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**Cardiac Magnetic Resonance for Assessment of Cardiac Involvement in Takotsubo  
Syndrome: Do we still need contrast administration?**

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This author takes responsibility for all aspects of the reliability and freedom  
from bias of the data presented and their discussed interpretation.

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### **Conflict of interest**

The authors have nothing to disclose.

## **1. Introduction**

Takotsubo syndrome (TTS) is a transient myocardial dysfunction in the absence of significant coronary disease, often triggered by emotional or physical stress [1].

Although the pathogenesis is not completely understood, myocardial edema with the absence of fibrosis have been previously described as markers for reversible myocardial injury using cardiovascular magnetic resonance (CMR) with T2-weighted images and late gadolinium enhancement (LGE) sequences [2] . More recent techniques, overcoming limitations of T2 weighted sequences, such as parametric techniques ( native and post contrast T1 mapping and T2 mapping) allow non invasive detection of interstitial edema and extracellular matrix abnormalities, a direct result of myocardial injury and one of the characteristic findings in stress-induced cardiomyopathy [3]. However, contrast administration is required to calculate extracellular volume (ECV) fraction from T1 mapping data which can be a limitation in old patients with renal impairment and with concerns about possible gadolinium accumulation deposits in the brain. Moreover, CMR data using T1 and T2 mapping in TTS are still scarce with small studies [4],[5],[6].

The aim of the study was to assess the diagnostic use of native T1 and T2 mapping for the identification of cardiac involvement in a homogenous population of 30 patients referred with TTS.

## **2. Methods**

The local institutional committee approved this prospective and single center study of patients with clinical TTS who gave written informed consent. In addition, 34 local controls (age  $54\pm 19$  years) were included to determine the reference values of T1 T2 mapping and ECV at mid level .

CMR study was carried out on a 1.5 T system (Avanto, Siemens medical solution) using previously described acquisition parameters [7]. CMR was performed a mean 5 days after the onset of symptoms and after a mean 3 month follow-up using T2 mapping, native and post contrast T1 mapping and LGE sequences in short axis view at 3 levels (basal, mid and apical). Global and segmental T1 and T2 values were measured as described previously [7].

“SPSS IBM version22” was used for the statistical analysis. Student t test was applied and Receiver Operating Characteristic was performed to assess the diagnostic performance.

### **3. Results**

A total of 30 patients were included, median age was 73 years, with a majority of female (86.7%). In the acute phase, mean LV ejection fraction was 48% with CMR, with an apical form associated with a mid-ventricular involvement in the majority of patients (70%). Wall motion abnormalities (WMA): hypokinesia or akinesia were present in the 4 segments (anterior, septal, inferior and lateral) at the apical level and in the 6 segments (anterior, anteroseptal, inferoseptal, inferior, anterolateral and anterior) at the mid level in 21 patients (70%), 8 patients (26.6%) had WMA limited at the apical level (apical form) and no patient had a basal form. Coronary angiogram performed in 26 patients (89.7%) did not show significant lesion.

Global T2 values showed a gradient from base to apex:  $54 \pm 5$  ms at basal,  $59 \pm 9$  ms at mid-ventricular and  $67 \pm 10$  ms at apical level.

Compared to controls, T2 values ( $59 \pm 8$  versus  $51 \pm 4$  ms,  $p < 0.001$ ), native T1 ( $1053 \pm 75$  versus  $960 \pm 61$  ms,  $p < 0.001$ ) and ECV ( $29 \pm 5$  versus  $23 \pm 3\%$ ,  $p < 0.001$ ) were significantly higher in TTS group. A cut off of 56ms for T2, 1011ms for native T1 and 27% for ECV had the best diagnostic performance to diagnose TTS with a sensitivity of 62%, 76% and 72% respectively

and a specificity of 94%, 91% and 97% respectively; AUC (area under the curve) of 0.89 (IC:0.80-0.98), 0.89 (IC:0.80-0.98) and 0.91 (IC:0.83-0.99) respectively (Fig.1).

Combining T2 with native T1 provided the best sensitivity (91.7%) with a very good specificity (88.2%).

Segmental analysis showed that T2, native T1 and ECV were significantly higher in segments with wall motion abnormalities compared to normokinetic segments ( $62\pm 9$  versus  $55\pm 5$  ms  $p<0.001$ ;  $1060\pm 65$  versus  $1025\pm 56$  ms  $p=0.02$ ; and  $34\pm 5$  versus  $29\pm 1\%$   $p=0.02$ ).

No patients had LGE visually assessed.

At 3 month follow up: all patients had a complete LV recovery (EF:  $63\pm 9\%$ ) without significant WMA. Global T2 were normalized at 3 levels ( $52\pm 2$ ,  $51\pm 4$  and  $54\pm 6$  ms), global and segmental native T1 and ECV values did not significantly decreased.

#### **4. Discussion**

Using technical advances, T1 and T2 mapping in a prospective study with a homogeneous population of mid and apical TTS, we have demonstrated that T2 and native T1 mapping have the ability to detect acute myocardial injury with a high diagnostic accuracy without need of contrast administration.

T2 mapping appears to be more specific (94% in our study) for acute inflammation compared to native T1 mapping. Combining T2 and native T1 augments the sensitivity (91.7%) for inflammation and edema.

Moreover, we have showed that myocardial inflammation is global but predominantly involves segments with WMA with a base to apex intensity suggesting that the areas with normal contractility are likely involved by the process but perhaps to a milder degree.

Interestingly, global and segmental native T1 values and ECV did not normalized at follow up despite a normalization of T2 values suggesting that T1 mapping technique has the ability to detect persistent inflammation which could support the concept of persistent structural changes in TTS [8].

Edema and inflammation are major components in TTS but it rarely leads to necrosis contrary to myocardial infarction or myocarditis. When LGE is present, it is a low-intensity LGE: less than 5SD [2]. Increase of native T1 in TTS is unlikely due to areas of fibrosis where free water may accumulate but reflects vasodilation, hyperemia and increased interstitial space.

Arguing that LGE is rarely present in TTS and ECV does not provide strong additional diagnostic accuracy, it may be possible to perform gadolinium free CMR imaging using T2 and T1 mapping for tissue characterization in patients with suspected TTS, which may be useful for particularly old patients in this population.

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## Figure Legend

Fig.1. ROC (receiver-operating characteristic) curves of native T1, T2 mapping and ECV.

ROC curves of native T1, T2 and ECV

