SPECT and PET in Sympathetic Innervation

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CHAPTER 4

Cardiac sympathetic innervation is disrupted before the start of renal replacement therapy

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ABSTRACT

Purpose: patients with chronic kidney disease (CKD) who undergo chronic haemodialysis (HD) show altered sympathetic tone, increased norepinephrine levels and decreased global myocardial perfusion, which are related to higher cardiovascular mortality. The purpose of this study was to investigate the effect of transition from pre-dialysis to HD on cardiac sympathetic innervation.

Methods: patients with CKD stage G5 were included in this prospective study between May 2010 and December 2013. All patients underwent iodine-123 labelled meta-iodobenzylguanidine ([^{123}I]-MIBG) and technetium-99m labelled tetrofosmin scintigraphy prior to (baseline) and six months after the start of HD (follow up). Heart-to-mediastinum ratio (HMR) and wash out (WO) were determined after administration of [^{123}I]-MIBG. Results of [^{123}I]-MIBG scans were compared to healthy control subjects (HC). Denervation was defined as either HMR<1.6 or WO>20%.

Results: 18 patients and 9 healthy control subjects, mean age 58±18 and 52±17 years (ns) respectively, were included. HMR did not differ between baseline and follow up. However, HMR was lower and wash out was higher in patients at follow up than in HC (HMR 2.3 ± 0.64 vs 2.9 ± 0.58 (p=0.035), and 3.5% (-2.0 – 41) vs -2.1% (-22 – 12) (p=0.013), respectively). At baseline, three patients had cardiac denervation, which was unchanged at follow up. Two patients developed new denervation at follow up. In three out of the five patients with denervation at follow up denervation seemed to coincide with myocardial perfusion abnormalities.

Conclusion: cardiac sympathetic denervation is disrupted before initiation of maintenance HD, and seems to be related with myocardial perfusion abnormalities.

INTRODUCTION

Patients with chronic kidney disease (CKD) who undergo haemodialysis (HD) show increased sympathetic tone, increased serum norepinephrine levels and decreased global myocardial perfusion (1-3). In the normal population, cardiac ischemia and autonomic dysfunction are reliable predictors for future cardiac events and these are also associated with increased long term mortality (4-6). The presence of these findings in CKD patients is related to higher cardiovascular mortality, exceeding that of age and gender matched healthy control subjects (7). Myocardial blood flow decreases significantly during HD, indicating that acute dialysis-associated factors play a role in myocardial perfusion abnormalities (8, 9).

There is a large, but as yet unknown number of individuals with CKD completely asymptomatic for coronary artery disease, especially those with diabetes, who have myocardial ischemia and concomitant diabetic autonomic neuropathy. However, the extent of cardiac ischemia and sympathetic dysfunction on one hand, and the timepoint of development during CKD (i.e. during or even before starting haemodialysis) on the other are unclear. It was previously shown that cardiomyocytes are more vulnerable to innervation abnormalities than to ischemia, which may indicate that cardiac sympathetic dysinnervation precedes myocardial ischemia (10). Autonomic dysfunction is also commonly present in end-stage renal disease, but whether this results in lack of symptoms in cardiac ischemia is unknown.

Analysis of the autonomic function of the heart can be performed by iodine-123 labelled metaiodebenzylguanidine ([^{123}I]-MIBG) a norepinephrine analogue. This is a well established additional method to evaluate the sympathetic innervation of the heart (11). ECG-gated single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy, using technetium-99m tetrofosmin ([^{99m}Tc]-tetrofosmin) is a widely used non-invasive modality to evaluate ischemia of (non-) significant stenosis, and provides information about wall motion, left ventricular volumes and ejection fraction.

Thus far the presence and severity of cardiac autonomic dysfunction and coronary artery disease (CAD) has never been studied in asymptomatic patients with CKD stage G5 who are not yet on dialysis. Our hypothesis is that cardiac sympathetic innervation abnormalities in CKD stage G5 patients can already be visualized before the start of maintanance HD. Furthermore we hypothesize that cardiac sympathetic dysinnervation precedes myocardial perfusion abnormalities in asympatomatic patients. Therefore, the purpose of this study was to determine baseline cardiac sympathetic innervation using [^{123}I]-MIBG in asymptomatic patients with CKD stage G5 and to investigate the effect of the initiation of maintenance HD on cardiac sympathetic innervation. In addition, we studied whether myocardial ischemia using [^{99m}Tc]-tetrofosmin coincides with the development of cardiac sympathetic innervation abnormalities in patients with CKD.

SUBJECTS AND METHODS

Patients

Between May 2010 and December 2013 a total of 18 consecutive patients (13 male) with CKD stage G5 were included in this prospective study. Diagnosis of CKD was based on serum levels of creatinine, and subsequent estimated glomerular filtration rate (eGFR), the latter determined by Modification of Diet in Renal Disease (MDRD) method (12).Included were patients > 18 years of age that had no history of CAD and were asymptomatic for present CAD, no history of Parkinson's disease or dementia with Lewy bodies, no current use of tricyclic antidepressant agents (TCA) which could interfere with [^{123}I]-MIBG uptake, and were expected to start HD within the next 6 months. All patients underwent laboratory tests (including serum creatinine (µmol/L), urea (mmol/L), eGFR (mL/min*1.73m^2), total calcium (mmol/L), phosphate (mmol/L), serum albumin (g/L), and urinary protein excretion (g/24h)). ECG's at baseline and follow up were retrieved from the digital patient chart. [^{123}I]-MIBG scintigraphy for cardiac sympathetic innervation and [^{99m}Tc]-tetrofosmin scintigraphy for myocardial perfusion imaging were performed at baseline (before the start of HD), and 6 months after the start of HD (follow up). If patients showed CAD at baseline they were not excluded from the study to investigate the progression of CAD during maintenance HD. Patients were followed until 6 months after the start of HD. All scans were performed on interdialytic days.

For [^{123}I]-MIBG imaging, 9 age-matched consecutive normal volunteers were scanned, each on one occasion, to collect a healthy control database. All subjects were in good health and did not use medication.

Haemodialysis treatment

Patients were dialyzed thrice weekly. All patients were on bicarbonate dialysis with a low-flux polysulfone hollow-fiber dialyser F8 (Fresenius Medical Care, Bad Hamburg, Germany). Blood flow and dialysate flow rates were 250–350 ml/min and 500 ml/min, respectively. Dialysate temperature was 36.0 or 36,5 °C. Dialysate composition was sodium 139 mmol/L, potassium 1.0 or 2.0 mmol/L, calcium 1.5 mmol/L, magnesium 0.5 mmol/L, chloride 108 mmol/L, bicarbonate 34 mmol/L, acetate 3.0 mmol/L, and glucose 1.0 g/dl.

[^{123}I]-MIBG scintigraphy

Scintigraphy was performed after blockade of thyroid uptake of free [^{123}I] by iodine-potassium iodide (Lugol's solution). After a 15-min resting period, subjects were injected with 185 MBq [^{123}I]-MIBG (General Electric (GE) Healthcare Medical Diagnostics, Eindhoven, The Netherlands) by an intravenous catheter. At 15 min (early image) and 4 h (delayed image) after tracer administration, a 10-min static acquisition was performed in anterior view of the chest, using Symbia S gamma

camera (Siemens Medical System, Knoxville, Tennessee, USA) with a medium-energy low-penetration parallel-hole collimator [15]. A 15% energy window centred on 159 keV, a 256 x 256 matrix size and a 1.45 zoom factor were used. According to the proposed guidelines for [^{123}I]-MIBG scintigraphy, the use of beta-adrenoceptor blocking agents (β-blockers) and angiotensin converting enzyme inhibitors (ACE-i) were not discontinued (13).

Image analysis [^{123}I]-MIBG scintigraphy

For planar images, left ventricular (LV) activity was measured over the raw static image using a region of interest (ROI) along the contour of the LV. A second ROI was placed over the upper mediastinum [13]. Heart-to-mediastinum activity ratio (HMR) was measured three times, and the average of measurements was taken into account. Cardiac [^{123}I]-MIBG wash out rate was defined as percentage change in activity from the early to the late images within the LV ROI as follows: $((H_{early}-H_{late})/H_{early}) \times 100\%$, data being corrected for the physical decay of [^{123}I]. The presence of either HMR < 1.6 or wash out rate > 20% was considered as a sign of impaired cardiac sympathetic, or denervation. Data were also compared with our local normal database.

[^{99m}Tc]-tetrofosmin scintigraphy

Adenosine stress [^{99m}Tc]-tetrofosmin (250 MBq) and rest [^{99m}Tc]-tetrofosmin (600 MBq) SPECT were performed in consecutive order in a 1-day protocol to analyse cardiac ischemia. Patients were asked to withdraw caffeine containing beverages and/or food 24 hours before [^{99m}Tc]-tetrofosmin SPECT. [^{99m}Tc]-tetrofosmin SPECT studies were obtained 1 h after tracer administration using a dual-headed gamma camera (equipped with low-energy high-resolution collimators (Symbia T16 gamma camera (Siemens Medical System, Knoxville, Tennessee, USA)), ECG-gating, and low dose CT for attenuation correction. All data from the [^{99m}Tc]-tetrofosmin SPECT studies were reorientated in short-axis, horizontal and vertical long-axis sections. Data was analyzed and displayed in a 17-segment polar map, using the Quantitative Perfusion SPECT (QPS) application, a commercially available gated cardiac software package (developed by the Cedars-Sinai Medical Center, Los Angeles, CA, USA) (14). Average counts per segment were obtained from the 17 segments and the measured counts were normalized to the segment with the highest average counts.

Statistical analysis

Baseline descriptive statistics are presented as mean ± standard deviation or median (range) for continuous variables and numbers with percentages for categorical variables as required. We evaluated differences between the two study groups using the χ^2 test and Fisher's exact test for categorical data and the Student's *t*-test and Mann–Whitney *U* test for continuous data, according to whether data were

normally distributed. In all analyses, $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS package version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. The mean age was 58 ± 18 years. For the 9 healthy controls (6 women and 3 men), the age was not significantly different: 52 ± 17 years. As expected in patients with stage 5 CKD, eGFR indicated very severely reduced kidney function (<15 mL/min) in all patients. A majority of the patients had hypertension (78%), and used anti-hypertensive medication, mainly β-blockade and diuretics. Diabetes mellitus was present in 33% of the patients. None of the patients appeared to have a history of coronary artery disease or any other severe cardiac event.

At baseline, none of the patients had electrocardiographic signs of ischemia or infarction. One patient had a first degree atrio-venticular block, whereas one other patient had a left bundle branch block (QRS duration 138 ms).

[^{123}I]-MIBG scintigraphy

Table 2 shows the results of the [^{123}I]-MIBG scans. All 18 patients underwent [^{123}I]-MIBG scintigraphy at baseline and during follow up. Follow up [^{123}I]-MIBG scans were performed within 6 ± 2 months after the start of HD. Early and late HMR in patients at baseline were not different from healthy controls. In healthy control subjects, there was no difference between early and late HMR. However, a statistical significant decrease in patients' HMR was observed at both baseline and follow up: mean early HMR 2.6 ± 0.70 versus (vs) late HMR 2.4 ± 0.76 (p=0.005) at baseline, and mean early HMR 2.5 ± 0.51 versus (vs) late HMR 2.3 ± 0.64 (p=0.006) at follow up. This was not present in healthy controls. At baseline four patients had signs of impaired cardiac sympathetic innervation, whereas five patients showed denervation at follow up.

In patients, early HMR at baseline was not different from early HMR at follow up, nor was late HMR at baseline different from late HMR during follow up. However, patients at follow up showed significant lower late HMR and higher wash out than healthy controls: mean late HMR 2.3 ± 0.64 vs 2.9 ± 0.58 (p = 0.035), and mean wash out 10 ± 13% vs -2.1 ± 10% (p = 0.013, Figure 1 and 2). No statistical difference in wash out of [^{123}I]-MIBG between follow up compared to baseline was observed. Figure 3 shows the wash out values of the individual patients at baseline and follow up.

Interestingly, none of patients with signs for denervation on [^{123}I]-MIBG scintigraphy at follow up used ACE-i. Four of those patients did use β-blockers. Only one patient with diabetes mellitus developed cardiac sympathetic denervation during HD.

Table 1
Patient characteristics at baseline

	Frequency (n), median (range) or mean ± SD
Gender (*n*)	
Male	13 (72 %)
Age (years)	58 ± 18
Medical history (*n*)	
Hypertension	14 (78%)
Hypercholesterolemia	6 (33%)
Diabetes Mellitus	6 (33%)
Smoking	2 (11%)
Coronary artery disease	0 (0%)
Medication at baseline (*n*)	
Beta-blocker	11 (61%)
ACE-inhibitor	6 (33%)
Diuretics	8 (44 %)
Laboratory at inclusion	
Leucocytes (x 10^9/L)	7.1 (3.3 - 9.8)
Haemoglobin (mmol/L)	6.8 (6.0 - 9.7)
Trombocytes (x10^9/L)	208 (117 - 347)
C-reactive protein (mg/L)	0 (0 - 59)
Sodium (mmol/L)	140 (135 - 145)
Potassium (mmol/L)	4.9 (4.0 - 5.9)
Chloride (mmol/L)	107 (98.0 - 114)
Urea (mmol/L)	26 (15 - 38)
Creatinine (µmol/L)	584 (339 - 1.31x103)
eGFR (mL/min*1.73 m^2)	8.0 (4.0 - 12)
Uric acid (mmol/L)	0.45 (0.23 - 0.72)
Calcium (mmol/L)	2.25 (2.07 - 2.53)
Phosphate (mmol/L)	1.60 (1.07 - 2.12)
Total protein (g/L)	67 (60 - 77)
Albumin (g/L)	41 (29 - 46)
HDL (mmol/L)	1.0 (0.70 - 2.7)
LDL (mmol/L)	2.2 (0.80 - 4.8)
Glucose (mmol/L)	6.7 (4.1 - 14)
Urinary protein excretion (g/24h)	2.7 (0.40 - 6.8)

HDL High-density lipoprotein cholesterol, LDL Low-density lipoprotein cholesterol

Table 2
[^{123}I]-MIBG findings

	Frequency (n), or mean ± SD		
	Healthy controls (N=9)	Patients Baseline (N=18)	Follow up (N=18)
Early HMR	2.8 ± 0.63	2.6 ± 0.70	2.5 ± 0.61
Late HMR	2.9 ± 0.58	2.4 ± 0.76	2.3 ± 0.64
Wash out rate (%)	-2.1 ± 10	9.2 ± 11	10 ± 13
Cardiac sympathetic innervation abnormalities (*n*)	0	4	5

HMR Heart-to-mediastinum ratio, Cardiac sympathetic innervation abnormalities (*n*) = low late HMR and/or high wash out rate

Figure 1
Late [^{123}I]-MIBG heart-to-mediastinum ratio's patients at baseline and follow up, and of healthy control subjects. Late HMR was significantly lower in patients at follow up than in healthy controls.

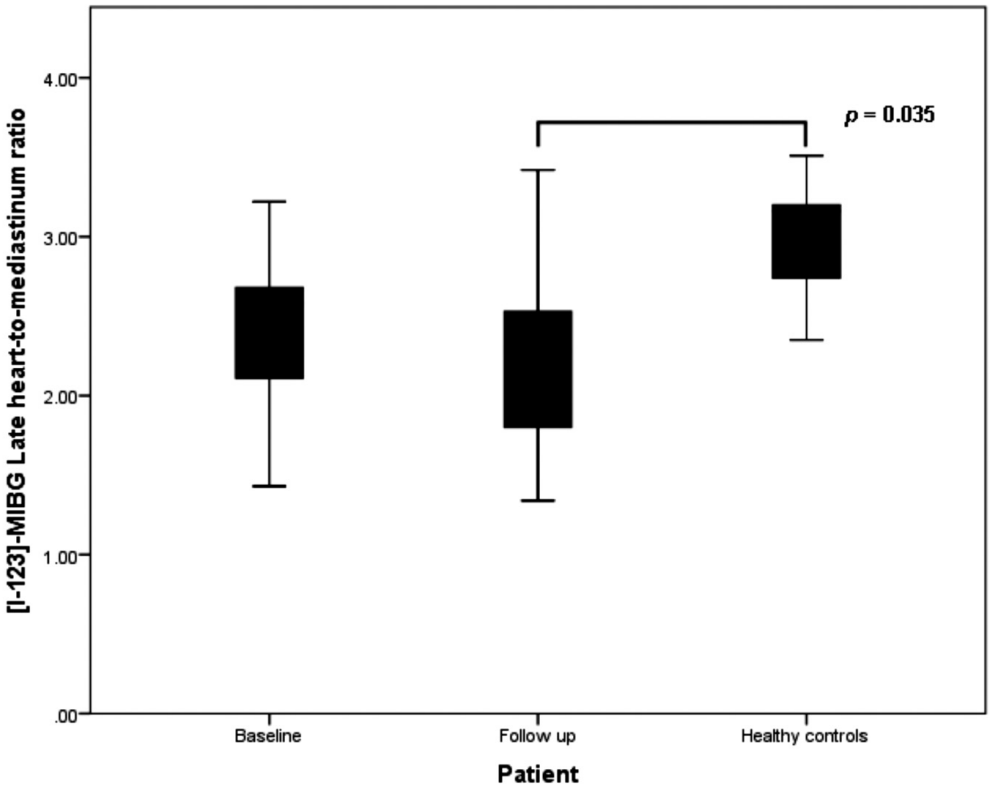
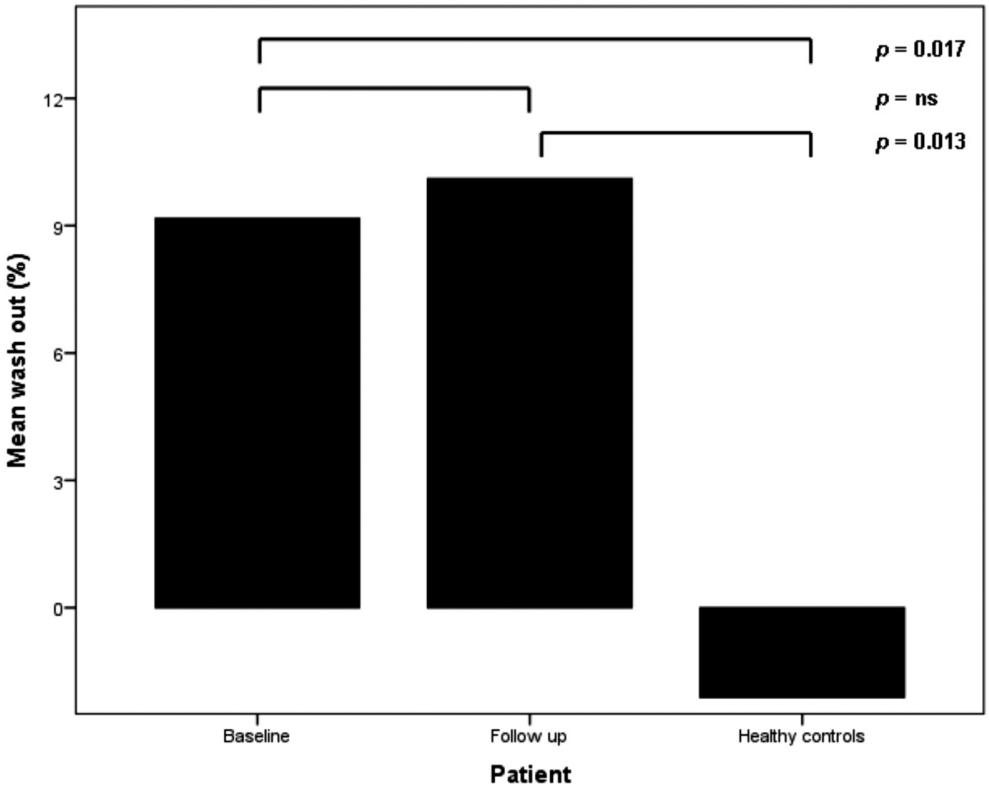


Figure 2
Mean [^{123}I]-MIBG wash out values of patients at baseline and follow up, and of healthy controls. Wash out was significantly lower in healthy controls than in patients at both baseline and follow up. In patients, there was no significant difference in wash out between baseline and follow up.



[^{99m}Tc]-tetrofosmin scintigraphy

The results of myocardial perfusion SPECT are summarized in Table 3. Baseline myocardial perfusion SPECT was performed in 17 of 18 (94%) patients. One patient was not able to undergo the investigation before the start of HD. Myocardial ischemia was present in six (35%) patients, and five of these six patients also showed wall motion abnormalities, especially hypokinesia of the affected LV wall. None of patients had signs of infarction at baseline. Mean left ventricular ejection fraction (LVEF) was within a normal range (56 ± 17 %).

After the start of HD, follow up myocardial perfusion SPECT was performed within 6 ± 2 months. At follow up four patients showed myocardial ischemia, and two of these patients had developed a new myocardial infarction compared with the baseline study. Thus, of these four patients with myocardial ischemia at follow up, two patients had developed new myocardial ischemia during HD, while two patients had myocardial ischemia at baseline that did not change after the start

of HD. Two patients with myocardial ischemia at baseline had normal myocardial perfusion SPECT results at follow up. Both patients with myocardial infarction at follow up showed progression of myocardial ischemia compared to baseline findings.

At follow up, neither mean LVEF, nor mean end-diastolic volumes were statistically different from baseline.

Figure 3
Individual [^{123}I]-MIBG wash out values of all 18 patients.

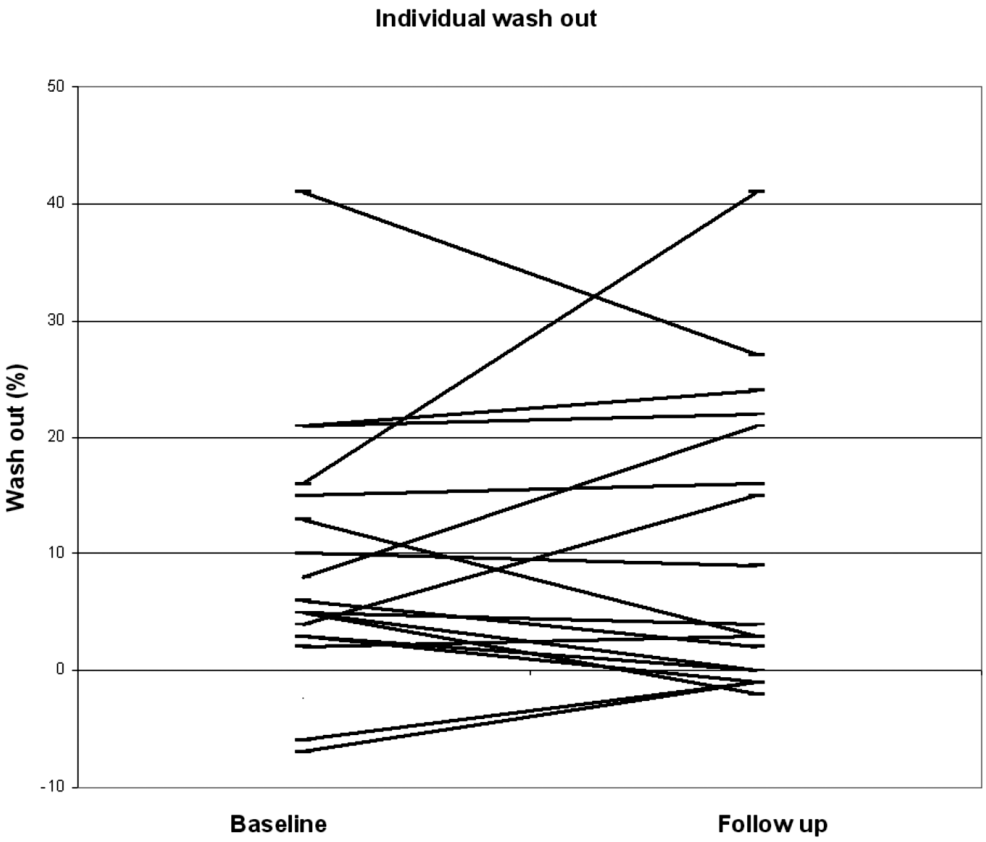


Table 3
Gated myocardial perfusion SPECT results

	Frequency or mean ± SD	
	Baseline (N=17)	Follow up (N=18)
End-diastolic volume (mL)	137 ± 41.2	122 ± 51.6
Left ventricular ejection fraction (%)	56 ± 7.0	58 ± 7.0
Ischemia (n)	6	4
Infarction (n)	0	2

Relationship between myocardial perfusion and sympathetic innervation

The baseline characteristics and scan results of the five patients who had cardiac denervation at follow up are presented in Table 4. Four patients already had signs of cardiac sympathetic innervation abnormalities at baseline. One patient with a positive [^{123}I]-MIBG scan at follow up developed new myocardial ischemia, one patient developed an infarction out of ischemia at baseline (Figure 4 and 5), and one patient showed an increase in ischemic area. Two patients with positive [^{123}I]-MIBG scans at follow up had normal myocardial perfusion scans at both baseline and follow up. Two other patients, who showed normalization of myocardial ischemia at baseline, had no signs of cardiac sympathetic innervation abnormalities at baseline or follow up.

Figure 4
Polar map reconstruction of the myocardial perfusion SPECT of a patient during follow up: A stress image, B rest image. The persisting perfusion defect in the antero-apical segments of the left ventricle wall indicates myocardial infarction.

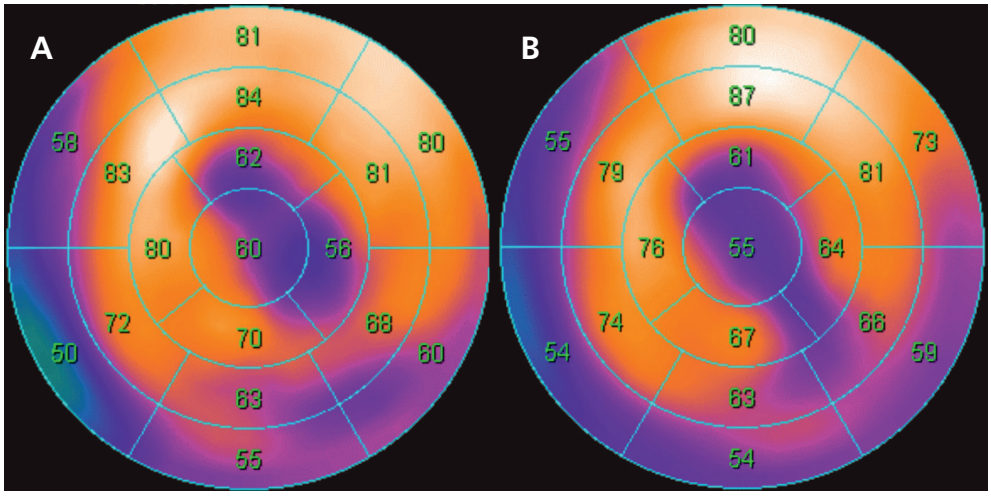
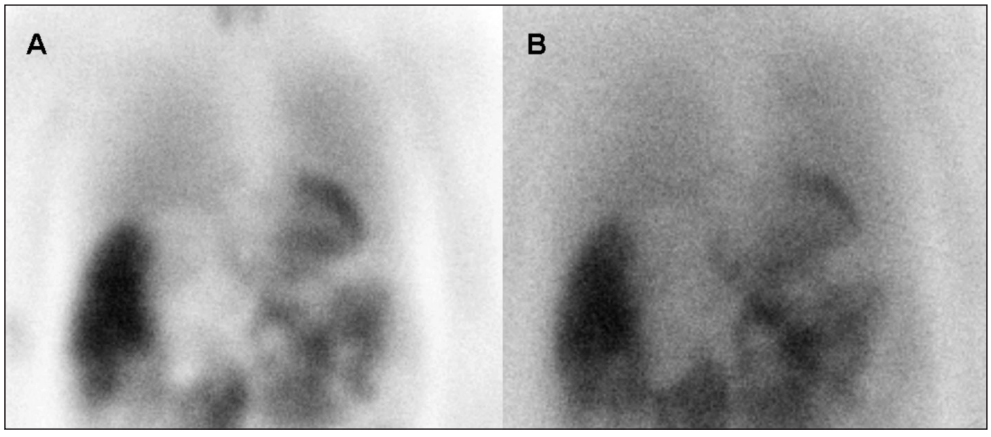


Table 4
Baseline characteristics and results of the patients with denervation at follow up

	Patient				
	1	8	14	16	17
Age (y)	53	82	82	50	82
Gender	Male	Female	Female	Female	Male
DM	No	Yes	No	No	No
Medication					
ACE-i	No	No	No	No	No
β-blocker	Yes	Yes	No	Yes	Yes
MPS Baseline					
Ischemia	No	Yes	Yes	No	No
Infarction	No	No	No	No	No
MPS follow up					
Ischemia	Yes	No	Yes	No	No
Infarction	No	Yes	No	No	No
[^{123}I]-MIBG Baseline					
Late HMR	1.20	1.06	1.43	2.63	2.51
Wash out (%)	21	8	41	16	21
[^{123}I]-MIBG Follow up					
Late HMR	1.80	1.34	1.58	1.80	1.42
Wash out (%)	24	21	27	41	22

DM = diabetes mellitus, ACE-i = angiotensin converting enzyme inhibitor, MPS = myocardial perfusion SPECT, HMR = heart-to-mediastinum ratio.

Figure 5
Planar images of [^{123}I-MIBG] scintigraphy of a patient during follow up. (**A**) Early image 15 minutes, and (**B**) late image 4h after tracer administration. The HMR of panel A was 3.03, of panel B 1.80, resulting in a wash out of 41%.



DISCUSSION

The present study provides the novel information that baseline cardiac sympathetic innervation in CKD stage G5 patients is already disrupted, according to the significant lower mean late HMR compared to mean early HMR. This was not the case in age and gender matched healthy control subjects. Late HMR and wash out at follow up were not statistically different from baseline; however innervation at follow up was significantly different from healthy controls.

These data may suggest that cardiac sympathetic denervation precedes myocardial perfusion defects, since three patients with signs of innervation abnormalities at baseline showed alteration in myocardial perfusion from baseline to follow up. This suggestion supports the fact that cardiomyocytes are more susceptible to sympathetic innervation abnormalities than to decreased blood flow. Furthermore, two patients in this study also developed sympathetic denervation without myocardial perfusion abnormalities, which may support the presence of microvascular coronary dysfunction.

The presence of cardiac sympathetic innervation abnormalities detected by [^{123}I]-MIBG scintigraphy in HD patients is not a novel concept. Earlier studies using [^{123}I]-MIBG scintigraphy in HD patients showed that [^{123}I]-MIBG wash out was significantly higher than in healthy control subjects (15,16). Both studies did not find a statistical difference in HMR between patients and healthy controls.

Cardiac [^{123}I]-MIBG wash out was reported higher in children with CKD on peritoneal dialysis and HD, compared to conservatively treated patients and those who underwent kidney transplantation (17). Furthermore, cardiac sympathetic innervation seems to improve, by means of lower wash out and higher HMR, early after kidney transplantation (15,18). So, the results of the present study that CKD patients treated with HD show lower HMR and higher wash out seems to be in line with earlier results.

The results of this study should be interpreted with caution, due to limited power. A power analysis was performed and resulted in a required number of 44 included patients. Due to very slow inclusion, the study was terminated before the necessary number of patients was included. Eventually, only 18 patients completed the study protocol. If the required number of patients would have been included, the results might have been more evident. However, the present study comprises the largest group of patients in which cardiac sympathetic innervation is evaluated during the initiation in maintenance HD.

Further, in this study the follow up interval was relatively short. A previous study showed that HMR is lower in those patients who are treated with HD for a prolonged period of time, up to 120 months (19). However, in that study [^{123}I]-MIBG scintigraphy was only performed at one single time point: the effect of transition from predialysis to HD on HMR was not studied. The present study provides

additional information that cardiac sympathetic denervation already occurs in CKD stage G5, before the transition from predialysis to HD.

Of the six patients with diabetes mellitus, only one developed cardiac sympathetic denervation during HD. This was one out of the two patients who also developed myocardial infarction out of pre-existing ischemia. For this patient, diabetes mellitus could be considered as a confounder, since microvascular dysfunction is known to contribute to lower HMR (20) was an elderly patient with long-lasting stable history of diabetes mellitus.

The use of ACE-i is known to have a cardioprotective effect in patients with CKD, by means of decreasing sympathetic hyperactivity (21). Also, HMR increases significantly in patients with chronic heart failure during treatment with ACE-I (22,23). In patients with CKD treated with HD, this improvement in HMR has not been evaluated with [^{123}I]-MIBG yet. Furthermore, according to the proposal for standardisation of [^{123}I]-MIBG scintigraphy, there is no evidence to withdraw ACE-I before performing the scan (13). So, up till now there is no supportive evidence that the patients using ACE-i in our present study may have false-negative [^{123}I]-MIBG scans.

Clinical implications and future perspectives

As stated before, the prevalence of CAD in HD patients is high (7). These patients are therefore at risk of developing ischemic heart failure and severe cardiac events. According to the 2012 United States Renal Data System annual report, arrhythmia and sudden cardiac arrest (SCA) accounted for 63% of the cardiovascular and 27% of all-cause mortality in dialysis patient (24). In a recent study of 75 HD patients with an implantable cardioverter defibrillator (ICD), nearly 80% of all SCA were caused by ventricular tachycardia and ventricular fibrillation (25). The authors reported an improved survival after SCA than previously assumed. The results of [^{123}I]-MIBG scans are known to have predictive implications for successful ICD therapy in patients with heart failure (26). Therefore, [^{123}I]-MIBG scintigraphy has the potential to play a guiding role in clinical ICD decision making in HD patients. Until that time, prospective studies have to demonstrate the relationship of low HMR and high [^{123}I]-MIBG wash out on one hand, and the development of heart failure related arrhythmia on the other.

CONCLUSION

This study showed that cardiac sympathetic innervation in patients with CKD undergoing HD was already disrupted before the start of HD. In these patients, late HMR at follow up was lower and wash out was higher compared with healthy controls, indicating cardiac sympathetic denervation. Furthermore, the development of sympathetic denervation seems to precede that of myocardial perfusion abnormalities.

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