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Imaging myocardial perfusion with [^{99m}Tc] Tc-HMPAO: Fiction or reality? – Preliminary results

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Keywords: myocardial perfusion scintigraphy; epilepsy; HMPAO; myocardial SPECT.

Abbreviations: MPS: Myocardial perfusion scintigraphy; i.v: Intravenous; SA: Short Axis; VLA: Vertical Long Axis; HLA: Horizontal Long Axis; EF: Ejection Fraction.

Abstract

Introduction and objectives: [^{99m}Tc] Tc-HMPAO, developed for brain imaging, is taken up by the heart, but never used to study it.

We aimed to compare cardiac images with [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, using imaging techniques.

Materials and methods: Cardiac gated SPECTs with [^{99m}Tc] Tc-HMPAO were compared with myocardial perfusion scintigraphies (MPS) with [^{99m}Tc] Tc-Tetrofosmin in three inpatients, from the vascular surgery ward.

We developed algorithms in MATLAB R2016 to compare the [^{99m}Tc] Tc-Tetrofosmin/ [^{99m}Tc] Tc-HMPAO images. Pixel-wise correlations for slices, reversibility, and polar maps were obtained.

Results: Correlations of both radiotracers' myocardial images were as high as 0.93. Polar maps correlations were 0.93-0.95 (for both stress and rest) and 0.62-0.90 (reversibility).

One of the patients (smoker) had significant lung [^{99m}Tc] Tc-HMPAO uptake.

Conclusions: Cardiac SPECT with [^{99m}Tc] Tc-HMPAO might be a screening method for myocardial ischemia in non-smoking patients with epilepsy suspected of having heart changes, and who need to perform a brain perfusion SPECT.

Introduction

[^{99m}Tc] Tc-HMPAO is a radiotracer developed in the 1980s to study regional cerebral blood flow [1-4]. It has been widely used since then, in patients with epilepsy, to localize the epileptogenic zone.

Although this radiotracer's biodistribution includes the heart [4], to the best of our knowledge, it has never been used to study that organ. The main reason, aside from the excellent existent alternatives, maybe the proximity of the heart to organs with high [^{99m}Tc] Tc-HMPAO uptake (lungs and liver) [4,5], potentially interfering with cardiac imaging quality.

Being a brain perfusion radiotracer, mapping of myocardial perfusion seemed also possible, permitting the use of a single radiotracer in patients with epilepsy (known to be prone to cardiac alterations) with less radioactive exposure.

Our aim was to compare myocardial gated SPECT images made with both [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, using imaging techniques.

Several authors have compared different radiotracers for myocardial imaging, using varying methodologies [6-12].

We believe this is the first study not only evaluating the possibility of imaging myocardial perfusion with [^{99m}Tc] Tc-HMPAO, but also comparing myocardial images with different radiotracers, quantifying the similarities.

Material and methods

We selected 3 inpatients from the Vascular Surgery ward, who already had to perform a myocardial perfusion scintigraphy (MPS) with [^{99m}Tc] Tc-Tetrofosmin, as part of their clinical evaluation [one-day protocol, stress/rest, 370 MBq (10 mCi)/1110 MBq (30 mCi), i.v., respectively], and additionally acquired myocardial stress/rest SPECT images with stabilized [^{99m}Tc] Tc-HMPAO [two-day protocol, 555 MBq (15 mCi), i. v., each]. The stress agent was adenosine for both studies and images were acquired in gated mode, 40 min after the i.v. injections.

The interval between each radiotracer scintigraphy varied between 4 months and 1 year, and no major cardiac event was registered in that period, except for patient 3, who developed heart failure.

All studies were processed with a cardiac dedicated software (QGS/QPS), providing three reconstructed planes (short axis – SA –, vertical long axis – VLA –, and horizontal long axis – HLA) and exported into DICOM files.

Due to the inexistence of a heart model on which to calculate normally used clinical parameters, a quantitative analysis of [^{99m}Tc] Tc-Tetrofosmin and [^{99m}Tc] Tc-HMPAO image similarity is proposed here.

Processing algorithms were developed in MATLAB R2016 to compare the [^{99m}Tc] Tc-Tetrofosmin and [^{99m}Tc] Tc-HMPAO images of each reconstructed plane (SA, VLA, and HLA).

For image pre-processing, the first and last two slices of the reconstructed images were removed, since no important heart structures were clearly visible. Then, we applied a 2-dimensional median filter, which replaces each pixel by the median value of its 1 by 1 neighbourhood. Due to low image resolution, higher window sizes lead to a significant distortion of the image shape, so we found 1 by 1 value to be optimal for the available dataset.

Afterwards, images were aligned, applying the affine transformation that maximized the mutual information [13] between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin. Figure 1 exemplifies the initial and final results.

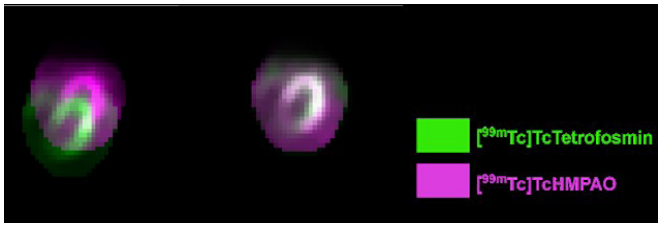


Figure 1: Image alignment algorithm example. On the left, images not aligned; on the right, images aligned after an affine transformation with maximum mutual information.

Then, we thresholded the images by selecting all pixels above an intensity of 0 as the region of interest, and identified the bounding box (minimum rectangle on which all image points are included. The purpose was to calculate image correlation metrics corresponding only to this region. We calculated a pixel-wise correlation for every slice, using Pearson's Correlation Coefficient.

Reversibility of the defects was also evaluated (correlation of the rest-stress subtraction with each radiotracer), as were the polar maps.

We analyzed the LV ejection fraction (EF) and volumes (end diastolic and end systolic) with QGS, in every patient, with both radiotracers.

Ethical approval

This study was approved by our Institution Ethics Committee, as it was in accordance with their ethical standards and with the 1964 Helsinki declaration and its later amendments. All participants gave their informed consent.

Data availability

All datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

We evaluated 3 patients with stress/rest images with both [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin.

All of them had high correlations for perfusion images (Figure 2), better in the VLA: 0.88 to 0.93 (stress), and 0.88 to 0.90 (rest). Reversibility correlations (Table 1, Figure 3) varied between 0.46 and 0.80 (3 axes).

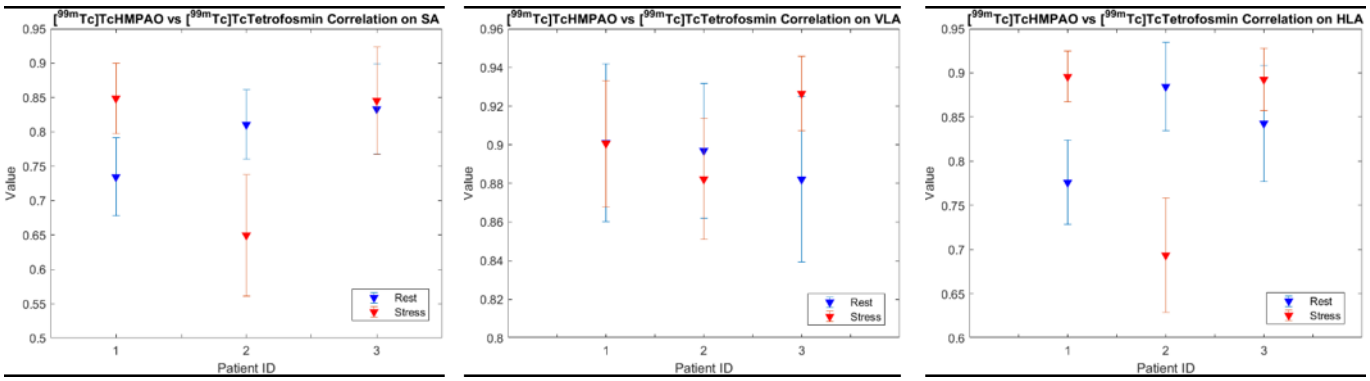


Figure 2: Correlation between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin on the 3 axes, for all patients.
SA: short axis; VLA: vertical long axis; HLA: horizontal long axis.

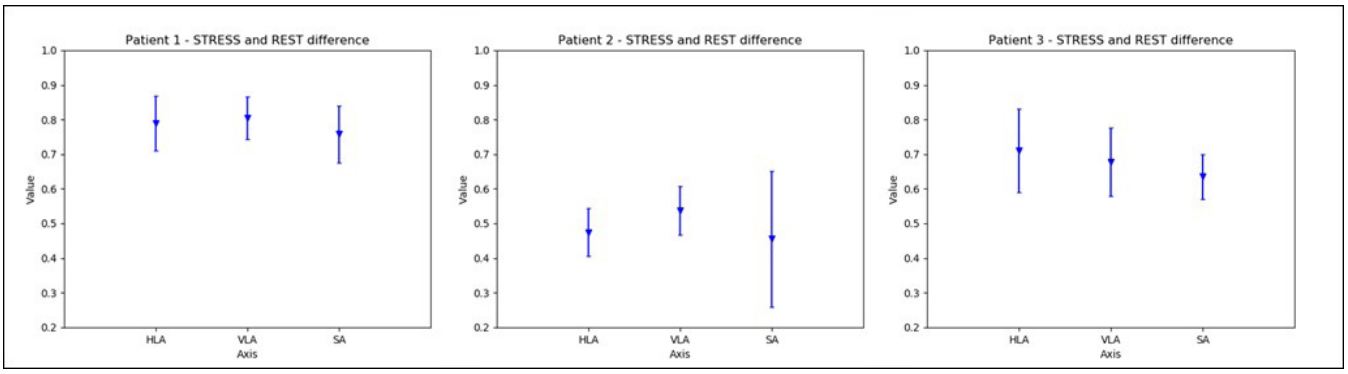
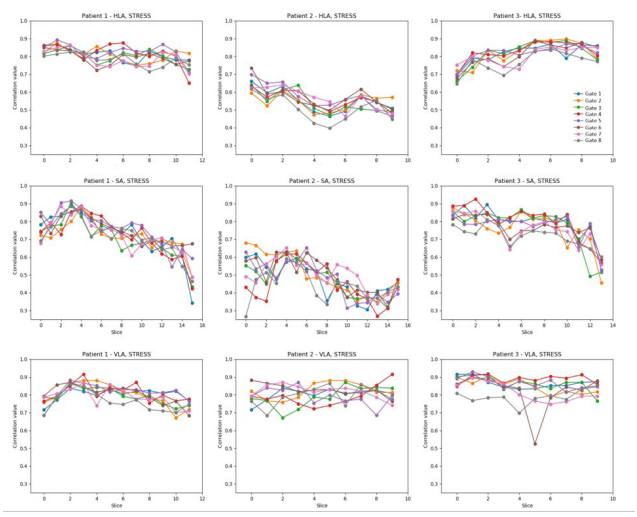
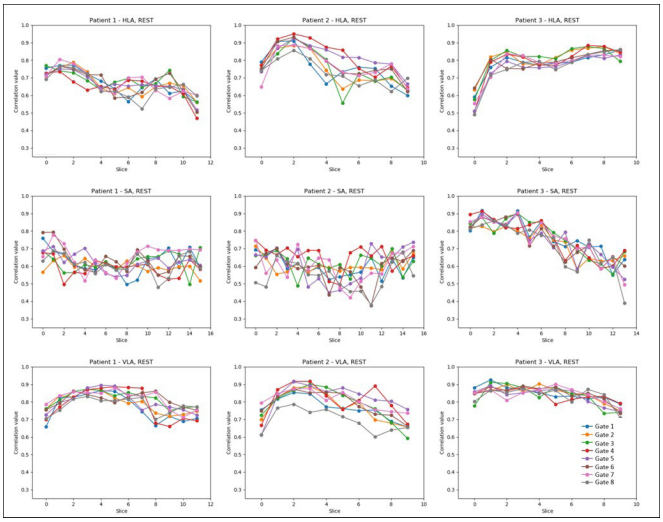


Figure 3: Correlation of reversibility (3 axes) between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin images, for patients 1, 2 (smoker) and 3.



(A)



(B)

Figure 4: Gated images correlations of each slice, between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin.
a. Gated stress images. b. Gated rest images.

Gated images correlations between each slice of each gate were also better in VLA [mean values: 0.78-0.89 (stress), 0.78-0.84 (rest)]. Figure 4 shows the correlations of gated images for all patients.

Table 1: Correlation of **reversibility** (3 axes) between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin images, for patients 1, 2 (smoker) and 3.

Patient	Correlation Mean (SD)		
	Short Axis	Vertical Long Axis	Horizontal Long Axis
1	0.76 (0.08)	0.80 (0.06)	0.79 (0.08)
2	0.46 (0.20)	0.54 (0.07)	0.47 (0.069)
3	0.63 (0.06)	0.68 (0.10)	0.71 (0.12)

Table 2: Correlation of [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin polar maps: stress, rest, and reversibility, for patients 1-3

Patient	Polar Maps Correlation		
	Stress/Stress	Rest/Rest	Reversibility
1	0.93	0.95	0.82
2	0.95	0.93	0.62
3	0.94	0.94	0.90

The LV ejection fraction (EF) with both radiotracers was equivalent in almost all patients (Table 3). The exception is Patient 3, whose EF calculated with [^{99m}Tc] Tc-Tetrofosmin was significantly lower (severely compromised) when compared to the one calculated with [^{99m}Tc] Tc-HMPAO (normal). Patient 2 had only one value significantly different from the others, which was the rest EF evaluated with [^{99m}Tc] Tc-HMPAO (mildly compromised compared to normal).

LV volumes with [^{99m}Tc] Tc-HMPAO were generally inferior to the ones calculated with [^{99m}Tc] Tc-Tetrofosmin.

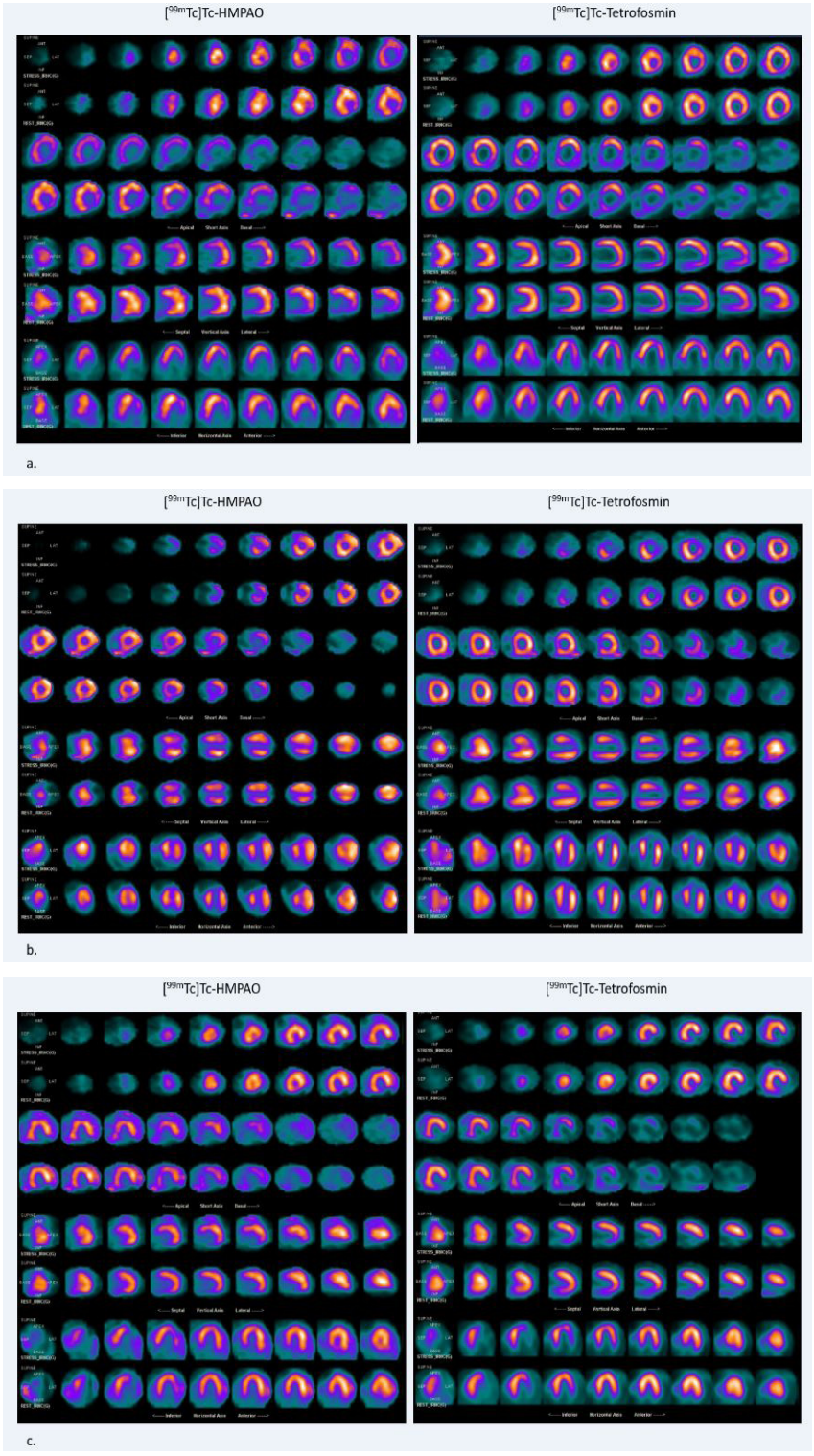


Figure 5: Reconstructed slices in the three axes (SA – short axis; VLA – vertical long axis; HLA – horizontal long axis), with both radiotracers ([^{99m}Tc]Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin), for each patient (a. Patient 1; b. Patient 2; c. Patient 3).

Table 3: Left Ventricle Ejection Fraction and volume values for each patient with [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin. EF: Ejection Fraction; ESV: End systolic volume; EDV: End diastolic volume.

Subject (Age in years)	Evaluated Parameter	Stress		Rest	
		[^{99m}Tc]Tc-HMPAO	[^{99m}Tc]Tc-Tetrofosmin	[^{99m}Tc]Tc-HMPAO	[^{99m}Tc]Tc-Tetrofosmin
P1 (63)	EF (%)	23	20	20	23
	ESV (mL)	113	183	124	159
	EDV (mL)	147	230	156	207
P2 (76)	EF (%)	51	51	40	50
	ESV (mL)	32	55	55	56
	EDV (mL)	65	112	91	111
P3 (75)	EF (%)	53	27	55	30
	ESV (mL)	35	62	47	67
	EDV (mL)	74	84	105	96

Discussion

[^{99m}Tc] Tc-HMPAO mechanism of localization in the brain is related to its lipophilic nature, which allows the passage through the intact blood brain barrier. Once into the cell, the conversion to a hydrophilic form is crucial for intracellular retention [14-18]. Debate exists about the role of intracellular glutathione content [19], pointed by some authors as an important factor for the conversion of the [^{99m}Tc] Tc-HMPAO to the hydrophilic form [20,21]. Jacquier-Sarlin et al., in their *in vitro* study, reported that [^{99m}Tc] Tc-HMPAO retention inside the cell is far more dependent on the redox activity than on the glutathione content in the cell [17]. El-Shirbiny et al. also reached the conclusion that [^{99m}Tc] Tc-HMPAO retention was not related to the intracellular glutathione content [22].

Regional [^{99m}Tc] Tc-HMPAO uptake by the brain reflects regional cerebral blood flow [4,15,23,24]. Brain perfusion can thus be effectively evaluated by this radiotracer.

In the heart, the mechanism of [^{99m}Tc] Tc-HMPAO uptake/retention in the myocytes remains unknown. However, we show that this uptake may also reflect regional myocardial blood flow.

To the best of our knowledge, this is the first study evaluating the possibility of imaging myocardial perfusion with [^{99m}Tc] Tc-HMPAO.

Overall, we obtained high correlations for cardiac studies with [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, especially in VLA. Patient 2 was a smoker and, probably because of that, had poorer correlations due to lung [^{99m}Tc] Tc-HMPAO uptake. Shih et al. had already demonstrated that lung [^{99m}Tc] Tc-HMPAO uptake was related to smoking habits, and they hypothesized that it was dependent on increased vascular permeability [25].

Other methodologies have been previously used for comparing different radiotracers for myocardial imaging. Maddahi et al [6] compared [^{99m}Tc] Tc-Sestamibi and Thallium-201 SPECTs, presenting only the final patient's diagnosis characteristics. Other authors [7,8] compared the same radioisotopes, using different patients and different times. Image quality, final patient's diagnosis, 'normalcy' rate, sensitivity and specificity, were presented for detecting stenosis. Functional parameters were compared by unpaired t-test comparison of several parameters (mean stress EF, mean rest EF, and ΔEF) computed by SPECT software – semi-quantitative analysis 8. In another paper, a comparison between ECG-Gated [^{99m}Tc] Tc-Sestamibi SPECT with ECG-Gated Rubidium-82 PET was made [9].

Declerck et al [10] and Gilardi et al [11] used methods similar to ours to compare cardiac studies, but none quantified the similarities, which became our major input.

In our study, we used for the first time imaging techniques to compare myocardial images obtained with different radiotracers. We opted to use a simple approach in this preliminary work. We filtered, aligned, selected the regions of interest using a bounding box, and then correlated the images. Our algorithm worked better for the central sections, where the difference between the background noise and the heart was more visible, compared with the initial or final sections, which had a lot more background noise due to the high radiotracer uptake by the surrounding organs. Therefore, we excluded the initial and the final frames.

We obtained high correlations for cardiac studies between [^{99m}Tc] Tc-HMPAO and [^{99m}Tc] Tc-Tetrofosmin, especially in VLA, in non-smoking patients.

The LV EF was similar with both radiotracers in the majority of patients. Patient 3, showed a normal EF with [^{99m}Tc] Tc-HMPAO but had a severely compromised EF with [^{99m}Tc] Tc-Tetrofosmin (4 months later). Two weeks before the latter, the patient was admitted to the hospital with a severe respiratory infection and decompensated heart failure, which could justify the EF drop. Patient 2 had only one significantly altered value (rest EF evaluated with [^{99m}Tc] Tc-HMPAO). This is the smoker patient, whose lung [^{99m}Tc] Tc-HMPAO uptake was significant.

LV volumes with [^{99m}Tc] Tc-HMPAO were inferior to the ones with [^{99m}Tc] Tc-Tetrofosmin, so this method might not be useful to evaluate them.

Limitations

Our major limitation is the reduced number of cases, not allowing a formal statistical analysis. With these promising preliminary results of myocardial perfusion SPECTs with [^{99m}Tc] Tc-HMPAO, we now intend to increase the sample.

The second limitation is the extended time gap between both radiotracers' scintigraphies. Our Institution Ethics Committee limited our patient recruitment to inpatients that already had performed (or would need) a MPS, posing difficulties in performing both scintigraphies in a lesser time interval.

New knowledge gained

With our work, we describe a potential new application for an old radiotracer, which might allow the simultaneous evaluation of two organs in a selected population, with less radioactive exposure.

Conclusion

Myocardial SPECT with [^{99m}Tc] Tc-HMPAO might be a screening method for myocardial ischemia in non-smoking patients already performing a [^{99m}Tc] Tc-HMPAO brain perfusion SPECT. It might serve as a gateway to MPS, in a subset of patients with epilepsy that are prone to have heart changes (e.g. those with rises in ictal Troponin I).

Although promising, these preliminary results must be confirmed with a larger cohort.

Meanwhile, our group is also trying different approaches to improve the image quality with [^{99m}Tc] Tc-HMPAO.

Declarations

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Declarations of Interest: none.

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