



# Detection of acute myocarditis by ECG-triggered PET imaging of somatostatin receptors compared to cardiac magnetic resonance: preliminary results

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**Abstract.** Somatostatin receptors are overexpressed by inflammatory cells but not by cardiac cells, under normal conditions. This study assesses the detection of acute myocarditis by the ECG-triggered digital-PET imaging of somatostatin receptors (<sup>68</sup>Ga-DOTATOC-PET), as compared to Cardiac Magnetic Resonance (CMR) imaging, which is the reference diagnostic method in this setting.

**Methods.** Fourteen CMR-defined acute myocarditis patients had a first 15-minutes ECG-triggered <sup>68</sup>Ga-DOTATOC PET recording, 4.4 ± 3.0 days from peak troponin, and 10 had a second 4.3 ± 0.3 months later. Myocardial/blood SUVmax ratio was analyzed relative to the normal upper limit of 2.18, which had been previously determined from oncology <sup>68</sup>Ga-DOTATOC-PET recordings of patients with a similar age range as the myocarditis patients.

**Results.** An increased myocardial <sup>68</sup>Ga-DOTATOC uptake relative to blood activity was invariably observed during the acute phase. SUVmax ratio exceeded 2.18 in all patients during the acute phase but also in 3/10 patients at 4-months, at a time when there were no more signs of active inflammation on CMR. A residual myocardial <sup>68</sup>Ga-DOTATOC uptake was still observed on all gated-PET cine loops at 4-months.

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**Conclusion.** These preliminary results suggest that  $^{68}\text{Ga}$ -DOTATOC ECG-triggered digital-PET may be as sensitive as CMR at detecting myocarditis during the acute phase and more sensitive at later stages. (J Nucl Cardiol 2022)

**Key Words:**  $^{68}\text{Ga}$ -DOTATOC • digital-PET • myocarditis • cardiac MRI • somatostatin receptor

#### Abbreviations

CMR	Cardiac magnetic resonance
CRP	C reactive protein
CT	Computed tomography
FDG	$^{18}\text{F}$ -fluorodesoxyglucose
LV	Left ventricle
OSEM	Ordered subset expectation maximization
PET	Positron emission tomography
SD	Standard deviation
SUV	Standardized uptake value
VOI	Volume of interest

## INTRODUCTION

Myocarditis which evolves toward left ventricular dysfunction, heart failure, or arrhythmia is associated with a poor prognosis.<sup>1</sup> Cardiac Magnetic Resonance (CMR) imaging has become the non-invasive gold-standard method for diagnosing myocarditis using the updated Lake-Louise diagnosis criteria.<sup>2</sup> Unfortunately, this CMR-based diagnosis remains challenging in certain patients (i.e., those with irregular cardiac rhythms, claustrophobia, pacemakers, or severe obesity). CMR also lacks sensitivity for detecting subacute or chronic forms of myocarditis, characterized by cardiomyopathy-like or arrhythmia presentations.<sup>1</sup>

The Positron Emission Tomography (PET) imaging of somatostatin receptors may constitute an alternative diagnostic tool in this setting. Somatostatin receptors are overexpressed in lymphocytes, macrophages, and activated monocytes, the primary cell subsets involved in myocarditis.<sup>3</sup> In contrast, somatostatin receptors are poorly expressed by cardiac cells under normal physiological conditions, and the observation of a significant cardiac uptake is rare on somatostatin-PET images recorded for conventional oncology indications.<sup>4</sup>

To date, only one single pilot study has provided evidence supporting a potential role of somatostatin-PET imaging for diagnosing myocarditis of suspected infectious origins.<sup>5</sup> However, a high diagnostic potential was also previously shown for myocardial sarcoidosis<sup>6</sup> and for myocarditis associated with immune check point inhibitor therapy.<sup>7</sup> A recently published case report from our team has also provided supportive evidence for the potential of  $^{68}\text{Ga}$ -DOTATOC ECG-triggered digital-

PET to delineate areas of myocarditis following COVID-19 vaccination.<sup>8</sup> We postulated that this particular PET recording technique may be well adapted to this setting, given the capacity of digital-PET to image low-count structures<sup>9</sup> and of ECG-triggered PET to prevent cardiac motion-related image blurring.<sup>10</sup>

The current study assesses the detection of acute myocarditis by ECG-triggered digital-PET imaging of somatostatin receptors ( $^{68}\text{Ga}$ -DOTATOC PET), as compared to CMR imaging, the reference diagnostic method in this setting.

## MATERIALS AND METHODS

This ongoing study, which aims to ultimately include a total of 30 patients, has to date enrolled 14 patients hospitalized for an acute myocarditis of a presumed infectious origin who fulfill the CMR 2018-updated Lake Louise criteria of acute myocarditis,<sup>2</sup> with significant increases in plasma troponin-Ic levels and no other evident cardiac disease. Patients were referred for a first cardiac ECG-triggered  $^{68}\text{Ga}$ -DOTATOC PET/CT at  $\leq 72$  h after the initial CMR. Ten patients had a second ECG-triggered  $^{68}\text{Ga}$ -DOTATOC PET/CT on the day of the CMR follow-up, 4 months later. A venous blood sample was collected just before each  $^{68}\text{Ga}$ -DOTATOC PET/CT to determine C Reactive Protein (CRP) and Troponin Ic levels.

### $^{68}\text{Ga}$ -DOTATOC PET/CT

One hour after the injection of 2 MBq/kg of  $^{68}\text{Ga}$ -DOTATOC, the CT was recorded and immediately followed by a single bed position 15-minutes cardiac ECG-triggered PET on a digital hybrid PET/CT system (Vereos, Philips, Cleveland, Ohio), with the patient set in the prone position to reduce any respiratory motion-related cardiac displacements.

Ungated-PET images were reconstructed with parameters favoring the contrast-to-noise ratio of small structures—i.e., 2-mm voxels, OSEM algorithm with 3 iterations and 3 subsets, a deconvolution of the point spread function and further corrections for scatter, random coincidences and attenuation.<sup>9</sup> Gated-PET images were reconstructed with 8 interval-frames, 4-mm isotropic voxels, 2 iterations, 10 subsets, and further corrections for scatter, random coincidences, and attenuation.

Ungated- and gated-PET images were analyzed with image scaling ranging from 0 to 3 Standardized Uptake Values (SUV). The uptake of  $^{68}\text{Ga}$ -Dotatoc was quantified on ungated-PET images according to a myocardial/blood ratio of maximal Standardized Uptake Values (SUVmax). SUVmax were determined from 2 cm diameter spherical volumes of interest (VOI) placed at a  $> 1$  cm distance from liver activity (i) on the myocardial region showing the highest level of activity by visual analysis and (ii) on a blood region at the center of the right atrial cavity.

The normal upper limit of this myocardial/blood SUVmax value had been defined as 2.18 according to the 95% confidence interval computed from 19 non-myocarditis patients consecutively selected on the basis of (i) age  $< 35$  years (mean:  $26 \pm 6$  years), so as to be in the age range of our myocarditis patients, (ii) no known cardiac history, and (iii) having undergone a whole-body  $^{68}\text{Ga}$ -DOTATOC PET/CT for an oncology indication with the Vereos camera.

The non-myocarditis patients had  $^{68}\text{Ga}$ -DOTATOC PET for: (i) a suspected neuroendocrine tumor ( $n = 10$ ) or (ii) the monitoring of a known somatostatin receptor-expressing tumor ( $n = 9$ ). Two had a known paraganglioma, 1 was followed for a Von Hippel Lindau disease, 1 for a mesenchymal tumor and 5 had other types of neuroendocrine tumors. None of the non-myocarditis patients had a carcinoid syndrome, and 3 had a metastasis.

### CMR investigations

CMR images were recorded on a 1.5T Avento or a 3T Prisma system (Siemens, Erlangen, Germany) to assess LV function and to detect signs of myocarditis:<sup>2</sup> (i) on longitudinal (T1) and transversal (T2) relaxation maps recorded with Modified Look-Locker Inversion Recovery (MOLLI) and 2D TurboFlash sequences, respectively, and (ii) on contiguous delayed retention images covering the LV with a multi-slice phase-sensitive inversion recovery sequence, 10 to 15 minutes after the injection of 0.1 mmol/kg body weight of Dotarem® (GUERBET, France).

### Statistical analysis

Qualitative variables are expressed as numbers and percentages, and quantitative variables as means  $\pm$  SD. Wilcoxon and Mann–Whitney tests are used for paired and unpaired comparisons of quantitative variables and  $p$  values  $< 0.05$  are considered to reflect significant differences.

## RESULTS

As detailed in Table 1, the first 14 sequentially enrolled patients with a myocarditis presumed to be of infectious origin included thirteen men and one woman. Their mean age was  $25 \pm 8$  years (ranging from 18 to 49 years). All presented with elevated plasma troponin-Ic (mean troponin peak:  $11.4 \pm 12.3$  ng/mL), associated with chest pain in 12 cases and with symptoms evocative of a gastrointestinal or respiratory tract infection in 5.

On the initial CMR, all myocarditis patients exhibited a characteristic sub-epicardial late gadolinium enhancement predominantly in the inferior and/or lateral walls, together with myocardial areas with increased T2 ( $> 54$  ms on 1.5T Avento<sup>11</sup> and  $> 47$  ms on 3T Prisma<sup>12</sup>) and T1 ( $> 1140$  ms on 1.5T Avento<sup>13</sup> and  $> 1305$  ms on 3T Prisma<sup>14</sup>), fulfilling the diagnostic criteria of acute myocarditis.<sup>2</sup> The LV ejection fraction was  $< 50\%$  in 5 cases (21% in one patient, who died before the 4-month follow-up; 40% in another one, 45% in two patients, and 49% in one patient). This contrasts with the 4-month follow-ups, where none of the patients had any abnormal T2 or ejection fractions (Table 2).

As detailed in Tables 1 and 2, both troponin and CRP were still higher than normal in 9 patients on the day of the first PET. Three patients had elevated CRP values on the day of the second PET, whereas all troponin values were normal.

### PET imaging of acute phase

The initial  $^{68}\text{Ga}$ -DOTATOC ECG-triggered PET was recorded at  $4.4 \pm 3.0$  days from peak troponin and showed areas of increased myocardial uptake relative to blood activity in all myocarditis patients. These areas were consistently located in the inferior and/or lateral walls, and in most cases with multifocal or diffuse forms they were combined with a patchy distribution. Representative images of focal, multifocal, and diffuse forms are displayed in Figure 1. The gated-PET cine loops are available in an online supplement and allow the myocardial  $^{68}\text{Ga}$ -DOTATOC uptake to be visualized more easily, with better separation from the liver and less cardiac motion-related image blurring (see supplemental figure). The myocardium/blood SUVmax ratio was  $2.99 \pm 0.49$  and was abnormal ( $> 2.18$ ) in all myocarditis patients (Figure 2).

### PET imaging at the 4-month follow-up

This second  $^{68}\text{Ga}$ -DOTATOC ECG-triggered PET was recorded  $4.4 \pm 0.2$  months after the first in 10 of the 14 myocarditis patients and showed a marked decrease

in the myocardium/blood SUVmax ratio (from  $2.99 \pm 0.49$  to  $1.97 \pm 0.38$ ,  $p = 0.005$ , see Figure 2 and Table 2). However, this SUVmax ratio remained higher, on average, than that computed in the control group (Figure 2), and it was still definitely abnormal ( $> 2.18$ ) in 3 of the 10 patients (30%), at a time when there were no signs of persisting inflammation by CMR (i.e., when all myocardial T2 values had returned to normal).

A residual myocardial  $^{68}\text{Ga}$ -DOTATOC uptake was still observed on the gated-PET images of all patients at 4-months, in the areas of high  $^{68}\text{Ga}$ -DOTATOC uptake during the acute phase. This point is best illustrated on the gated-PET cine loops in the supplemental figure.

**Table 1.** Main characteristics of the overall study population during the acute phase

Age (years)	$25 \pm 8$
Male	13 (93%)
Peak troponin Ic in acute phase (ng/mL)	$11.4 \pm 12.3$
LV ejection fraction at CMR (%)	$49 \pm 9$
Abnormal ( $< 50\%$ )	5 (36%)
Day of the 1st PET/CT	
Delay time from peak Troponin (days)	$4 \pm 3$
Troponin Ic (ng/mL)	$2.1 \pm 5.3$
Abnormal ( $> 0.053$ ng/mL)	9 (64%)
C Reactive Protein (mg/mL)	$12 \pm 14$
Myocardial SUV max	0.50
Myocardial/blood SUV max ratio	$2.99 \pm 0.49$
Abnormal ( $> 2.18$ )	100%

## DISCUSSION

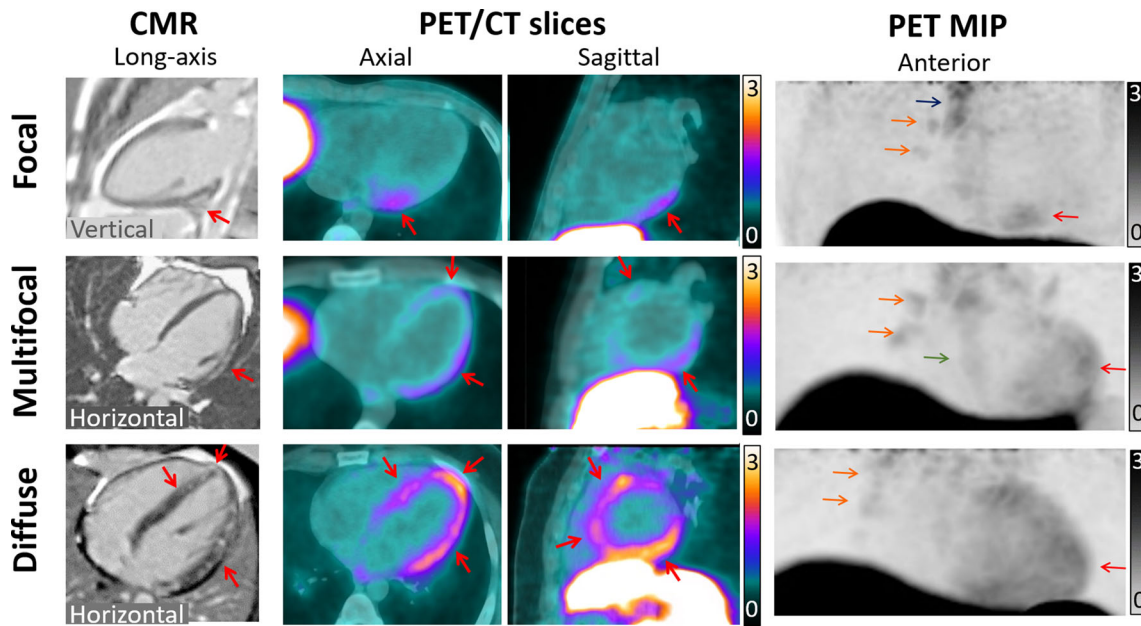
These preliminary results suggest that patients with acute myocarditis may be identified by increased myocardial  $^{68}\text{Ga}$ -DOTATOC uptake relative to blood activity and in most cases, with an ECG-triggered digital-PET pattern evocative of a patchy distribution of inflammatory cells predominantly in the lateral wall. This pattern is consistent with (i) the predominance of CMR abnormalities observed in the lateral wall of myocarditis patients, particularly for abnormalities associated with positive biopsy findings,<sup>1</sup> and (ii) the heterogeneity reported between biopsy samples from different LV locations in this setting.<sup>1</sup>

In myocarditis, the density of inflammatory cells may be low, only a few dozen per  $\text{mm}^2$  on biopsy slices,<sup>15</sup> and the density of somatostatin receptors is likely much lower than those of tissues commonly targeted by  $^{68}\text{Ga}$ -DOTATOC PET (i.e., neuro-endocrine tumors, sarcoidosis, or inflammatory nodes). This is the reason why the SUVmax from myocarditis areas was rather low here, 1.78 on average (Table 1). However, we used a fully digital-PET, whose performance is higher than that of current analog PET in low-count conditions (i.e., higher signal/noise ratio),<sup>9</sup> and we made methodological choices expected to decrease the image blurring due to breathing (patient prone positioning) or cardiac motion (i.e., gated-PET with 8-frame per cardiac cycle, as already validated for the detection of infective endocarditis with FDG-PET<sup>10</sup>). It is currently not known whether more conventional PET cameras or protocols provide comparable results, even with higher injected doses.

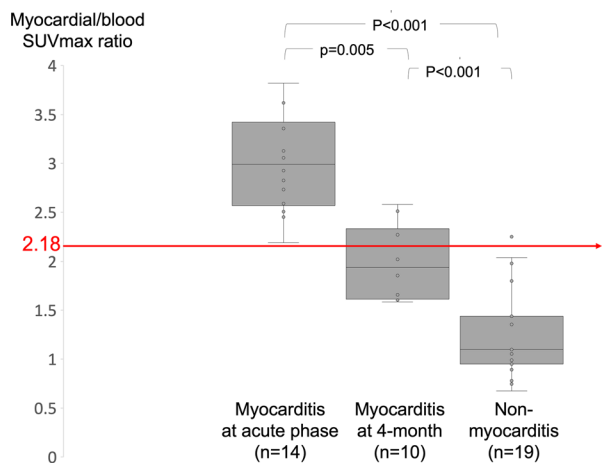
As illustrated in the supplemental file, the gated-PET images provide an easy identification of the mobile

**Table 2.** Evolution of the PET, CMR, and venous blood parameters between the acute phase and the 4-month follow-up in the 10 patients who had undergone the complete study protocol

	Acute phase	At 4-months	p values
Troponin Ic (ng/mL)	$0.648 \pm 1.329$	$0.006 \pm 0.003$	0.005
C reactive protein (mg/mL)	$10 \pm 12$	$4 \pm 8$	0.575
CMR			
LV ejection fraction (%)	$51 \pm 6$	$54 \pm 2$	0.058
Abnormal ( $< 50\%$ )	2 (20%)	0 (0%)	0.500
Abnormal T1	10 (100%)	1 (10%)	0.004
Abnormal T2	10 (100%)	0 (0%)	0.002
Late gadolinium enhancement	10 (100%)	5 (50%)	0.063
PET/CT			
Myocardial/blood SUV max ratio	$2.90 \pm 0.52$	$1.97 \pm 0.38$	0.005
Abnormal ( $> 2.18$ )	10 (100%)	3 (30%)	0.016



**Figure 1.** Late contrast enhancement CMR images, and <sup>68</sup>Ga-DOTATOC PET images represented as fused PET/CT slices and as maximal intensity projection (MIP) images, for representative myocarditis patients with a focal, multifocal, or diffuse myocardial increase in <sup>68</sup>Ga-DOTATOC uptake during the acute phase. Image scaling ranges from 0 to 3 SUV. The myocardial areas with a CMR delayed retention and those with increased <sup>68</sup>Ga-DOTATOC uptake are indicated with red arrows. Tracheobronchial nodes are indicated with orange arrows and esophagus and sternal bone marrow with green and blue arrows, respectively.



**Figure 2.** Box plot graph of the myocardial/blood SUVmax ratio in myocarditis patients during the acute phase ( $n = 14$ ) and at 4-months ( $n = 10$ ), relative to the non-myocarditis reference group ( $n = 19$ ). The normal upper SUVmax limit of 2.18 is indicated with a red line.

sites of myocardial <sup>68</sup>Ga-DOTATOC uptake, even if the distal part of the inferior wall remains challenging to separate from liver activity in most cases. ECG-triggered FDG-PET images have previously been shown to be useful, when compared to conventional non-triggered

FDG-PET images, for the detection of infective endocarditis, due to the decrease in cardiac motion-related image blurring.<sup>10</sup>

The gated-PET cine loops also provided evidence of areas of residual myocardial <sup>68</sup>Ga-DOTATOC uptake in all of the 4-month follow-up investigations. These areas closely corresponded to those for which the <sup>68</sup>Ga-DOTATOC uptake was high in the acute phase (see illustrations in the supplemental figure). At the present time, it is not known whether this residual uptake corresponds to a more or less active inflammation, to the normal healing process or both. Somatostatin receptors would not only be expressed on inflammatory cells (activated macrophage, lymphocytes and monocytes), but also on fibroblasts and fibrotic tissue.<sup>16</sup> Also, the persistence at 4-months of a high myocardial/ blood SUVmax ratio in 3 of the 10 patients, at a time when there are no more signs of active inflammation according to the CMR (normal T2) and the blood biomarkers (normal troponin Ic), and its potential correlation with the evolution of LV function, will need to be further assessed.

Initially 5 of our patients had a decreased LV ejection fraction. This decrease was mild to moderate (i.e., ranging from 40% to 49%) in 4 patients, and

returned to normal in all 3 patients that had the 4-month follow-up. Peak troponin was not very high in these 5 patients ( $16 \pm 16$  ng/mL, on average), nor in the overall population (see Table 1), in accordance with previous observation that plasma troponin is not correlated with cardiac function in myocarditis.<sup>17</sup>

Cases of increased myocardial uptake by nuclear imaging of somatostatin receptors have been previously observed in various myocarditis and cardiac sarcoidosis,<sup>5-8</sup> but also in subacute myocardial infarction<sup>18</sup> and vulnerable coronary plaques.<sup>19</sup> Increased myocardial uptake was also observed in patients who underwent <sup>68</sup>Ga-DOTATOC PET for an oncology indication, in line with an older age, and with the presence of a history of cardiac disease and of cardiovascular risk factors.<sup>20</sup> That is why we used a specific oncology reference patient population, who did not have any history of cardiac disease and who were as young as our myocarditis patients. However, the results of our ongoing study need to be confirmed using other reference populations and larger sample sizes.

The PET imaging of somatostatin receptors is increasingly used worldwide, specifically using the theranostic approach (i.e., pre-therapeutic workup and treatment monitoring of neuro-endocrine tumors<sup>21</sup>). It is likely that the availability of these tracers will further improve in the future, and that their cost will be reduced, thereby favoring their use for inflammatory cardiac diseases.

In conclusion, and although this remains to be confirmed on a larger scale, our preliminary results suggest that <sup>68</sup>Ga-DOTATOC ECG-triggered digital-PET may be as sensitive as CMR for detecting myocarditis during the acute phase and more sensitive at later stages.

These interim results were considered remarkable enough to be communicated, given the long time (2 years) required for inclusion of the initial 14 patients into the study and the potential usefulness of our preliminary observations for patients for whom a CMR diagnosis of acute myocarditis remains challenging (i.e., those with irregular cardiac rhythms, claustrophobia, pacemakers, severe obesity, and later myocarditis stages). The final results, expected to comprise data from 30 myocarditis patients, will not only allow to contribute more detail to these preliminary results but also determine whether differences in the evolution of LV function during follow-up may relate to concomitant changes in myocardial <sup>68</sup>Ga-DOTATOC uptake. This uptake was unexpectedly variable and sometimes abnormally high at the 4-month follow-up, an observation that deserves a more specific evaluation.

## NEW KNOWLEDGE GAINED

<sup>68</sup>Ga-DOTATOC ECG-triggered digital-PET may be as sensitive as CMR for detecting myocarditis during the acute phase and more sensitive at later stages, a property that may be particularly useful in patients for whom the CMR diagnosis of myocarditis remains challenging and when myocarditis is investigated at later stages.

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## Disclosures

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## Declarations

## Conflict of interest

*The authors declare that they have no conflict of interest.*

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