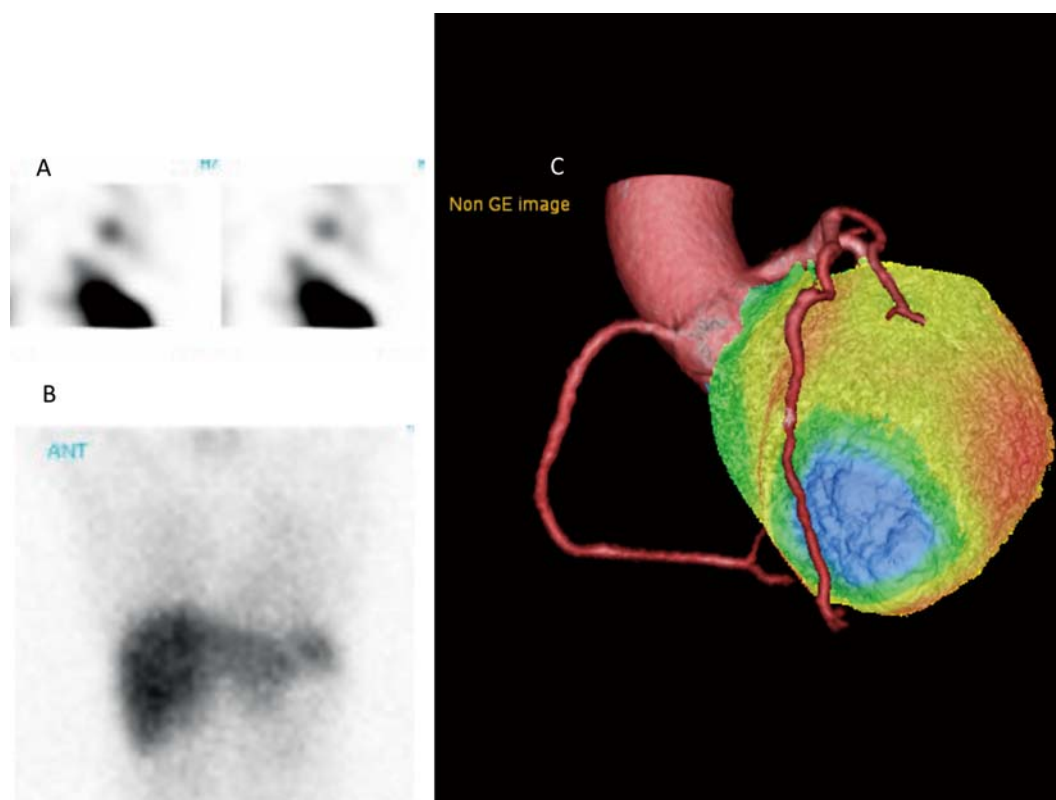
Brain SPECT showed that brain activation patterns such as cerebral blood flow are increased in the hippocampus, brainstem and basal ganglia and CBF are decreased in the prefrontal cortex (27). This suggests a close relationship between brain and heart in the pathophysiology of this disease.

## Conclusion

Takotsubo syndrome involves left ventricular apical metabolic and sympathetic abnormalities as well as perfusion, including apical wall motion abnormality. A nuclear cardiology approach for Takotsubo syndrome provides better understanding for the patient management.

## Acknowledgment

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**Fig. 2** Fusion image  $^{123}\text{I}$ -MIBG Imaging of a 30 y.o. patient with Takotsubo syndrome.  
An abnormality in the apex was observed (A and B). This occurred when the contrast CT and the SPECT image showed the apical decreases irrespective of the anterior descending coronary artery.

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#### Conflicts of interest

None.

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