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Assessment of Cardiac Sympathetic Function with Iodine-123-MIBG Imaging in Obstructive Sleep Apnea Syndrome

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Iodine-123-MIBG imaging has been used to evaluate myocardial sympathetic function in various cardiac diseases. In patients with obstructive sleep apnea syndrome (OSAS), increased sympathetic activity has been widely recognized, as assessed by measuring the plasma concentration and urinary excretion of catecholamines and by measuring muscle sympathetic nerve activity. However, these measurements are not specific indices of cardiac sympathetic function. Therefore, this study was undertaken to assess cardiac sympathetic function in patients with OSAS using MIBG cardiac scintigraphy. **Methods:** This study consisted of 11 patients (10 men, 1 woman; mean age 43 ± 16 yr) with a diagnosis of OSAS established by polysomnography, and 8 age-matched normal control subjects (7 men, 1 woman; mean age 45 ± 18 yr). Early (15 min) and delayed (3 hr) planar images were taken after the injection of 111 MBq of [^{123}I]MIBG. The mean counts of the whole heart and the mediastinum were obtained to calculate heart-to-mediastinum count ratios from the early images (H/Me) and from the delayed images (H/Md) and the myocardial washout rate (WR). Eight patients were restudied after 1 mo of nasal continuous positive airway pressure treatment. **Results:** The H/Me and H/Md ratios were significantly lower in the patients than in the control subjects (H/Me, 2.49 ± 0.32 versus 2.84 ± 0.34, p = 0.0207; and H/Md, 2.33 ± 0.30 versus 3.02 ± 0.36, p = 0.0013). The WR was higher in the patients than in the control subjects (36.2 ± 9.0% versus 23.6 ± 4.9%, p = 0.0022). The H/Me and H/Md ratios in the patients were significantly correlated with the apnea-hypopnea index and the degree of hypoxemia during sleep. After treatment, H/Me and H/Md remained unchanged, but WR significantly recovered (from 34.9 ± 10.4% to 26.3 ± 7.7%, p = 0.0357). **Conclusion:** Cardiac sympathetic function and integrity are impaired in subjects with OSAS when compared with age-matched control subjects. MIBG cardiac imaging can be helpful in evaluating cardiac involvement and efficacy of therapy in OSAS.

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Obstructive sleep apnea syndrome (OSAS) is a condition characterized by repetitive cycles of upper airway occlusion, resulting in repeated inspiratory efforts against this occlusion. Reopening of the upper airway usually follows an arousal from sleep. The resumption of airflow is characterized by a brief period of hyperventilation with snoring, and a subsequent return to sleep. Several hemodynamic changes occur during this apnea/ventilation cycle (*1*). OSAS has been associated with long-term cardiovascular sequelae, including systemic and pulmonary hypertension, heart failure, arrhythmias, stroke and myocardial infarction (*2,3*). In addition, there appears to be an excess of cardiovascular mortality in untreated OSAS (*4–6*). The exact causes of this increased cardiovascular morbidity are unknown. However, in patients with OSAS, increased sympathetic activity has been reported during sleep with repetitive apnea and even while the patients were awake (*7–12*). Increased sympathetic activity has been thought to contribute significantly to the pathophysiology of myocardial infarction, arrhythmia, heart failure and sudden death (*13,14*). Taken together, this sympathetic activation may be one of the causative factors of the increased mortality and the frequent cardiovascular complications mentioned above. Sympathetic function in OSAS has been assessed by measuring plasma concentration (*7,8*) and urinary excretion (*9,10*) of catecholamines, and by measuring muscle sympathetic nerve activity (MSNA) (*11,12*). However, these parameters are not specific indices of cardiac sympathetic activity.

Metaiodobenzylguanidine (MIBG), an analog of guanetidine, shares many neuronal transport and storage mechanisms with norepinephrine (NE) (*15–17*). Noninvasive radionuclide imaging with [^{123}I]MIBG permits assessment of efferent adrenergic

TABLE 1
Characteristics of the Patients with Obstructive Sleep Apnea Syndrome

Patient no.	Sex	Age (yr)	BMI (kg/m^2)	Blood pressure (mmHg)		Results of polysomnography				
				Systolic	Diastolic	AHI (no./hr)	lowest Sao_2 (%)	mean Sao_2 (%)	%T <90 (%)	%T <85 (%)
1	M	16	41.5	131	89	116.4	61	87	58.5	47.0
2	M	56	25.9	123	89	45.9	76	92	6.5	2.8
3	M	60	37.3	121	84	148.3	49	85	85.4	56.6
4	M	28	26.9	145	87	60.9	75	94	17.5	5.5
5	M	50	28.3	109	73	73.7	49	86	52.8	38.8
6	M	67	28.8	113	64	82.5	82	94	12.3	0.4
7	M	32	35.2	124	83	71.0	55	93	21.0	7.7
8	M	52	26.7	111	78	58.7	31	87	55.8	32.1
9	M	28	29.4	114	77	85.8	74	90	35.1	13.3
10	F	38	35.5	101	61	106.1	66	89	46.5	17.2
11	M	43	28.7	138	82	88.1	29	85	55.0	40.2
Mean		43	31.3	121	79	85.2	59	89	40.6	23.8
s.d.		16	5.2	13	10	29.3	18	4	24.2	19.8

BMI = body mass index; AHI = apnea-hypopnea index; %T <90 and 85 = the percentage of time spent with an Sao_2 below 90 and 85% during sleep.

neuronal function and integrity in the heart. Recently, MIBG cardiac imaging has been performed in various cardiac diseases and in neuropathy (*18–25*).

We hypothesized that cardiac sympathetic function and integrity, which could be detected by MIBG imaging, might be impaired in patients with OSAS. Therefore, this study was undertaken to compare myocardial MIBG uptake and washout rate between patients with OSAS and age-matched normal control subjects.

MATERIALS AND METHODS

Patients

Eleven patients (10 men, 1 woman; mean age 43 ± 16 yr, range 16–67) with a diagnosis of OSAS established by polysomnography were studied. The characteristics of the patients are shown in Table 1. The body mass index (BMI) was calculated according to the formula in which body weight (kilograms) is divided by the square of the height (meters). All of the patients were obese, habitual snorers, and had excessive daytime sleepiness. None suffered from significant chronic pulmonary disease. The presence of primary cardiac diseases was excluded by history, electrocardiogram and echocardiography. In all of the patients, the left ventricular mass index was within normal range (mean 101 ± 14 g/m^2, range 82–124 g/m^2), which was estimated according to the method of Devereux and Reichek (*26–28*). Thus, the absence of left ventricular hypertrophy (LVH) was ascertained. Other exclusion criteria were daytime hypertension, antihypertensive medications, diabetes mellitus (DM), hyper- and hypothyroidism and diseases of the liver and central nervous system, because each of these diseases or conditions may affect MIBG cardiac imaging. Eight age-matched normal control subjects (7 men, 1 woman; mean age 45 ± 18 yr, range 16–66 yr) were also studied. The control subjects did not undergo polysomnography, but had no history of habitual snoring or excessive daytime sleepiness. None of the subjects took any medications that might have affected the cardiac uptake of MIBG, such as reserpine, tricyclic antidepressants or others. The study protocol was approved by the Institutional Ethical Committee, and all of the subjects gave written informed consent.

Polysomnography

Surface electrodes were applied using standard techniques to obtain an electroencephalogram, an electromyogram of the chin, an electrocardiogram and an electrooculogram. Sleep was defined according to the criteria of Rechtschaffen and Kales (*29*). Ventilation was monitored by inductive plethysmography. Airflow was monitored by use of thermistors placed at the nose and mouth, and arterial O_2 saturation (SaO_2) was monitored continuously with a pulse oximeter. A polygraph was run continuously at 10 mm/sec to simultaneously record all of the above physiological data throughout the course of polysomnography. All parameters were stored in a data recorder for subsequent analysis. Apnea was defined as complete cessation of airflow for 10 sec or more. Hypopnea was defined as a greater than 50% decrease in oronasal airflow lasting at least 10 sec.

Protocol for MIBG Scintigraphy

The patients with OSAS underwent the scintigraphic study 4–5 hr after awakening, during which period they were instructed to remain awake. Each subject received 30 mg of potassium iodine daily from the day before the study until the day after the study to block tracer uptake in the thyroid gland. The planar images were obtained at rest in an anterior view over a 3-min interval at 15 min (early image) and at 3 hr (delayed image) after the injection of 111 MBq of MIBG, using a gamma camera equipped with a low-energy, parallel-hole, general-purpose collimator.

The regions of interest in the whole heart were set manually on these planar images. The mean heart counts from the early image (He) and from the delayed image (Hd) were calculated. On the planar images, a region (10 × 10 mm^2) in the upper mediastinum was used to calculate the mean mediastinum counts (Me and Md). The heart-to-mediastinum count ratio (H/M) was calculated as an index of myocardial uptake of MIBG (*30*). The heart-to-mediastinum count ratios from the early image (H/Me) and from the delayed image (H/Md) were analyzed. The washout rate (WR) from the myocardium was determined over 3 hr without correction for the physical decay of ^{123}I label, according to the formula: WR (%) = [(He − Me) − (Hd − Md)] × 100/(He − Me).

SPECT was also performed about 3 hr after the tracer administration with data collections of 30–40 sec each, starting in the 45° right anterior oblique projection and finishing in the 45° left posterior oblique projection, after which a series of transaxial images was reconstructed using filtered backprojection.

Eight out of the 11 patients (excluding Patients 2, 7, and 10) were restudied after the application of successful nasal continuous positive airway pressure (nCPAP) for 1 mo. The mean pressure of

TABLE 2
Comparison of BMI and Sleep Parameters: At Baseline and After nCPAP Treatment

		Baseline	with nCPAP	p value
BMI	(kg/m^2)	31.0 (5.4)	30.4 (5.5)	NS
AHI	(no./hr)	89.3 (29.9)	5.4 (3.5)	.0117
Lowest Sao_2	(%)	56 (20)	86 (5)	.0117
Mean Sao_2	(%)	89 (4)	94 (2)	.0178
%T <90	(%)	46.6 (23.9)	11.6 (29.7)	.0117
%T <85	(%)	29.2 (20.5)	1.5 (3.2)	.0117

n = 8. Values represent means (s.d.). nCPAP = nasal continuous positive airway pressure; BMI = body mass index; AHI = apnea-hypopnea index; %T <90 and 85 = the percentage of time spent with an Sao_2 below 90 and 85% during sleep. p values were calculated with Wilcoxon signed-rank test.

nCPAP was 9 ± 2 cm H_2O. Self-reported compliance of nCPAP treatment was good in all of the patients.

Plasma Norepinephrine

The plasma NE (pNE) concentration was measured in the morning after the polysomnography while the patients were awake and at rest.

Statistical Analysis

The data were expressed as means ± s.d. The Mann-Whitney U test was used to compare the results between groups, Spearman rank correlation coefficients were calculated to analyze the correlation between variables and the Wilcoxon signed-rank test was used to compare the results in the subgroup of the patients between at baseline and after nCPAP treatment. A p value of <0.05 was considered to be significant.

RESULTS

All of the patients had severe OSAS, and the mean apnea-hypopnea index (AHI) was 85.2 ± 29.3 (no./hr) (Table 1). Mean BMI was significantly larger in the patients than in the control subjects (31.3 ± 5.2 versus 23.2 ± 2.5 kg/m^2, p = 0.0007).

The mean values of BMI and sleep parameters without and with nCPAP treatment in eight patients who were restudied after 1-mo nCPAP treatment are listed in Table 2. With nCPAP, sleep apnea was successfully treated, while the BMI remained unchanged.

TABLE 3
Results of MIBG Study and Plasma Norepinephrine

Patient no.	H/Me	H/Md	WR (%)	pNE (pg/ml)
1	1.72	1.85	29.2	310
2	2.88	2.44	41.8	190
3	2.32	1.96	53.1	10
4	2.54	2.67	28.6	230
5	2.50	2.13	48.0	180
6	2.64	2.81	26.4	70
7	2.88	2.44	39.1	330
8	2.60	2.60	25.0	390
9	2.27	2.33	31.9	410
10	2.41	2.26	38.2	190
11	2.62	2.19	36.7	770
Mean	2.49	2.33	36.2	280
s.d.	0.32	0.30	9.0	204

H/Me and H/Md = the heart-to-mediastinum count ratio from the early and the delayed image; WR = washout rate; pNE = plasma norepinephrine.

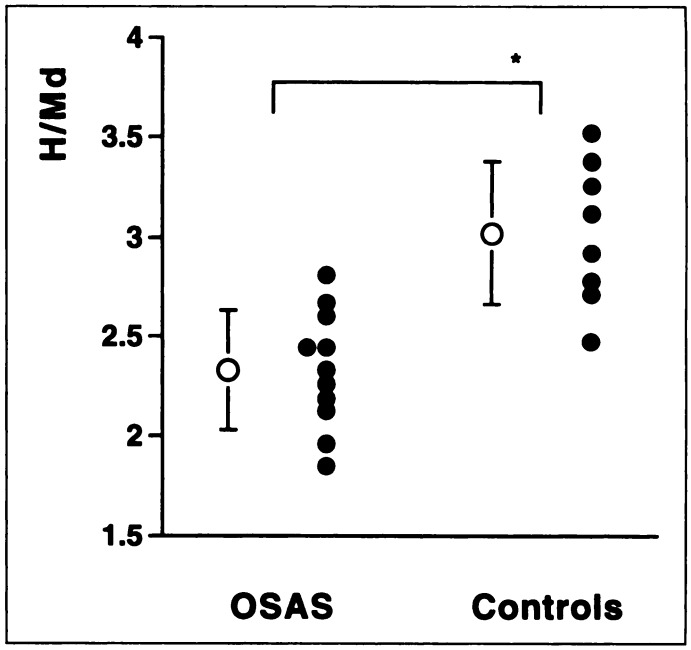

FIGURE 1. Comparison of H/Md between patients with OSAS and control subjects. H/Md is significantly lower in the patients than in the control subjects. *p = 0.0013.

MIBG Study

The results of MIBG in the patients are presented in Table 3. The H/Me was significantly smaller in the patients than in the control subjects (2.49 ± 0.32 versus 2.84 ± 0.34, p = 0.0207). The H/Md was also significantly smaller in the patients than in the control subjects (2.33 ± 0.30 versus 3.02 ± 0.36, p = 0.0013) (Fig. 1). The WR was significantly larger in the patients than in the control subjects (36.2% ± 9.0% versus 23.6% ± 4.9%, p = 0.0022) (Fig. 2).

Both the Md, as the measurement of the background activity, and the Hd were significantly lower in the patients than in the control subjects (Md, 28 ± 4 versus 32 ± 3 counts, p = 0.0436; Hd, 65 ± 15 versus 94 ± 8 counts, p = 0.0006) (Table 4). However, since the injected dose of MIBG was the same in each subject regardless of body size, we corrected the respective counts for body surface area (BSA). The BSA-corrected Md was not statistically different (54 ± 5 versus 53 ± 7 counts·m^2, ns), but the BSA-corrected Hd was yet lower in the patients than in the control subjects (127 ± 22 versus 157 ± 19 counts·m^2, p = 0.0118) (Table 4). Similarly, both the Me and the He were significantly lower in the patients than in the control subjects (Me, 39 ± 4 versus 46 ± 6 counts, p = 0.0202; He, 99 ± 19 versus 128 ± 14 counts, p = 0.0019). However, neither the BSA-corrected Me (Me·BSA) nor He (He·BSA) were statistically different (Me·BSA, 78 ± 5 versus 76 ± 13 counts·m^2, ns; He·BSA, 193 ± 25 versus 215 ± 32 counts·m^2, ns).

The H/Md of the patients correlated with some indices of the severity of OSAS. The percentage of time spent with an Sao_2 below 85% during sleep (%T < 85) showed the best correlation with H/Md (r = −0.87, p = 0.0062) (Fig. 3). H/Me was correlated with AHI (r = −0.69, p = 0.0296) and %T < 90 (r = −0.62, p = 0.0484). WR was not correlated with any indices of OSAS severity. The BMI correlated with AHI (r = 0.87, p = 0.0058) and tended to be correlated with H/Md and H/Me (both, r = −0.59, p = 0.0631), and was not correlated with WR. There were no significant relationships between age and MIBG results in either groups.

Only Patient 2 showed a complete defect at the inferior wall in the SPECT study, but his coronary angiogram was normal.

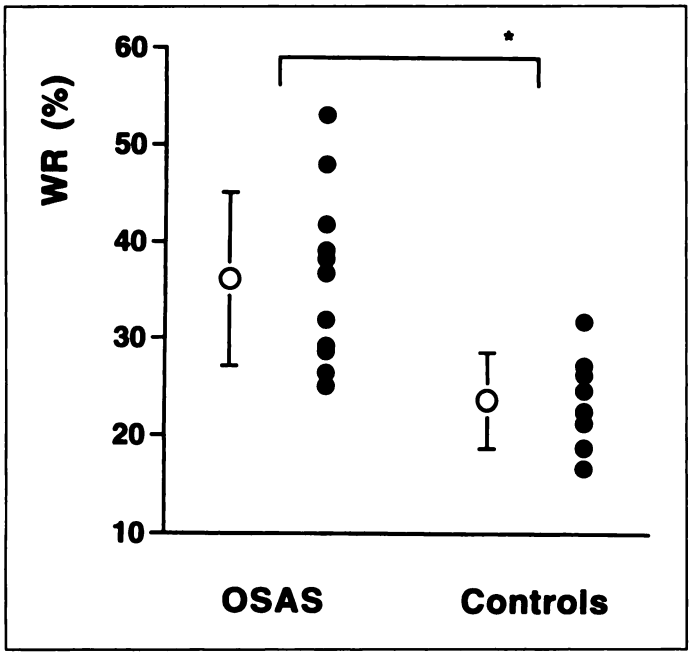

FIGURE 2. Comparison of the WR between the patients with OSAS and control subjects. The WR is significantly higher in the patients than in the control subjects. *p = 0.0022.

The remaining 10 patients did not show any significant regional defects in myocardial MIBG uptake.

MIBG Study After nCPAP Treatment

After 1-mo nCPAP treatment in eight patients, the decreased H/Me and H/Md remained unchanged (H/Me, 2.40 ± 0.31 at baseline versus 2.34 ± 0.31 after nCPAP, ns; H/Md, 2.32 ± 0.35 at baseline versus 2.42 ± 0.40 after nCPAP, ns), but the elevated WR was significantly decreased (34.9% ± 10.4% at baseline versus 26.3% ± 7.7% after nCPAP, p = 0.0357) (Fig. 4). After nCPAP treatment, the difference in the WR between the groups disappeared.

Plasma Norepinephrine

The mean pNE concentration in the patients was 280 ± 204 pg/ml (Table 3), and was not correlated with H/Me, H/Md, WR or severity of OSAS.

DISCUSSION

We have demonstrated that H/M, as an index of myocardial MIBG uptake, is lower and the WR, as an index of myocardial clearance of MIBG, is higher in patients with OSAS than in age-matched control patients.

In this study, we excluded patients with hypertension, DM and any other known diseases or conditions that have ever been reported to produce abnormal findings in MIBG cardiac imaging (*18–25*). Therefore, we concluded that cardiac sympathetic function and integrity were impaired in patients with OSAS, in the absence of other known causes.

Several mechanisms have been proposed to explain the decreased cardiac uptake and increased clearance from the myocardium of MIBG, mainly based on the evidence of the experimental studies. However, the definitive mechanisms responsible for these phenomena, for example in heart failure (*23,24*), remain to be elucidated. These phenomena may indicate a derangement or imbalance in cardiac sympathetic nerve supply to the myocardium and may be a common feature of the damaged myocardium due to various diseases (*25*).

In patients with OSAS, there is a possibility that hypoxemia itself, sympathetic activation due to repetitive hypoxemia and hypercapnia and/or microarousals, highly fluctuating heart rate and blood pressure and large negative intrathoracic pressure during obstructive respiratory efforts, may all place a load on the heart during sleep (*1*) and may also impair the function of efferent cardiac sympathetic nerves.

Hedner et al. (*31*) reported that patients with OSAS had a higher left ventricular mass than normal control subjects, as assessed by echocardiography, which was independent of hypertension and even obesity. Such chronic effects induced by hemodynamic changes during sleep might explain our findings. However, more recently, Noda et al. (*28*) reported that only hypertensive patients with OSAS had LVH, as assessed by echocardiography according to the same method that we have used. Consistent with the latter report, none of our patients had daytime hypertension or showed any LVH in echocardiography.

Richalet et al. (*32*) recently reported that [^{123}I]MIBG scintigraphy performed after exposure to high altitude hypoxia for 8 days revealed a decrease in H/M, although the scintigraphic study was initiated 2–5 hr after the return to complete normoxia. Our patients were also studied about 4–5 hr after awakening without hypoxemia. However, the H/Md showed good correlation with the indices of desaturation during sleep. Hypoxemia in our patients occurs only during sleep and is more chronic, although intermittent, than that in the subjects in the preceding report. Therefore, the decrease in the H/Md in our patients could be related to this nocturnal hypoxemia.

pNE in our patients was not generally elevated. No relation-

TABLE 4
Heart and Mediastinum Counts from Delayed Images

	Hd (counts)	Md (counts)	Hd·BSA (counts·m^2)	Md·BSA (counts·m^2)
Patients				
1	37	20	90	48
2	78	32	144	59
3	47	24	95	48
4	72	27	151	57
5	64	30	123	58
6	82	29	141	50
7	66	27	142	58
8	88	34	154	60
9	53	23	109	47
10	61	27	120	53
11	70	32	133	61
Mean	65*	28†	127‡	54
s.d.	15	4	22	5
Control subjects				
1	88	25	128	37
2	84	34	137	55
3	95	35	175	64
4	94	32	157	53
5	97	30	176	54
6	99	32	165	53
7	108	32	177	52
8	87	32	144	53
Mean	94	32	157	53
s.d.	8	3	19	7

*p = 0.0006.
†p = 0.0436.
‡p = 0.0118; compared with controls (Mann-Whitney U-test).
Hd = the mean heart count from the delayed image; Md = the mean mediastinum count from the delayed image; BSA = body surface area.

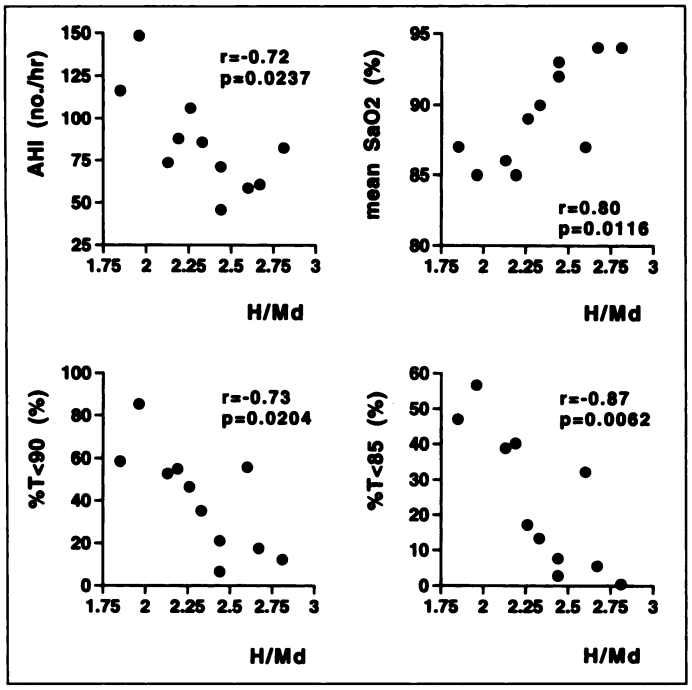

FIGURE 3. Correlation between H/Md and the indices of OSAS severity. %T < 85 (%) showed the best correlation with H/Md ($r = -0.87$, $p = 0.0062$). %T < 90 and 85 (%) = the percentage of time spent with an Sao_2 below 90 and 85% during sleep.

ships could be found between pNE and the severity of OSAS or the results of MIBG imaging. However, pNE is not a specific index of cardiac adrenergic activity. Therefore, cardiac sympathetic activation could not be precluded as a possible mechanism on the basis of this observation alone.

The major limitation of this study was the inability to match the BMI between the patients and the control subjects. BMI has been shown to be inversely correlated with plasma NE levels in humans and animals (*33*). Awake levels of MSNA in obese subjects without a history of OSAS have also been reported to be significantly lower than those seen in patients with OSAS (*34*). These reports indicate that obesity alone does not appear to be associated with increased sympathetic activity. However, we cannot completely preclude the effects of obesity on our findings, because the relation of obesity to cardiac sympathetic function has never been assessed with MIBG cardiac imaging.

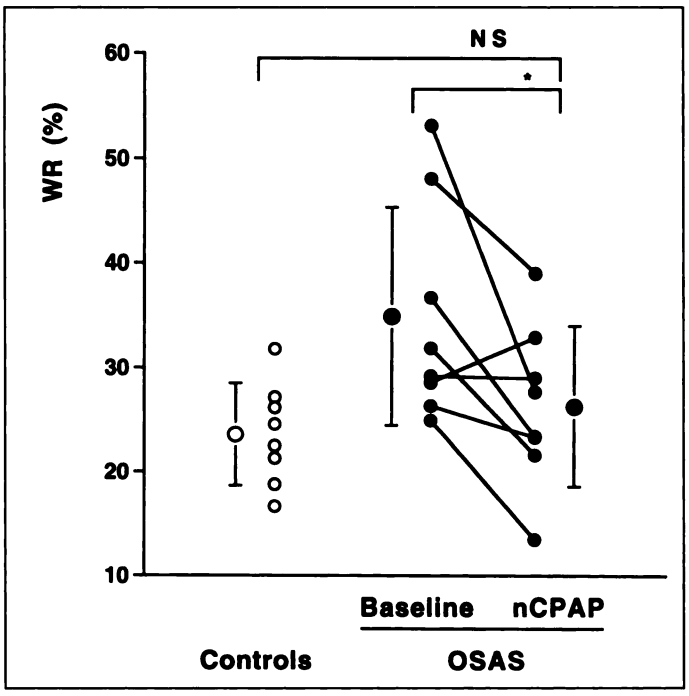

FIGURE 4. Effect of nCPAP treatment for 1 mo on WR in OSAS. WR significantly decreased after treatment (*p = 0.0357), and the difference between the groups disappeared.

In this study, we compared the mediastinum counts (Md), as the measurement of the background activity, and the myocardial counts (Hd), respectively, between the patients and the control subjects. The results revealed that not only the Hd but the Md were lower in the patients than in the control subjects. As the same dose of [^{123}I]MIBG was injected into each subject regardless of body size, the dilution effect due to obesity could be a possible explanation for the reduced Hd and Md in the patients. However, BSA-corrected Hd, not Md, was significantly lower in the patients than in the control subjects. These observations indicate that the dilution effect alone cannot explain the decreased myocardial MIBG uptake in our patients. Radiation attenuation due to obesity may also be a plausible explanation for the reduced Md in the patients. However, it is reasonable to consider that such attenuation effect has affected not only Md but also Hd, and could therefore be canceled out when Hd was divided by Md. Presently, there is no information available regarding the effect of the differences in the radiation attenuation on radioisotope levels in the heart and the mediastinum. Therefore, we cannot completely exclude the possible effects of radiation attenuation on our findings.

To rule out a potential role of obesity in the decreased myocardial uptake of MIBG, we should have selected control subjects matched for BMI. However, obesity is a significant contributing factor in OSAS, and it is very difficult to select obese normal subjects without OSAS. BMI has been reported to be one of physiological predictors of OSAS, and correlation between the BMI and the severity of OSAS (especially AHI) has also repeatedly reported (*35,36*). Such correlation was also found in our patients. The BMI tended to be correlated inversely with H/Me and H/Md in our patients, although this tendency may be secondarily produced by significant correlations between AHI and each of these variables.

Since we did not have control subjects matched for BMI, we restudied the subgroup of our subjects after 1-mo nCPAP treatment. After treatment, elevated WR was significantly reduced without any change in BMI. Therefore, the increased WR at baseline in our patients cannot be attributed to obesity. However, myocardial uptake (H/M) did not recover. Richalet et al. (*32*) demonstrated that H/M of normal subjects who had been exposed to high altitude hypoxia for 8 days recovered 2–3 mo after complete return to normoxia. Since our patients had been exposed to hypoxia during sleep for much longer periods than their subjects, one possible explanation for our results is insufficient duration of therapy for the recovery of myocardial MIBG uptake. The effects of longer term nCPAP treatment on myocardial uptake should be studied in the future.

Untreated patients with OSAS, especially with an apnea index > 20, have been associated with an increased death rate, which may be due to cardiovascular morbidity (*4–6*). Our patients were all severe cases with an AHI > 45, and were probably in this risk category. Our findings suggest that [^{123}I]MIBG cardiac scintigraphy can be used as an index of the level of myocardium stress in a patient with OSAS. Therefore, it may be important to evaluate cardiac sympathetic function in OSAS with [^{123}I]MIBG scintigraphy, because it is simple and noninvasive. However, the clinical relevance of a decreased H/M and an increased WR in patients with OSAS remains to be examined.

Recently, increased incidence of OSAS or sleep-related breathing disorders (SRBD) has been reported in patients with myocardial infarction (*37*), cardiomyopathy (*38*) and heart failure (*39*). Moreover, the occurrence of OSAS has been considered to be common in middle-aged persons (*40*). Our findings suggest that associated OSAS or SRBD may modify the results of MIBG scintigraphy in patients with these cardiac diseases and even in normal subjects. A larger series of clinical studies including milder and/or nonobese cases of OSAS, in addition to obese normal subjects, may be required to solve these problems.

Despite the limitations of this study, we believe this study raises new issues in the application of MIBG cardiac imaging.

CONCLUSION

We demonstrated that cardiac sympathetic function and integrity are impaired in patients with OSAS, as evidenced by a decreased H/M and an increased WR. H/M was closely correlated with severity of OSAS. MIBG cardiac imaging can be helpful to evaluate cardiac involvements and efficacy of therapy in OSAS. Moreover, as the occurrence of OSAS is common in middle-aged persons, and the association of OSAS with certain cardiac diseases is also common, severe OSAS should not be overlooked in the assessment of cardiac sympathetic function with MIBG scintigraphy.

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