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Cardiac sympathetic dysfunction in haemodialysed patients

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Abstract

BACKGROUND: The aim of this study was to evaluate the cardiac sympathetic nervous system function in haemodialysed (HD), non-diabetic patients by iodine-123 meta-iodo-benzyl-guanidine (^{123}I-*m*IBG).

MATERIALS AND METHODS: Planar scintigraphy of the chest was performed in 36 HD, male patients; 15 minutes and 4 hours post injection of 370 MBq of ^{123}I-*m*IBG. The semiquantitative analysis of myocardial tracer uptake was expressed as routine heart to mediastinum (H/M) ratio: 15 minutes (early H/M) and 4 hour (late H/M) post administration as well as washout of the tracer from myocardium (WR). 24-hour Holter studies were recorded and heart rate variability (HRV) was evaluated. Patients were divided into two groups according to the H/M value: group A patients with H/M > 1.8 which has been accepted as a norm, and group B patients with H/M < 1.8.

RESULTS: In 21/36 patients H/M ratio was below normal values. Significant differences between groups A and B were found among the following parameters: early H/M and late H/M ratios, WR and duration of haemodialysis therapy.

CONCLUSIONS: In patients with abnormal function of cardiac sympathetic nervous system, expressed by means of H/M ratio below 1.8, duration of haemodialysis treatment was longer. Duration of HD appears to be an important factor influencing cardiac sympathetic nervous system.

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Background

In the Central Europe, the number of patients treated by renal replacement therapy has doubled every decade since 1980 [1]. In countries with low rate of renal transplant procedures, complications accompanying with long-term haemodialysis (HD) therapy are often observed. Among them, the cardiovascular complications are the leading cause of death, accounting at least 40% of deaths in end-stage renal disease (ESRD), 20% of which are sudden [2]. The hyperactivity of the cardiac sympathetic nervous system (CSNS) is observed in all stages of chronic renal disease (CRD) [3]. The CSNS function can be partly improved along with duration of dialysis [4] or after renal transplant [5]. But, despite the effectiveness of dialysis, circulating uremia-related toxins cause excitation of renal afferent nerves and activate CSNS [6]. Overhydration as well as accumulation of uremic toxins stimulate development of the left ventricular hypertrophy and dysfunction [2]. Nuclear medicine procedures are the only imaging modalities which enable in vivo visualization of global and regional cardiac CSNS functions. Iodine-123 meta-iodo-benzylguanidine (^{123}I-*m*IBG) SPECT depicts presynaptic uptake and storage of radiolabelled neurotransmitter [7, 8]. It is well known, that dysfunction of CSNS is enhanced in diabetic patients, where diabetes mellitus (DM) is the most frequent cause of nephropathy [9, 10]. However, the current report specifically evaluates the CSNS function in haemodialysed (HD), non-diabetic patients by iodine-123 meta-iodo-benzylguanidine (^{123}I-*m*IBG).

Materials and methods

Study population

The study group comprised 36 HD male patients (aged 29–79; 54.7 ± 12.3 years). All had HD sessions three times per week. Patients in poor general condition, unable to exercise, with DM, amyloidosis, dialysis-induced hypotension and neoplastic diseases were excluded from the study. The underlying cause of renal failure was chronic glomerulonephritis (18 patients) and other miscellaneous causes (18 patients). Patients who receive

drugs that might affect cardiac sympathetic system (e.g. tricyclic antidepressants, sympathetic agents) were not included. An antihypertensive medications such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in patients with hypertension were not withdrawn before ^{123}I-*m*IBG scintigraphy, as suggested by Flotas et al. [11].

^{123}I-mIBG myocardial uptake

Cardiac adrenergic system was evaluated on the day without HD sessions, at rest conditions, after IV injection of 370 MBq ^{123}I-*m*IBG. The anterior planar images of the chest were performed on double-head, large field of view gamma camera Varicam (Elscint, Haifa, Israel), in two stages: after 15 minutes (early imaging) and after 4 hours (late imaging) post injection. In all studies 15% energy window was set symmetrically at 159 keV and low-energy high-resolution collimators were used. The images were collected on 128 x 128 matrix for 400 seconds. The ^{123}I-*m*IBG uptake was evaluated semiquantitatively by calculation of heart to mediastinum (H/M) ratio and myocardial washout rate (WR) according to EANM proposed standard [11] and to previously described methods [12]. To calculate H/M ratio, two regions of interest (ROI) in anterior planar image were determined. The ROI of the heart (H) was irregular, drawn over the entire outline of the heart and its size depending on the patient. The ROI of the mediastinum (M), was rectangle, 7 × 7 pixels in size, selected from the central superior mediastinum sector (Figure 1). The H/M was calculated from early and late imaging as follows:

$$H/M = \frac{\textit{mean count per pixel in heart R01(H)}}{\textit{Mean count per pixel in mediastinum R01 (M)}}$$

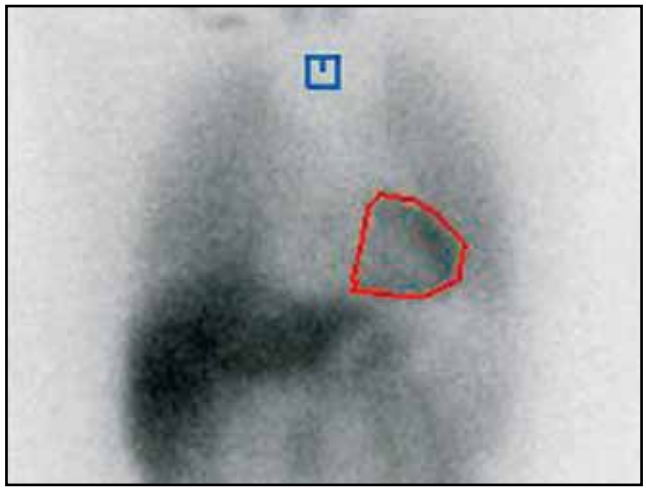

Figure 1. I-123 *m*IBG planar anterior projection of the thorax with examples of the heart (H) and mediastinum (M) ROI

The myocardial WR was expressed as decreasing myocardial activity over time between early and late imaging, normalized to mediastinal activity [11] in the following manner:

$$WR = \frac{\textit{early imaging (H – M) – late imaging (H – M)}}{\textit{early imaging (H – M)}} \times 100\%$$

Cardiac sympathetic nervous system was considered to be dysfunctional if H/M ratio was below 1.8 [7, 10, 13]. According this value patients were divided into two groups: group A with normal function of CSNS and group B with impaired CSNS function (Table 1).

Table 1. The comparison of studied parameters within group A and B

	Group A; n = 15			Group B; n = 21			
Parameters	**Median**	**Minimum**	**Maximum**	**Median**	**Minimum**	**Maximum**	**P***
Age (years)	53	29	69	58	36	79	NS
mHD (months)	12	4	108	53	7	132	0.03
Duration of hypertension (months)	24	4	120	25	0	120	NS
Body mass index [kg/m^2]	23.3	15.9	30.7	24.3	18	36.2	NS
Calcium [mg/dl]	8.8	8.1	10	8.7	7.84	10	NS
Phosphate [mg/dl]	5.1	3.2	7.7	4.6	2.25	7.6	NS
Calcium-phosphate product	45.6	30	62	44	16	66.12	NS
Parathyroid hormone [mg/dl]	301	135	794	421	29	2670	NS
Haemoglobin [mg/dl]	11.2	9.7	13.2	11.2	9.1	13.7	NS
Serum albumin [mg/dl]	3.99	3.5	4.3	3.9	3.5	4.38	NS
KtV**	1.48	1.27	1.76	1.47	1.03	1.89	NS
Early H/M	1.93	1.8	2.44	1.74	1.37	1.76	0.01
Late H/M	1.89	1.8	2.24	1.59	1.18	1.70	0.001
Washout rate (WR)	22.19	17.42	27.25	40.01	29.56	69.15	0.001
Heart rate variability [ms] (SDNN)	108	79	160	85	53	201	NS

*Mann-Whitney test; **Kt/V — marker of dialysis adequacy; K — clearance; t — time; V — volume; H/M — heart to mediastinum ratio; NS — not significant

Heart rate variability (HRV)

In all patients a 24-hour ambulatory Holter recordings were performed using OXFORD CardioScan Suprima 12 system. For time-domain heart rate variability (HRV) measures, the standard deviation of normal-to-normal R-R intervals (SDNN) obtained during 24 hours were calculated.

Statistical analysis

All calculations were expressed as median, minimal and maximal values. The differences between the study groups were assessed with Mann-Whitney test; p value < 0.05 was considered to indicate statistical significance. Data was analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL) statistical software.

Ethics

Each of the patients signed an informed consent form. The study protocol and informed consent forms were approved by The Bioethical Council, Medical University of Lublin, Poland. The test was well tolerated by all of the patients.

Results

The semiquantitative evaluation of ^{123}I-*m*IBG myocardial uptake revealed abnormal (lower than 1.8) value of early and late H/M ratio in 21 (58%) out of 36 patients (B group). Normal values were found in 15 (42%) of 36 patients (group A). There were significant differences between group A and B among this indices. The values of myocardial WR were significantly higher in group B compare with A. Moreover the duration of haemodialysis therapy in patients in group B was significantly longer than in group A. The heart rate variability, expressed by SDNN was not significantly different between groups A and B (Table 1).

Discussion and conclusions

The uremic changes in the circulatory system leads to the heart failure, the main cause of death in CRD. Dysfunction of CSNS largely influences presentation of cardiovascular complications in HD patients. The major cardiac events (MCE) often occur within the first year of HD [14–16]. Nevertheless, HD patients are often undiagnosed with abnormal cardiac sympathetic nervous system function.

In current study, patients were divided into two groups according to the H/M value, where 1.8 was considered as a normal, based on previous studies performed in similar method [10, 13, 17]. Patients with DM and amyloidosis were excluded from our study, because of evident influence on CSNS [9, 13, 18, 19–21]. The semiquantified evaluation of ^{123}I-*m*IBG myocardial uptake was expressed as early and late H/M ratios as well as WR. The early H/M ratio reflects the integrity of pre-synaptic nerve endings and neuronal uptake of neurotransmitters, whereas the late H/M ratio combines information on neuronal function from uptake to release through the storage vesicle at the nerve endings. This functionality were impaired in 58% of studied patients. The value of both: early and late H/M ratios in group B were significantly lower than in group A. But, values of both early and late H/M ratios in group B were not as low as 1.2, which value indicated patients with high risk of cardiovascular death [22]. Myocardial ^{123}I-*m*IBG WR is an index of the degree of sympathetic tone. The increased CSNS activity manifests as high myocardial WR and low late uptake of ^{123}I-*m*IBG. It is considered as the poor prognostic factor of major cardiac events [23, 24]. The normal WR values range from 20% $\pm$ 10% [25]. In our patients this index exceeded normal value only in group B, whereas in group A the maximal value came to 27.25. According to Kioka et al. the value of myocardial WR higher or equal than 27% is the only independent predictor of sudden cardiac death (SCD) [26]. Our main fining is that, in patients with abnormal H/M ratio, which reflects sympathetic function, the duration of haemodialysis is significantly longer in comparison with patients with normal H/M ratio.

Decreased HRV, reflected by low values of SDNN in 24-hour Holter monitoring (especially below 50 ms) identifies patients at an increased risk for SCD, which is also proven in the population of HD patients [27, 28]. In group B, the minimal value of SDNN was close to 50, but there is no significant different in HRV between groups A and B, similarly to other authors [13].

The semiquantitative assessment of ^{123}I-*m*IBG myocardial uptake is an important tool in evaluation of the cardiac sympathetic nervous system function. This function may deteriorate with duration of haemodialysis. It has been found that, in patients with abnormal function of cardiac sympathetic nervous system, expressed by means of lower than 1.8 H/M ratio, duration of haemodialysis treatment was longer. It brings us to conclusion that duration of haemodialysis treatment appears to be an important factor influencing cardiac sympathetic nervous system. The H/M ratios and WR are more sensitive indices of CSNS damage than heart rate variability.

Conflicts of interest — none

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