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RESEARCH ARTICLE

Usefulness of 5 Minutes ^{123}I-mIBG Scan in Parkinson's Disease and Heart Failure

Viviana Frantellizzi[1,*], Maria Ricci[2], Alessio Farcomeni[3], Mariano Pontico[4], Arianna Pani[5] and Giuseppe De Vincentis[2]

[1]*Department of Molecular Medicine, Sapienza, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy;* [2]*Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy;* [3]*Department of Economics and Finance, University of Rome "Tor Vergata", Via Columbia, 2, 00133, Rome, Italy;* [4]*Ph.D. Program in Morphogenesis & Tissue Engineering, Sapienza University of Rome, Rome, Italy;* [5]*Postgraduate School of Clinical Pharmacology and Toxicology, University of Milan "Statale", Italy*

Abstract: ***Background:*** The use of ^{123}I-mIBG has been approved for decades for Parkinson's disease (PD) diagnosis and as a predictor of mortality and potentially fatal events in patients with Heart Failure (HF). The standardized technique includes an early acquisition (15 minutes from injection), and a late acquisition (240 minutes). Early images mainly represent interstitial uptake, whereas delayed images represent actual neuronal uptake, however, it is reasonable to affirm that different pathological situations, such as PD and HF, imply a different meaning for early and late imaging.

Objective: This prospective study aims to investigate the clinical usefulness of an immediate planar ^{123}I-mIBG image acquisition (5 minutes) both in patients with PD and in patients with HF.

Methods: 115 patients referred to ^{123}I-mIBG cardiac imaging in Nuclear Medicine Center have been enrolled (60 patients with PD, absence of diabetes and/or cardiologic pathology, Hoehn e Yahr classification ≤ 1.5; 55 patients with cardiomyopathy, diagnosis of HF, NYHA class I–III). ^{123}I-mIBG planar anterior thoracic acquisitions were performed after 5 (immediate), 15 (early) and 240 (late) minutes from injection and H/M ratios were calculated.

Results: In PD group H/M mean values resulted in 1.58±0.22 for immediate (5 min), 1.61±0.26 for early (15 min) and 1.59±0.37 for late (240 min) acquisitions. In the HF group, H/M mean values resulted in 1.63±0.24 for immediate (5 min), 1.65±0.22 for early (15 min) and 1.57±0.17 for late (240 min) acquisitions, respectively. H/M values obtained at 5 min and 15 min are provided similar results, with no statistical difference (p = ns) regardless of the pathology examined (PD or HF groups). The statistical analyses validated the diagnostic role of immediate acquisition (5 min) and early acquisition (15 min) in PD group as compared to the standardized late acquisition (240 min). On the contrary, in HF group, immediate and early acquisition, as compared to late acquisition (240 min), is not validated as a major cardiac events predictor.

Conclusion: Our results indicate the potential role of immediate (5 min) or early (15 min) acquisition in replacement of standardized 240 minutes acquisition in PD patients, but this result is not confirmed in HF patients, in which the acquisition at 240 min is confirmed as the most affordable timing for image interpretation, emphasizing the different pathophysiology that underlies these two pathologies.

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1. INTRODUCTION

The cardiac sympathetic activity can non-invasively be assessed with meta-iodobenzylguanidine (^{123}I-mIBG) using both planar and SPECT techniques [1-3]. ^{123}I-mIBG is a radiolabeled norepinephrine (NE) analog and accumulates in the presynaptic myocardial sympathetic nerve endings. The use of ^{123}I-mIBG has been approved for decades for Parkinson's disease (PD) [4] and, more recently after ADMIRE-HF trial's publication [5], for dilated cardiomyopathy [6] in patients with chronic heart failure (HF) [7]. Even if the ^{123}I-mIBG imaging includes both planar and SPECT imaging, the former tech-

*Address correspondence to this author at the Department of Molecular Medicine, Sapienza, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy; Tel: 0649978573; Fax: 0649978592;
E-mail: viviana.frantellizzi@uniroma1.it

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nique results are widely standardized. Moreover, quantified myocardial 123I-mIBG parameters have proved to be of diagnostic value in PD and prognostic value in HF, reporting worse prognosis in impaired myocardial ^{123}I-mIBG parameters (i.e., reduced late heart to-mediastinum (H/M) ratio and increased ^{123}I-mIBG myocardial washout (WO)) [5, 8]. The late H/M < 1.6 is assumed as the gold standard both for assessing the diagnosis of PD and predicting a major risk of arrhythmia in patients with HF [9]. During years, the possible diagnostic/prognostic value of early H/M has been studied because of its possible role in receptor physiopathology. The standardized technique of early H/M establishes the image acquisition after 15 minutes from radiolabeled-compound injection [10]. It is a general opinion that early images mainly represent interstitial uptake, whereas the delayed images represent actual neuronal uptake. Several previous papers focused on the best timing of the early acquisition, by observing 3-minute and delayed heart uptake ratios calculated from dynamic and static studies [11, 12]. The study of the impact of acquisition time on the early H/M may improve receptor physiopathology knowledge and, on the other hand, may help in the logistic organization of Nuclear Medicine center. Our prospective study aims to focus on variation in acquisition time between the standardized early acquisition at 15 minutes and an immediate acquisition at 5 minutes from the injection, both in patients with PD and in patients with HF.

2. MATERIALS AND METHODS

From 2015 to 2017, 115 patients consecutively referred to ^{123}I-mIBG cardiac imaging in Nuclear Medicine Center have been enrolled in this prospective study. Of 115, 60 patients were suspected of Parkinson's disease, whereas 55 patients presented dilated cardiomyopathy and HF. In all patients, in concordance with specific guidelines, an optimal treatment was administrated from both neurologic and cardiologic teams of our center for the entire period of the study. The study complied with the Declaration of Helsinki and was approved by the Local Ethics Committee, moreover written informed consent was obtained from all patients. The characteristics of the population have been described in Table **1** for PD group and Table **2** for HF group.

Table 1. Patient Characteristics in PD group.

	Total Group (n=60)
Age (years); mean (SD)	64.8 (8.7)
Sex (male)	50%; n=30
Height (cm); mean (SD)	166.6 (8.5)
Weight (Kg); mean (SD)	70.9 (11.7)
Cardiovascular risk factors	
Diabetes mellitus	none
Obesity, BMI>30(kg/m2)	25%; n=15
Hypercholesterolemia	15% n=9
Hypertension	18.3% n=11
Smoker	33.3%; n=20
Medication	
ACE/AT-II inhibitor	6.7%; n=4
Beta-blockers	none
Calcium antagonist	1.7%; n=1
Lipid-lowering agents	13.3%; n=8
Antiplatelet/oral anticoagulant therapy	10.0%; n=6
Diuretics	8.3%; n=5
Oral antidiabetics	none
Insulin	none
Nitrates	none
Hoehn e Yahr class	
1	58.3%; n=35
1.5	41.7%; n=25

ACE angiotensin-converting enzyme, At-II angiotensin II, BMI body mass index.

Table 2. Patient Characteristics in HF group.

	Total Group (n=55)
Age (years); mean (SD)	64.5 (9.7)
Sex (male)	85%; n=47
Height (cm); mean (SD)	171.3 (6.7)
Weight (Kg); mean (SD)	78.1 (15.5)
Cardiovascular risk factors	
Diabetes mellitus	9.1%; n=5
Obesity, BMI>30(kg/m2)	20.0%; n=11
Hypercholesterolemia	27.3%; n=15
Hypertension	27.3%; n=15
Smoker	25.5%; n=14
Ejection fraction (mean%)	29 (11-45 IQR)
Coronary artery disease *	47.3%; n=26
Medication	
ACE/AT-II inhibitor	65.5%; n=36
Beta-blockers	63.6%; n=35
Calcium antagonist	10.9%; n=6
Lipid-lowering agents	70.9%; n=39
Antiplatelet/oral anticoagulant therapy	83.6%; n=46
Diuretics	67.3%; n=37
Oral antidiabetics	9.1%; n=5
Insulin	1.8%; n=1
Nitrates	12.7%; n=7
NYHA class	
I	27.3%; n=15
II	52.7%; n=29
III	20.0%; n=11

ACE angiotensin-converting enzyme, At-II angiotensin II, BMI body mass index, IQR interquartile range, NYAH New York Heart Association.

2.1. PD Group Patients

In the PD group, the inclusion criteria were the absence of diabetes and/or cardiologic pathology, Hoehn e Yahr classification $\leq$ 1.5. The initial clinical evaluation was performed after the onset of symptoms (mean 3.12 ± 4.08 years) by neurologists, with a difference, between first and follow-up visits, of the meantime of 3.18 ± 2.03 years. The follow-up assessment included both semi-structured interviews and neurological examinations, probed motor system and cerebellar function, postural stability and gait, clinical symptoms of autonomic nervous system function, cranial nerves, and sensation. A follow-up diagnosis of PD was made according to both Gelb *et al*. [13] and Gilman *et al*. diagnostic criteria [14].

2.2. HF Group Patients

Consecutive patients in the HF group were part of a study whose results have already been published, in which early and late H/M ratios have been evaluated as arrhythmic event (AE) predictors [7]. The primary endpoint of the study was an AE: sustained ventricular tachycardia, resuscitated cardiac arrest, appropriate ICD therapy or SCD. The secondary endpoint was appropriate ICD therapy. Inclusion criteria were New York Heart Association functional class I–III; LVEF less than 35%; indication for an ICD implantation (primary or secondary prevention); expected survival more than1 years. Exclusion criteria were previous ICD implantation; cardiac resynchronization therapy (CRT) indication; cancer

history; severe valvulopathy; recent acute coronary syndrome (<3 months); contraindication to ICD implantation.

2.3. 123I-mIBG Data Acquisition

After thyroid blockade with the administration of 5% Lugol solution, 150-185 MBq of ^{123}I-mIBG (AdreView, GE Healthcare, USA) was administrated to each patient as an intravenous bolus, resulting in an effective dose of 2.5 to 3.3 mSv. Therefore, ^{123}I-mIBG planar static anterior thoracic acquisitions were performed in the supine position after 5 (immediate), 15 (early) and 240 (late) minutes from the injection. Images were acquired for 10 minutes with a zoom factor of 1, stored in a 128 x 128 matrix, with a dual-head gamma camera (Infinia, GE Healthcare, Milwaukee, USA) using a low energy parallel-hole high-resolution collimator (LEHR). Immediately, after the planar images at 15 and 240 minutes, and at 25 minutes and 250 minutes after injection, SPECT cardiac images were acquired with the dual-headed gamma camera over 180° using a 90°-rotation, starting at 45° right-anterior oblique projection and proceeding to the 45° left-posterior oblique projection. A 64 x 64 matrix was used for the SPECT studies (zoom factor 1) with the application of step-and-shoot technique (64 projections, 30 seconds of duration per frame in non-gated mode), as described in a previous work of our group [15]. For both planar and SPECT, the energy window was symmetrically centered to ± 10% of the 159-KeV 123I photopeak. For the inter-observer analysis, three observers with different degrees of expertise in nuclear cardiology techniques independently reviewed all planar and SPECT ^{123}I-mIBG images, both in PD and in HF groups.

2.4. Planar ^{123}I-mIBG Scintigraphy Analysis

Planar ^{123}I-mIBG images were analyzed to obtain semi-quantitative parameters of tracer distribution. A manually polygonal region of interest (ROI) was drawn on the planar images over the heart, around the epicardial border and the valve plane. The ROI includes the left ventricular cavity (H), while the lung and liver were excluded from the ROI. A second square ROI of 7 x 7 pixel was placed on the upper half of the mediastinum (M). H/M ratios were calculated as mean counts per pixel in the myocardial ROI divided by the mean counts per pixel in the mediastinal ROI [16] at 5 minutes (immediate H/M ratio), 15 minutes (early H/M ratio) and 240 minutes (late H/M ratio).

2.5. Statistical Analysis

Data are expressed as mean (± Standard Deviation). The outcome has been analyzed using mixed linear regression models, with H/M ratio as response variable, timing as predictor, and a patient-specific random intercept. Since multiple measurements (at different time points) have been observed from the same subject, we need to consider dependence emerged from this. Commonly, when only two repeated measurements are available and no other covariates are considered, one would use a paired T-test. In our analyses, we have three-time points and possibly other covariates, hence we must use a mixed model [17], which can be seen as a generalization of paired T-test to our context. In mixed models, dependence is taken into account through the random intercept as described above. Analyses were repeated in each subgroup, after pooling the subgroups, and also including other covariates (including group indicators and interactions thereof at the pooled analysis stage). Differences among time points have been evaluated by using timing as a predictor and evaluating Wald test statistics and Wald confidence intervals. A p-value of < 0.05 has been considered as statistically significant. All analyses have been conducted with R 3.4.0.

3. RESULTS

345 series of ^{123}I-mIBG images were analyzed. The HM values of all patients were reported in Table **3**. In PD group H/M mean values resulted in 1.58±0.22 for immediate (5 min), 1.61±0.26 for early (15 min) and 1.59±0.37 for late (240 min) acquisitions. In the HF group, H/M mean values resulted in 1.63±0.24 for immediate (5 min), 1.65±0.22 for early (15 min) and 1.57±0.17 for late (240 min) acquisitions, respectively. In the present study, the H/M values obtained at 5 min and 15 min provide similar results, with no statistical difference (p = ns) regardless of the pathology examined (PD or HF groups). In the PD group in fact, H/M values in immediate acquisition (5 min) and late acquisition (240 min) as compared to the early acquisition (15 min) showed 95% Confidence Interval of ti5min (-0.075, 0.015) and ti240min (-0.067, 0.023) (p=ns). Similarly, in HF group, the H/M value in immediate acquisition (5 min) and late acquisition (240 min), as compared to early acquisition (15 min), showed 95% Confidence Interval of ti5min (-0.072, 0.037) and ti240min (-0.129, -0.020) (p=ns).

By considering the clinical value of early imaging (5 or 15 min after injection), in the PD group, the statistical analyses validated the diagnostic role of H/M in immediate acquisition (5 min) and early acquisition (15 min) as compared to the standardized late acquisition (240 min) with 95% Confidence Interval of ti5min (-0.053, 0.037) and ti15min (-0.023, 0.067) (p=ns). Contrarily, in HF group, the H/M value in immediate acquisition (5 min) and early acquisition (15 min), as compared to late acquisition (240 min), with 95% Confidence Interval of ti5min (0.003, 0.112) and ti15min (0.020, 0.129) ($p<0.05$) and, therefore, resulted in not statistically validated in its usefulness as a "self-sufficient" diagnostic tool.

4. DISCUSSION

^{123}I-mIBG imaging can visualize cardiac sympathetic innervation by providing (semi-) quantitative information on the myocardial sympathetic activity and, even if the ^{123}I-mIBG imaging includes both planar imaging and SPECT imaging, the planar imaging technique results are widely standardized [18]. The standardized technique of H/M establishes the image acquisition after 15 and 240 minutes from radiolabeled-compound injection [10]. Nevertheless, a shorter time interval between the injection of ^{123}I-mIBG and the late scan reduces waiting time and may facilitate clinical use. However, only a few studies have investigated the impact of variation in acquisition time after ^{123}I-mIBG administration on the H/M [10]. Several previous papers focused on the best timing of the late acquisition, while a minority of paper focused on the best timing of the early acquisition.

Table 3. HM values of PD and HF patients groups.

Patient#	5 min	15 min	240 min
	PD patients		
1	1.41	1.36	1.20
2	1.31	1.41	1.19
3	1.32	1.32	1.27
4	1.88	1.68	2.45
5	2.17	2.06	2.15
6	1.61	1.43	1.42
7	1.31	1.44	1.09
8	1.39	1.36	1.24
9	1.41	1.33	1.52
10	1.84	1.80	1.87
11	2.15	1.99	2.13
12	1.44	1.54	1.14
13	1.76	1.69	1.77
14	1.75	1.72	1.97
15	1.54	1.47	1.59
16	1.68	1.67	1.80
17	1.82	1.74	1.85
18	1.68	1.64	1.62
19	1.66	1.55	1.59
20	2.00	2.08	1.74
21	1.83	1.80	1.96
22	1.11	1.17	1.04
23	2.00	1.69	1.63
24	1.77	1.75	1.82
25	1.85	1.79	2.25
26	1.34	1.29	1.34
27	1.96	1.82	2.05
28	1.69	1.70	1.45
29	1.93	1.88	1.87
30	1.69	1.73	1.91
31	1.83	1.76	2.21
32	1.77	1.64	1.96
33	1.80	1.60	1.82
34	1.63	1.63	1.48

Table (3) contd….

Patient#	5 min	15 min	240 min
35	1.69	1.71	1.76
36	1.22	1.24	1.04
37	1.83	1.81	1.99
38	1.26	1.13	1.27
39	1.57	1.52	1.38
40	1.15	1.26	1.13
41	1.68	1.61	1.54
42	1.64	1.65	1.71
43	1.87	1.72	1.93
44	1.95	1.88	2.03
45	1.84	1.84	2.34
46	1.52	1.56	1.21
47	1.50	1.53	1.26
48	1.63	1.66	1.48
49	1.48	1.56	1.31
50	1.43	1.39	1.20
51	1.26	1.21	1.11
52	1.26	1.44	1.46
53	1.43	1.48	1.29
54	1.38	1.43	1.22
55	1.29	1.29	1.27
56	1.95	1.87	1.94
57	1.28	1.27	1.12
58	1.54	1.48	1.52
59	1.63	1.68	1.46
60	1.15	1.17	1.03
	HF patients		
1	1.35	1.37	1.20
2	1.49	1.47	1.50
3	1.64	1.36	1.44
4	1.39	1.38	1.27
5	1.62	1.61	1.62
6	0.92	0.93	1.84
7	2.30	1.91	1.87
8	1.83	1.71	1.84
9	1.39	1.64	1.44

Table (3) contd….

Patient#	5 min	15 min	240 min
10	1.48	1.53	1.56
11	1.71	1.56	1.75
12	1.89	1.79	1.84
13	1.57	1.56	1.40
14	1.93	1.85	1.87
15	1.75	1.80	1.55
16	1.35	1.44	1.14
17	1.82	1.76	1.54
18	1.72	0.62	1.67
19	1.68	1.64	1.64
20	1.62	1.57	1.42
21	1.76	1.71	1.63
22	2.01	2.25	1.78
23	1.62	1.68	1.44
24	1.55	1.64	1.55
25	1.94	1.86	1.61
26	1.45	1.47	1.39
27	1.79	1.74	1.81
28	1.80	1.79	1.55
29	1.60	1.76	1.71
30	1.27	1.65	1.46
31	1.90	1.94	1.62
32	1.72	1.73	1.62
33	1.70	1.68	1.52
34	1.66	1.68	1.43
35	1.42	1.41	1.39
36	1.88	1.75	1.74
37	2.00	1.93	1.85
38	1.75	1.78	1.56
39	1.58	1.70	1.46
40	1.82	1.99	1.79
41	1.63	1.84	1.63
42	1.67	1.72	1.63
43	1.40	1.35	1.46
44	1.70	1.66	1.50
45	1.74	1.69	1.66

Table (3) contd….

Patient#	5 min	15 min	240 min
46	1.56	1.59	1.62
47	1.33	1.35	1.29
48	1.71	1.73	1.71
49	1.60	1.52	1.62
50	1.41	1.43	1.25
51	1.83	1.79	1.79
52	1.63	1.60	1.51
53	1.51	1.51	1.47
54	1.70	1.71	1.72
55	1.70	1.68	1.49

Three-minute delayed heart uptake ratios calculated from dynamic and static studies may help elucidate the uptake at non-vesicular sites, which reflect the severity of sympathetic nervous system abnormalities in the heart [11, 12, 19]. Nevertheless, as compared to our paper, these studies used rat models or smaller samples and, furthermore, focused only on the HF population. Moreover, previous work suggests that the washout rate of ^{123}I-mIBG in the early phase from 4 min to 30 min reflects cardiac sympathetic nervous integrity and is useful to evaluate the severity and prognosis of patients with cardiomyopathy [20, 21]. Nevertheless, to date, we cannot find papers concerning a different timing of early acquisition in PD. Therefore, the aim of this study was to investigate whether performing scan immediate post-injection has a relevant impact on the diagnostic and prognostic value of ^{123}I-mIBG imaging both in patients with PD and in patients with HF. Our findings in PD group, due to immediate (5min) and early (15 min) planar acquisition through statistical validation, may lead to a shortening of imaging protocols in PD group, while maintaining the accuracy and precision of estimated physiologic parameters in planar ^{123}I-mIBG imaging. In fact, as compared with the standardized late acquisition (240 min), both the immediate acquisition and the early acquisition are equivalent. Our results indicate the potential role of immediate (5 min) acquisition in replacement of the standardized 240 minutes acquisition, that may produce logistic advantages of Nuclear Medicine centers concerning PD patients. A significant reduction in the execution times can make this examination much easier for patients who often have reduced compliance.

Nevertheless, in HF group neither immediate (5 min) or early (15min) planar acquisition results validated as compared to late (240 min) acquisition. Therefore, in HF group, our data may lead to less strict protocols regarding the early (15 min) acquisition that may be replaced by an immediate (5 min) acquisition. But, necessarily, the early acquisition should be followed by a late (240 min) acquisition.

On the contrary, in PD group, considering both the physiopathology of PD and the absence of cardiovascular pathology in inclusion criteria that may cause sympathetic nervous system abnormalities, a positive scan on 5 minutes acquisition may be enough to maintain the accuracy and precision of ^{123}I-mIBG imaging, leading to a certain diagnosis of PD, avoiding the late acquisition. These differences between PD and HF may be partially explained by a different physiopathology. PD affects sympathetic nerves as well as parasympathetic fibers in the heart and sympathetic postganglionic fibers are markedly lost in the myocardium of patients with PD, denervation precedes the neuronal loss in the sympathetic ganglion and the extent reflects pathological changes in sympathetic ganglion cells [22]. Therefore, the denervation of the cardiac sympathetic nerve has been proven by ^{123}I-mIBG imaging [23]. In patients with HF, activation of the adrenergic nervous system is one of the important physiological responses elicited to compensate for depressed myocardial function and ^{123}I-mIBG shares many cellular transport properties with norepinephrine at the low concentrations used in clinical practice, and it is mainly taken up by adrenergic nerves at the presynaptic site [24]. In PD, the early H/M ratio depends on uptake-1 function at the sympathetic nerve ending [25] and the early H/M is extremely reduced in patients with systemic disorders. On the other hand, the ^{123}I-mIBG washout, which is influenced by the re-uptake rate and sympathetic turn-over rate as determined by sympathetic activity [26], is reported to be enhanced in HF. Contrarily to PD, in HF patients the ^{123}I-mIBG uptake reduction is mainly caused by accelerated sympathetic nerve activity rather than a dysfunction of uptake-1 because sufficient early H/M is maintained.

A limitation of this study is the lack of analyzing the role of SPECT images. Unfortunately, the need to compare H/M at 5 and 15 minutes does not allow to obtain SPECT imaging at 5 minutes.

CONCLUSION

If confirmed by further multicenter trials and bigger samples, a single immediate (5 min) acquisition may lead to shorter protocols at ^{123}I-mIBG imaging in PD group, with subsequent further advantages in logistics and costs fields

and improved patient comfort. The late acquisition (240 min) is confirmed to be mandatory in HF.

STANDARD OF REPORTING:

CARE guidelines and methodologies have been followed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Formal consent was obtained from the local ethics committee.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Informed consent was obtained from all individual participants included in the study and any accompanying images.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] Nakajima, K.; Verschure, D.O.; Okuda, K.; Verberne, H.J. Standardization of [123]I-*meta*-iodobenzylguanidine myocardial sympathetic activity imaging: phantom calibration and clinical applications. *Clin. Transl. Imaging,* **2017**, *5*(3), 255-263. http://dx.doi.org/10.1007/s40336-017-0230-2 PMID: 28596948

[2] Verberne, H.J. Assessment of cardiac sympathetic innervation with (123)I-mIBG SPECT comes to life: need for standardization! *Eur. Heart J. Cardiovasc. Imaging,* **2016**, *17*(4), 391-392. http://dx.doi.org/10.1093/ehjci/jev348 PMID: 26819325

[3] Boogers, M.J.; Borleffs, C.J.; Henneman, M.M.; van Bommel, R.J.; van Ramshorst, J.; Boersma, E.; Dibbets-Schneider, P.; Stokkel, M.P.; van der Wall, E.E.; Schalij, M.J.; Bax, J.J. Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. *J. Am. Coll. Cardiol.,* **2010**, *55*(24), 2769-2777. http://dx.doi.org/10.1016/j.jacc.2009.12.066 PMID: 20538172

[4] Nuvoli, S.; Palumbo, B.; Malaspina, S.; Madeddu, G.; Spanu, A. [123]I-ioflupane SPET and [123]I-MIBG in the diagnosis of Parkinson's disease and parkinsonian disorders and in the differential diagnosis between Alzheimer's and Lewy's bodies dementias. *Hell. J. Nucl. Med.,* **2018**, *21*(1), 60-68. PMID: 29550847

[5] Jacobson, A.F.; Senior, R.; Cerqueira, M.D.; Wong, N.D.; Thomas, G.S.; Lopez, V.A.; Agostini, D.; Weiland, F.; Chandna, H.; Narula, J. ADMIRE-HF Investigators. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J. Am. Coll. Cardiol.,* **2010**, *55*(20), 2212-2221. http://dx.doi.org/10.1016/j.jacc.2010.01.014 PMID: 20188504

[6] Vaccaro, F.; Caccavo, D.; Roumpedaki, E.; De Vincentis, G.; Di Gioia, C.R.; Gallo, P.; Palange, P. Dilated cardiomyopathy due to thrombotic microangiopathy as the only manifestation of antiphospholipid syndrome: a case report. *Int. J. Immunopathol. Pharmacol.,* **2008**, *21*(1), 237-241. http://dx.doi.org/10.1177/039463200802100128 PMID: 18336752

[7] De Vincentis, G.; Frantellizzi, V.; Fedele, F.; Farcomeni, A.; Scarparo, P.; Salvi, N.; Fegatelli, D.A.; Mancone, M.; Verschure, D.O.; Verberne, H.J. Role of cardiac [123]I-mIBG imaging in predicting arrhythmic events in stable chronic heart failure patients with an ICD. *J. Nucl. Cardiol.,* **2019**, *26*(4), 1188-1196. http://dx.doi.org/10.1007/s12350-018-1258-z PMID: 29594915

[8] Verberne, H.J.; Brewster, L.M.; Somsen, G.A.; van Eck-Smit, B.L. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. *Eur. Heart J.,* **2008**, *29*(9), 1147-1159. http://dx.doi.org/10.1093/eurheartj/ehn113 PMID: 18349024

[9] Parker, M.W.; Sood, N.; Ahlberg, A.W.; Jacobson, A.F.; Heller, G.V.; Lundbye, J.B. Relationship between quantitative cardiac neuronal imaging with (1)(2)(3)I-meta-iodobenzylguanidine and hospitalization in patients with heart failure. *Eur. J. Nucl. Med. Mol. Imaging,* **2014**, *41*(9), 1666-1672. http://dx.doi.org/10.1007/s00259-014-2819-2 PMID: 24915891

[10] Dimitriu-Leen, A.C.; Gimelli, A.; Al Younis, I.; Veltman, C.E.; Verberne, H.J.; Wolterbeek, R.; Zandbergen-Harlaar, S.; Bax, J.J.; Scholte, A.J.H.A. The impact of acquisition time of planar cardiac (123)I-MIBG imaging on the late heart to mediastinum ratio. *Eur. J. Nucl. Med. Mol. Imaging,* **2016**, *43*(2), 326-332. http://dx.doi.org/10.1007/s00259-015-3220-5 PMID: 26515715

[11] Arbab, A.S.; Koizumi, K.; Takano, H.; Uchiyama, G.; Arai, T.; Mera, K. Parameters of dynamic and static iodine-123-MIBG cardiac imaging. *J. Nucl. Med.,* **1995**, *36*(6), 962-968. PMID: 7769453

[12] Nakajo, M.; Shimabukuro, K.; Yoshimura, H.; Yonekura, R.; Nakabeppu, Y.; Tanoue, P.; Shinohara, S. Iodine-131 metaiodobenzylguanidine intra- and extravesicular accumulation in the rat heart. *J. Nucl. Med.,* **1986**, *27*(1), 84-89. PMID: 3941369

[13] Gelb, D.J.; Oliver, E.; Gilman, S. Diagnostic criteria for Parkinson disease. *Arch. Neurol.,* **1999**, *56*(1), 33-39. http://dx.doi.org/10.1001/archneur.56.1.33 PMID: 9923759

[14] Gilman, S.; Wenning, G.K.; Low, P.A.; Brooks, D.J.; Mathias, C.J.; Trojanowski, J.Q.; Wood, N.W.; Colosimo, C.; Dürr, A.; Fowler, C.J.; Kaufmann, H.; Klockgether, T.; Lees, A.; Poewe, W.; Quinn, N.; Revesz, T.; Robertson, D.; Sandroni, P.; Seppi, K.; Vidailhet, M. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology,* **2008**, *71*(9), 670-676. http://dx.doi.org/10.1212/01.wnl.0000324625.00404.15 PMID: 18725592

[15] De Vincentis, G.; Frantellizzi, V.; Fedele, F.; Farcomeni, A.; Scarparo, P.; Salvi, N.; Fegatelli, D.A.; Mancone, M.; Verschure, D.O.; Verberne, H.J. Role of cardiac 123I-mIBG imaging in predicting arrhythmic events in stable chronic heart failure patients with an ICD. *J. Nucl. Cardiol.,* **2018**. PMID: 29594915

[16] Flotats, A.; Carrió, I.; Agostini, D.; Le Guludec, D.; Marcassa, C.; Schäfers, M.; Somsen, G.A.; Unlu, M.; Verberne, H.J. EANM Cardiovascular Committee; European Council of Nuclear Cardiology. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. *Eur. J. Nucl. Med. Mol. Imaging,* **2010**, *37*(9), 1802-1812. http://dx.doi.org/10.1007/s00259-010-1491-4 PMID: 20577740

[17] Generalised linear mixed models. *Applied Mixed Models in Medicine,* **2014**,

[18] Verschure, D.O.; Poel, E.; Nakajima, K.; Okuda, K.; van Eck-Smit, B.L.F.; Somsen, G.A.; Verberne, H.J. A European myocardial [123]I-mIBG cross-calibration phantom study. *J. Nucl. Cardiol.,* **2018**, *25*(4), 1191-1197. http://dx.doi.org/10.1007/s12350-017-0782-6 PMID: 28120154

[19] Zan, Y.; Long, Y.; Chen, K.; Li, B.; Huang, Q.; Gullberg, G.T. Design of a short nonuniform acquisition protocol for quantitative analysis in dynamic cardiac SPECT imaging - a retrospective ^{123} I-MIBG animal study. *Med. Phys.,* **2017**, *44*(7), 3639-3649. http://dx.doi.org/10.1002/mp.12288 PMID: 28429371

[20] Arimoto, T.; Takeishi, Y.; Fukui, A.; Tachibana, H.; Nozaki, N.; Hirono, O.; Yamaguchi, H.; Itoh, M.; Miyamoto, T.; Takahashi, H.; Okada, A.; Takahashi, K.; Kubota, I. Dynamic 123I-MIBG SPECT reflects sympathetic nervous integrity and predicts clinical outcome in patients with chronic heart failure. *Ann. Nucl. Med.,* **2004**, *18*(2), 145-150. http://dx.doi.org/10.1007/BF02985105 PMID: 15195762

[21] Ceccacci, A.; Mancone, M.; Calcagno, S.; De Vincentis, G.; Sardella, G.; Fedele, F. Role of MIBG scintigraphy in reverse Tako-tsubo cardiomyopathy: Confirming a pathophysiologic hypothesis. *Int. J. Cardiol.,* **2016**, *223*, 54-55. http://dx.doi.org/10.1016/j.ijcard.2016.08.190 PMID: 27529592

[22] Kinbara, T.; Hayano, T.; Otani, N.; Furutani, Y.; Tanaka, S. Iodine-123 metaiodobenzylguanidine imaging can predict future cardiac events in Japanese patients with Parkinson's disease. *Ann. Nucl. Med.,* **2013**, *27*(2), 123-131. http://dx.doi.org/10.1007/s12149-012-0662-8 PMID: 23086545

[23] Strano, S.; Fanciulli, A.; Rizzo, M.; Marinelli, P.; Palange, P.; Tiple, D.; De Vincentis, G.; Calcagnini, G.; Censi, F.; Meco, G.; Colosimo, C. Cardiovascular dysfunction in untreated Parkinson's disease: A multi-modality assessment. *J. Neurol. Sci.,* **2016**, *370*, 251-255. http://dx.doi.org/10.1016/j.jns.2016.09.036 PMID: 27772769

[24] Imamura, Y.; Ando, H.; Mitsuoka, W.; Egashira, S.; Masaki, H.; Ashihara, T.; Fukuyama, T. Iodine-123 metaiodobenzylguanidine images reflect intense myocardial adrenergic nervous activity in congestive heart failure independent of underlying cause. *J. Am. Coll. Cardiol.,* **1995**, *26*(7), 1594-1599. http://dx.doi.org/10.1016/0735-1097(95)00374-6 PMID: 7594091

[25] Degrado, T.R.; Zalutsky, M.R.; Vaidyanathan, G. Uptake mechanisms of meta-[123I]iodobenzylguanidine in isolated rat heart. *Nucl. Med. Biol.,* **1995**, *22*(1), 1-12. http://dx.doi.org/10.1016/0969-8051(94)00084-W PMID: 7735158

[26] Uchiyama, Y.; Momose, M.; Kondo, C.; Kusakabe, K.; Uchiyama, S. Comparison of parameters of (123)I-metaiodobenzylguanidine scintigraphy for differential diagnosis in patients with parkinsonism: correlation with clinical features. *Ann. Nucl. Med.,* **2011**, *25*(7), 478-485. http://dx.doi.org/10.1007/s12149-011-0490-2 PMID: 21499991