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Original

Cardiac sympathetic hyperactivity in chronic kidney disease — a comparison between haemodialysis and peritoneal dialysis patients

Beata Chrapko[1], Agnieszka Grzebalska[2], Anna Nocuń[1], Andrzej Książek[2], Andrzej Drop[3]

[1]Chair and Department of Nuclear Medicine, Medical University of Lublin
[2]Chair and Department of Nephrology, Medical University of Lublin
[3]I Department of Radiology, Medical University of Lublin

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Abstract

BACKGROUND: The effect of renal replacement therapy on cardiac sympathetic function in patients with chronic kidney disease has not yet been completely elucidated. The aim of this study was to evaluate the impact of renal replacement therapy on the activity of cardiac sympathetic nervous system.

MATERIAL AND METHODS: Thirty-four patients with chronic kidney disease were studied: 14 patients (6 men, mean age 48 ± 11 years) were receiving peritoneal dialysis (PD) and 20 patients (20 men, mean age 52 ± 10 years) were receiving haemodialysis (HD). Patients with diabetes and heart failure were excluded from the study. All patients underwent resting gated myocardial perfusion and ^{123}I-*m*IBG myocardial scintigraphy from which early and late heart to mediastinum ratios (HRM) and myocardial washout rate (WR) values were calculated.

RESULTS: PD and HD patients did not differ with respect to left ventricular ejection fraction (52 ± 9% vs. 57 ± 7%) and summed rest score (3.8 ± 2.4 vs. 3.5 ± 0.3). Similarly, early (1.89 ± 0.23 vs. 1.87 ± 0.27) and late (1.76 ± 0.47 vs. 1.74 ± 0.25) HMR, and washout rate (35.5 ± 15.8% vs. 31.3 ± 9.4%) were not significantly different between the two groups of patients.

CONCLUSIONS: These results suggest that the applied method of renal replacement therapy has no significant influence on global activity of cardiac sympathetic nervous system.

KEY words: cardiac sympathetic activity, ^{123}I-mIBG cardiac scintigraphy, renal replacement therapy, myocardial perfusion study

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Background

^{123}I-meta-iodo-benzyl-guanidine (^{123}I-*m*IBG) is a structural analogue of the false neurotransmitter guanethidine, which is mainly taken up by the neuronal-specific uptake-1 into sympathetic nerve terminals. In negligible amount ^{123}I-*m*IBG is carried by a non-specific uptake-2 into non neuronal cells, probably as a result of the passive diffusion. In neuronal uptake-1, ^{123}I-*m*IBG is stored in the post-ganglionic, presynaptic endings of sympathetic neuron vesicles and released via exocytosis by the same mechanism as norepinephrine [1–6]. Therefore, the degree of the ^{123}I-*m*IBG heart uptake reflects the presynaptic tone of the cardiac sympathetic nervous system (CSNS) [1–5]. This direct, non-invasive evaluation of CSNS is widely described [1–7]. The usefulness of this method is underscored in cardiac autonomic neuropathy, especially in diabetes mellitus (DM) [8–10], cardiac amyloidosis [11], ventricular arrhythmias, cardiomyopathy and heart failure [12–15]. ^{123}I-*m*IBG cardiac scintigraphy is also used for the evaluation of the effectiveness of specific treatments, e.g.: beta-blockers therapy [16], post-biventricular pacing [17], cardiac transplantation [18–20], and in assessing the impact of renal transplantation on the cardiac adrenergic system [21], as well in assessing the degree of local cardiac damage caused by myocarditis [22].

The development of chronic kidney disease (CKD) is closely related to increased activation of the sympathetic nervous system [23], which has been suggested as an important mechanism in

Correspondence to: Beata E. Chrapko, MD, PhD
Chair and Department of Nuclear Medicine, Medical University of Lublin,
ul. Jaczewskiego 8c, 20–954 Lublin, Poland
Phone/fax: (+48) 81 72 44 339
E-mail: beata.chrapko@wp.pl

the cardiovascular events [24]. This is particularly important in Central Europe, where the number of patients treated with replacement renal therapy (RRT) has doubled every decade since 1980 [25]. What is more, in countries with low renal transplantation rate, a steady increasing amount of complications associated with RRT has been observed. This unfortunately increases the likelihood of sudden cardiac death (SCD) [26–28], which is the main cause of death in haemodialysis patients [29, 30]. Moreover, the incidence of cardiac arrest is 100 times higher in the dialysis population than in the general population [31].

The intermittent nature of HD and the electrolyte changes, which happen usually during haemodialysis sessions, activates sympathetic nervous system [32]. On the contrary, in peritoneal dialysis patients, especially in the commonly used continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD), the activation of sympathetic nervous system by the prior-mentioned factors seems not to be so extensive. However, to the best of our knowledge, little or no work has been done to show the effect of applied PD on the function of CSNS as measured by ^{123}I-*m*IBG myocardial uptake. Therefore, we decided to evaluate the impact of renal replacement therapy on the activity of cardiac sympathetic nervous system.

Material and methods

Patients

We studied a population of thirty-four patients in end stage renal disease (ESRD), who were receiving two different types of RRT: peritoneal dialysis (PD) and haemodialysis (HD).

The PD group consisted of fourteen patients (F/M: 8/6) aged 29–70 years (mean 47.93 ± 11.43 years of age) receiving peritoneal dialysis (mean time 31.07 ± 24.33 months). Hypertension was treated in nine patients, for 9 to 100 months (mean 54.6 ± 38.23); the mean body mass index (BMI) came to 26.14 ± 4.4 1kg/m^2 (Table 1). Patients received either peritoneal dialysis: CAPD (seven patients) or CCAPD (seven patients). The causes of ESRD were assessed as follows: glomerulonephritis (five patients), hypertension nephropathy (four patients), adult dominant polycystic kidney disease (one patient), chronic pyelonephritis (three patients) and obstructive nephropathy (one patient). None of these patients had peritonitis within 30 days before examination, nor did they show signs of any other inflammatory process. The imaging procedures were performed in all patients after the drainage of their peritoneal cavities (empty abdomen).

The HD group consisted of twenty patients (males; aged 34–67; averaging 51.6 ± 10.03 years of age), who were haemodialysed for 3 to 132 months (a mean 56.20 ± 47.43 months). In this group, hypertension was treated in seventeen patients for 3 to 120 months (mean 50.4 ± 47.43 months); BMI came to 24.83 ± 3.19 kg/m^2 (Table 1). What is more, the underlying cause of renal failure was found to be chronic glomerulonephritis in fifteen of these patients, and miscellaneous in five patients.

Exclusion criteria

Patients were excluded from this study if they had any of followings disorders: diabetes mellitus, amyloidosis, Parkinson's disease, degenerative cerebral disease, past cerebral stroke, impaired thyroid function, neoplastic conditions, inflammations of connective

Table 1. Results achieved in PD and HD groups

	Group PD			Group HD			U-Mann-Whitney test	
	N	Mean	SD	N	Mean	SD	Z	p
Age (years)	14	47.9	11.43	20	51.6	10.93	–0.78	0.431
DD (months)	14	31.1	24.33	20	54.35	40.75	–1.73	0.083
HA (months)	14	0.9	0.32	20	50.4	47.43	–3.12	0.002*
BMI [kg/m^2]	14	26,1	4,41	20	24.54	3.43	0.45	0.649
Ca^{2+} [mg/dl]	14	9.2	0.75	20	8.77	0.35	1.52	0.127
PO_4^{3-} [mg/dl]	14	6.2	1.92	20	5.44	1.42	0.52	0.599
CaxP	14	54.8	17.97	20	46.26	12.62	1.29	0.195
PTH [mg/dl]	14	767.2	549.84	20	617	615.94	1.04	0.293
Hb [mg/dl]	14	11.3	0.95	20	11.22	1.17	0.11	0.912
A [mg/dl]	14	3.9	0.26	20	3.91	0.23	0.31	0.752
Kt/v	14	2.3	0.55	20	1.48	0.19	4.65	0.000*
LVEF (%)	14	52.8	7.71	20	57.5	7.19	–1.43	0.153
EDV [ml]	14	84.2	25.34	20	97.7	27.01	–1.01	0.312
ESV [ml]	14	40	16.47	20	41.2	17.61	0.13	0.895
SMS (score)	14	15.2	8.53	20	3.85	3.41	3.28	0.001*
eHMR	14	1.87	0.26	20	1.87	0.27	0.64	0.524
dHMR	14	1.72	0.32	20	1.74	0.25	0.00	1.000
WR (%)	14	38.2	18.64	20	31.38	9.49	0.55	0.582
SRS (score)	14	3.8	2.44	20	0.35	0.59	3.23	0.001*

DD — dialysis duration; HA — duration of hypertension; BMI — Body Mass Index; Ca — calcium; P — phosphate; CaxP — calcium-phosphate product; Hb — haemoglobin; A — serum albumin; Kt/V — marker of dialysis adequacy: K (clearance), t (time), V (volume); eHMR — early heart to mediastinum ratio; dHMR — delayed heart to mediastinum ratio; WR — washout rate; LVEF — left ventricular ejection fraction; EDV — end-diastole volume; ESV — end systole volume; SRS — summed rest score; SMS — summed motion score

tissues, severe infections, dialysis-induced hypotension, relevant cardiovascular disease, left ventricular ejection fraction (< 50%), myocardial infarction, implanted pace maker or cardioverter/defibrillator, heart block (> 1st degree).

Anti-hypertensive medications, such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), in the patients with hypertension, were not withdrawn before ^{123}I-*m*IBG scintigraphy as suggested by Flotas et al. [33]. However, other drugs that might affect cardiac sympathetic system function were eliminated.

Ethics

Each of the patients signed an informed consent. The study protocol and informed consent forms were approved by the ethics committee of The Bioethical Council, Medical University of Lublin, Poland.

All patients underwent both rest myocardial perfusion study and ^{123}I-*m*IBG myocardial scintigraphy. The tests were well tolerated by all of the patient.

Myocardial perfusion imaging

Myocardial perfusion gated single photon emission computed tomography (GSPECT) was performed in the rest condition, 60 minutes after an intravenous injection of 740 MBq of technetium-99m methoxy-isobutyl-isonitrile (Tc-99m MIBI). GSPECT acquisition was performed on rotating, double-head, large field of view gamma camera Varicam (Elscint, Haifa, Israel) or Symbia T16 SPECT/CT hybrid gamma camera (Siemens, Erlangen, Germany), both equipped with low-energy, high-resolution collimators. A 20% analyser window was set symmetrically at 140 keV. The data was collected on a 64 × 64 matrix through a 180° rotation at 3° intervals; 60 projections (50 seconds/view) in total. Moreover, the heart cycle was divided into 8 sequences. To reconstruct these images, a Butterworth filter, order 5 and cut-off frequency 0.3 cycle/pixel, was used. The series of reconstructed images were analysed qualitatively and semi-quantitatively by the software program Quantitative Perfusion SPECT (QPS, Cedars-Sinai Medical Centre — CSMC). Using QPS, the perfusion of left ventricular myocardium in 17-segments was assessed automatically by comparing these to the norm as summed rest scores (SRS). In this respect, a value of SRS below a score of 3 was considered as a norm. In the use of Quantitative Gated SPECT (QGS, CSMC), the following parameters were assessed: left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), end-systolic volume (ESV), as well as summed motion score (SMS).

^{123}I-mIBG myocardial scintigraphy

The activity of cardiac sympathetic nervous system was evaluated at rest condition, after an intravenous injection of 370 MBq ^{123}I-mIBG. Following this, SPECT and anterior planar images of the chest were performed using the same gamma camera Varicam (Elscint, Haifa, Israel) or Symbia T16 SPECT/CT hybrid gamma camera (Siemens, Erlangen, Germany), in two stages: after 15 minutes (early imaging) and after 4 hours (delayed imaging). In all studies, a 15% energy window was set symmetrically at 159 keV. Moreover, low-energy, high-resolution collimators were used. Sixty (60) projections were collected (25s/projection) on a 64 × 64 matrix in the SPECT studies, by way of a Butterworth reconstruction filter, order 5 and cut-off frequency 0.3 cycle/pixel (Figure 1). The anterior planar images were collected on a 128 × 128 matrix

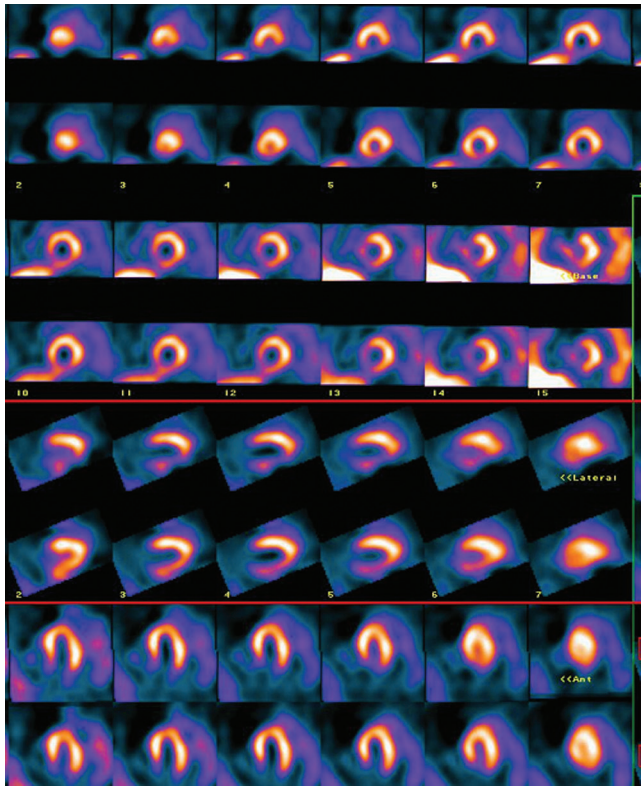

Figure 1. 123I-mIBG SPECT, upper row of slices — 15 minutes post radiotracer injection, lower row — 4 hours post radiotracer injection

for 400 seconds. In addition, the ^{123}I-mIBG uptake was evaluated visually and semi-quantitatively. The semi-quantitative assessment was comprised of a calculation of heart to mediastinum ratio (HMR) and myocardial washout rate (WR). This was done according to EANM proposal [33], as well as according to the previously described methods [34, 35]. To calculate HMR, two regions of interest (ROI) in the anterior planar image were determined (Figure 2). One was an irregular ROI of the heart (H), drawn over the entire outline of the heart (with its size depending on the patient's heart); while the other was a rectangle ROI of the mediastinum (M) of 7 × 7 pixels, selected from the central superior mediastinum sector. The HMR was calculated from early (eHMR) and delayed (dHMR) imaging as follows: HMR = mean count per pixel in H ROI/ mean count per pixel in M ROI. Furthermore, the myocardial WR was expressed as decreasing myocardial activity over time between the early and delayed imaging that was normalized to mediastinal activity in the following manner: WR = {early imaging (H-M) – delayed imaging (H-M)/early imaging (H-M)} × 100%.

A high observer reproducibility of planar HMR and SPECT defect scores using ^{123}I-mIBG cardiac imaging protocol in patients with heart failure has been recently reported [36].

It should be noted that the values of these indices depend on the calculation method [37] and the collimator type used [38]. According to the method applied in our study [33, 35], the normal ranges of global cardiac adrenergic function indices should be considered as follow: for eHMR: 1.89 ± 0.14; for dHMR: 1.93 ± 0.16 [35]; and for WR: 20% ± 10% [39]. All calculations were done by way of the use of the same methods, independently by two experienced, "blinded" nuclear medical physicists.

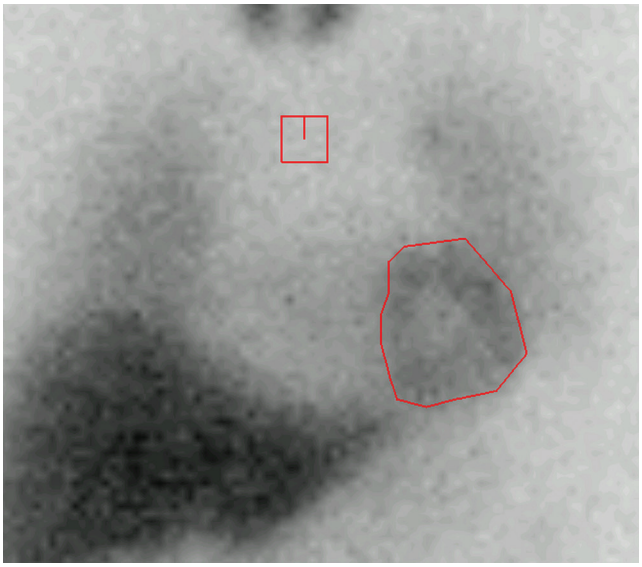

Figure 2. I-123 *m*IBG planar AP projection of the thorax. Examples of the heart (H) and mediastinum (M) ROIs

Statistical analysis

All values derived in this study are shown as mean value ± standard deviation (SD). The differences between parameters were estimated by employing the Mann-Whitney U test, while statistical significance was defined as being $p \leq 0.05$. All statistical analyses were performed using STATISTICA 6.0 (Stat Soft, Poland).

Results

Peritoneal dialysis group

The myocardial perfusion evaluated by GSPECT shows that normal rest myocardial perfusion was present only in three out of the fourteen patients (20%), while a single perfusion defect were found in seven patients (50%), and double perfusion defects were observed in four patients (30%). Thus, the mean SRS value in PD group was mildly increased compared with the norm. The mean values of the global parameters of the left ventricle function, like: LVEF, EDV, ESV were within the normal range (Table 1).

Visual analysis of ^{123}I-mIBG SPECT revealed homogenous distribution of the tracer within the myocardium in most of the patients (12 of the 14 patients from PD group). In rest of the patients the evaluation of the inferior wall of the left ventricle was problematical because of high activity within the abdominal cavity (Figure 3).

The results of the semi-quantitative evaluation of the planar ^{123}I-mIBG myocardial scintigraphy are as follows: eHMR = 1.89 ± 0.23 (ranging from 1.25 to 2.15) and dHMR = 1.76±0.47 (ranging from 1.07 to 2.87); mean WR = 35.54±15.89% (ranging from 20.25 to 78.54%) (Table 2, Figure 4). In 2/14 of these PD patients, all CSNS indices were abnormal.

Haemodialysis group

In the myocardial perfusion GSPECT study, the normal rest perfusion scans were found in 10/20 (50%) of the HD patients, while single area perfusion defects were seen in the remaining

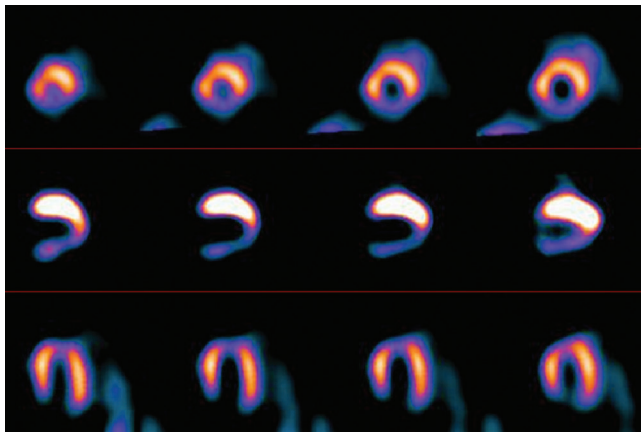

Figure 3. Poor quality of the ^{123}I-*m*IBG SPECT, low uptake in inferior wall of left ventricle

Table 2. The indices of the global CSNS function in PD patients. Red boxes — abnormal values, orange boxes — normal values

No	eHMR	dHMR	WR	RRT
1	1.63	1.33	56.25	PD
2	2.02	1.87	23.26	PD
3	1.99	2.06	21.00	PD
4	1.90	1.78	25.55	PD
5	1.99	1.88	30.52	PD
6	2.03	2.08	19.26	PD
7	1.25	1.07	78.41	PD
8	2.07	1.93	38.97	PD
9	2.07	1.70	44.32	PD
10	1.79	1.50	45.26	PD
11	1.77	1.59	36.00	PD
12	1.95	1.63	44.00	PD
13	1.8	1.78	22.00	PD
14	2.15	2.11	24.00	PD

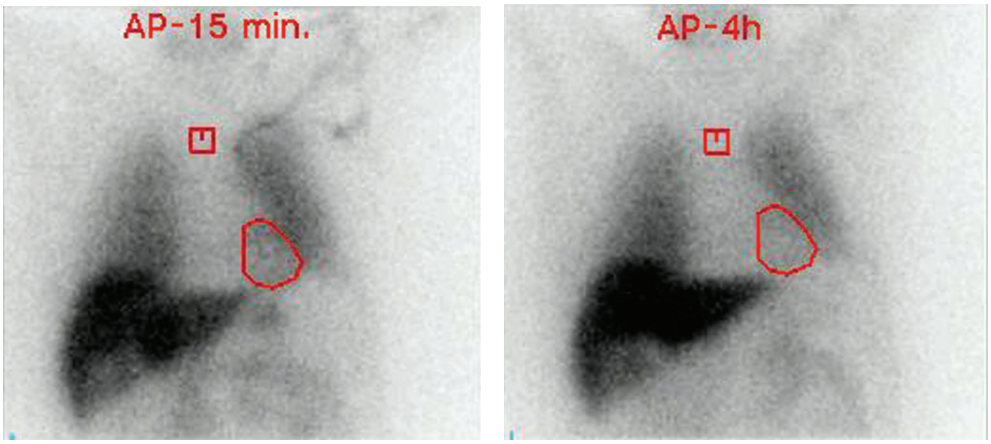

Figure 4. Global adrenergic indices in PD patient: eHMR = 1.99; dHMR = 1.88; WR = 28.67%

Table 3. The indices of the global CSNS function in HD patients. Red boxes — abnormal values, orange boxes — normal values

No	eHMR	dHMR	WR	RRT
1	2.44	2.24	33.86	HD
2	1.84	1.72	29.56	HD
3	1.87	1.62	41.85	HD
4	1.54	1.50	30.94	HD
5	2.05	1.97	27.25	HD
6	2.30	1.73	20.38	HD
7	1.93	1.89	22.47	HD
8	1.87	1.89	17.42	HD
9	2.15	2.12	21.75	HD
10	1.81	1.67	33.43	HD
11	1.46	1.42	48.8	HD
12	1.80	1.80	17.63	HD
13	1.82	1.63	43.83	HD
14	1.86	1.90	22.8	HD
15	1.76	1.60	34.66	HD
16	1.98	1.89	23.87	HD
17	1.54	1.39	36.83	HD
18	1.65	1.54	38.9	HD
19	2.23	2.04	36.5	HD
20	1.46	1.31	44.92	HD

10/20 patients (50%), so summed rest scores (SRS) were slightly increased compared with norm (Table 1). The mean values of the indices of the left ventricle function were in a normal range.

Normal distribution of ^{123}I-mIBG in SPECT study in the HD group was detected only in one patient, whereas in other cases, the examination reviled defects of radioisotope accumulation, mainly in the region of the posterior and postero-lateral walls and the heart apex.

In assessment of the planar ^{123}I-mIBG myocardial scintigraphy, the indices of global cardiac sympathetic nervous system function are as follows: mean value of eHMR = 1.87 ± 0.27 (ranging from 1.46 to 2.30); mean value of dHMR = 1.74 ± 0.25 (ranging from 1.31 to 2.24) and the mean value of WR = 31.38 ± 9.49 % (ranging 17.42 to 44.92) (Table 3). In 5/20 of the HD patients, all CSNS indices were abnormal (Table 3, Figure 5).

Peritoneal dialysis group vs. haemodialysis group

In a comparison of the achieved results of the studied groups, four significant differences were found: two of these were related to clinical aspects and the other two concerned myocardial perfusion assessment (Table 1). With regards to clinical information, hypertension was treated for a longer period of time in the HD patients in comparison to the PD group, and the dialysis adequacy ratios Kt/V were better in the HD group, compared with those of the PD patients. Moreover, rest myocardial perfusion scores (SRS) and motion

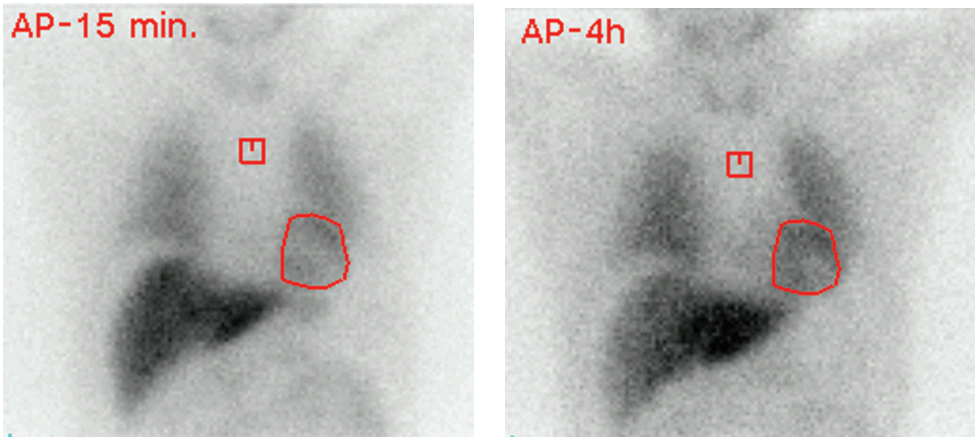

Figure 5. Global adrenergic indices in HD patient: eHMR = 1.99; dHMR = 2.06; WR = 22.37%

scores (SMS) were increased in the PD patients (which was confirmed in a visual analysis). However, there were no statistically significant differences between parameters of the global left ventricle function (LVEF, EDV, ESV), nor significant differences among the global cardiac sympathetic nervous system activity indices (eHMR, dHMR, WR).

Discussion

Despite the taken efforts to reduce typical cardiovascular risk, the cardiovascular mortality rates are still elevated in dialysis patients [40, 41]. Although the nature of peritoneal dialysis and haemodialysis are basically different, the cardiovascular outcomes of patients undergoing these methods of RRT are comparable [42]. However, one of the most important risk factors of SCD — myocardial stunning — is substantially lower in PD patients compared to HD patients [43]. Moreover, hemodynamic instability is associated with HD treatment rather than PD treatment. Yet, Jaar et al. concluded that mortality risk depends on dialysis type, and is significantly higher in PD patients. Moreover, it becomes more prominent in the second year of dialysis [44]. Due to the equivocal statements, we decided to investigate the differences in myocardial perfusion, global left ventricular function and cardiac sympathetic nervous system activation between HD and PD patients. Patients with accelerating myocardial ischaemia factors, like diabetes and dialysis-induced hypotension were excluded from this study [40, 43, 45].

Based on the clinical information, there were only two statistically significant differences between the studied groups. The first one was that the mean Kt/V index was higher ($p = 0.000$) in the PD patients, probably due to the residual diuresis that was preserved in this patients. And the second difference was that in the HD group hypertension was treated longer than in the PD patients ($p = 0.002$).

Patients with CKD have highly elevated cardiovascular morbidity and mortality when compared to the general population. Hypertension and atherosclerosis are major risk factors of extensive morbidity and mortality in those patients. Beyond traditional atherosclerosis accelerating factors like: diabetes, hypertension, obesity, dyslipidaemia, smoking, uraemia induced endothelial dysfunction and production of pro-inflammatory cytokines [46], there is also an increased activation of the sympathetic nervous system. Cardiovascular complications lead to death in 45–50% of all patients receiving dialysis, while 25% of the deaths in this group of patients were associated with CAD [46]. In respect to this situation, myocardial perfusion SPECT stress/rest study could be an excellent tool in predicting both cardiac events and the risk of SCD stratification in ESRD patients [47, 48]. However, most of our patients had a low exercise tolerance, thus, the myocardial perfusion SPECT was conducted only at a rest. Pharmacologic stress test was also a problem in our patients due to a risk of hypertension instability. There was also a concern that these patients would not develop submaximal heart rate. Thus, test results could have been unreliable and incomparable, yet, in both groups, myocardial perfusion SPECT revealed normal to mild perfusion defects.

In present study the mean value of SRS was significantly higher in the PD than in the HD patients ($p = 0.001$). Moreover, regional motion abnormalities (SMS) were more extensive in the PD group compared to HD group ($p = 0.001$). Overall, these findings coexist with normal global left ventricular function.

As it has been mentioned before, the development of CKD is strictly related to the increased activation of the sympathetic nervous system. Kidney injury acts as a trigger mechanism of activation of SNS and renin-angiotensin system (RAS) [49, 50]. Cardiac sympathetic stimulation has chronotropic (increase in heart rate), inotropic (increase in contractile force), dromotropic (elevated atrioventricular conduction) and bathmotropic (increase in excitability) effects. Sympathetic activation also causes a rise in peripheral vascular resistance, sodium and water retention and activation of RAS [2, 51, 52]. The consequences of sustained sympathetic nerve activation are the acceleration of hypertension and heart failure. In this respect, cardiac sympathetic nervous system hyperactivity can be diagnosed in all stages of CKD [23, 24, 26–28]. The distribution of the regional function of CSNS is evaluated visually by ^{123}I-mIBG SPECT. ^{123}I-mIBG SPECT studies are however often problematic due to high accumulation of the tracer in the lung, liver and relatively low uptake of ^{123}I-mIBG in the heart, which occurs in a few cases. Moreover, the heterogeneous distribution of ^{123}I-mIBG in the heart could portray a physiologic inhomogeneous function of sympathetic and parasympathetic innervations, which could be a source of misinterpretation. Furthermore, low inferior wall uptake of ^{123}I-mIBG (Figure 3), which was reported mostly in our HD patients, may predominantly result from innervations in this part of the heart

by parasympathetic fibres. In addition, the low uptake in the apex could be partially due to volume effect and imbalance between sympathetic and parasympathetic nerves [10, 37, 53].

The CSNS activation can be assessed directly by a semi-quantitative evaluation of ^{123}I-mIBG myocardial uptake by the means of calculation of global cardiac adrenergic function indices, such as: eHMR, dHMR and WR. In our opinion this approach is more reliable than visual assessment of SPECT slices. The early HMR portrays the density of the cardiac presynaptic adrenergic nerves terminals, whereas late HMR reflects sympathetic neuronal function from uptake through storage and then to neurotransmitter release, especially NE [2, 5, 37]. Thus, decreasing myocardial uptake of ^{123}I-mIBG and increasing radiotracer myocardial washout rate are considered as being poor prognostic factors [1, 4, 6–8, 14] and reveal a high risk of cardiac death [54]. As our results show, the mean values of eHMR and dHMR in both studied groups were lower than normal values [37], whereas the mean values of WR were slightly increased compared to the norm [39], especially in the PD groups. Furthermore, our work confirmed that sympathetic nervous system hyperactivity happened even in low-risk patients and can appear earlier than global dysfunction of the left ventricle, which was also suggested previously [5, 55].

Dialysed patients are extremely burdened with the factors arising from chronic kidney disease. The dysfunction of the one factor in the cardio-renal axis involves abnormalities in the others [28]. Thus, efforts are made to minimize the negative effects of RRT. In our study, two different modalities of RRT were compared. However, the assessment of the regional distribution of sympathetic activity by use of ^{123}I-mIBG SPECT was at times problematic to assess but the global indices of CSNS activation were similar in both the PD and HD groups. Hence, it can be said that the both methods of dialysis are comparable in the aspect of CSNS activation.

Conclusion

There are no significant differences between peritoneal and haemodialysed patients with regard to the influence of the applied method of RRT on global adrenergic activity, assessed by myocardial ^{123}I-mIBG scintigraphy.

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