Autonomic insufficiency as a factor contributing to dialysis-induced hypotension

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Abstract

Background. Autonomic insufficiency is considered a factor that contributes to dialysis-induced hypotension (DIH). However, the relationship between the two conditions has not been fully elucidated.

Methods. We investigated 44 haemodialysis patients using [123I]-meta-iodobenzylguanidine (MIBG) scintigraphy and power-spectral analysis (PSA) of heart rate variability. The patients were divided into four groups: a diabetic group with DIH, a diabetic group without DIH, a non-diabetic group with DIH, and a non-diabetic group without DIH. In these groups the heart to mediastinum average count rate (H/M), MIBG washout rate, and low- and high-frequency components of PSA were compared.

Results. From the [123I]-MIBG scintigraphy, for both early and delayed images, H/M of the groups with DIH were lower than in groups without DIH, in both diabetics and non-diabetics (P<0.05). For the early images, H/M of the diabetic groups were lower than in the non-diabetic groups, in the groups both with and without DIH (P<0.01). For the delayed images, H/M of the diabetic group was lower than in the non-diabetic group, in the groups with DIH (P<0.05). The MIBG washout rate was the highest in the diabetic group with DIH (P<0.05 vs diabetic and non-diabetic groups without DIH). The PSA of heart rate variability showed a good discrimination of the low-frequency component between the non-diabetic patients with and without DIH (P<0.05). Mean ultrafiltration volume and its rate were not different among the four groups.

Conclusion. Autonomic insufficiency is more severe in patients with DIH than in those without, and its degree may be enhanced in diabetic patients. For the management of DIH, special care should be addressed not only to dry weight but also to autonomic insufficiency.

Keywords: autonomic insufficiency; chronic renal failure; diabetic nephropathy; dialysis-induced hypotension; [123I]-MIBG myocardial scintigraphy; power spectral analysis

Introduction

Dialysis-induced hypotension (DIH), the most frequent complication of dialysis, occurs in 10–50% of dialysis treatments [1]. The pathogenesis and causes of DIH are complex [2]. Recent reports indicate that the critical factor is the decrease in blood volume induced by ultrafiltration [3]. However, we occasionally observe patients who show DIH during relatively low ultrafiltration volumes and slow ultrafiltration rates.

As an additional factor, previous reviews suggested that autonomic insufficiency contributed to DIH [4,5]. The relationship between autonomic insufficiency and DIH, however, is uncertain because traditional autonomic tests are non-steady-state measurements and cannot quantitatively evaluate autonomic function. Recently, new methods to provide more accurate evaluations of cardiovascular autonomic activity have become available. [123I]-meta-iodobenzylguanidine (MIBG) scintigraphy and power-spectral analysis (PSA) of heart-rate variability have been used to clarify autonomic insufficiency.

The [123I]-MIBG myocardial scintigram, a method for evaluating sympathetic neuropathy, is based on the property of sympathetic nerves to take up MIBG [6]. PSA of heart-rate variability offers the possibility of examining not only the function of parasympathetic and sympathetic pathways by two frequency bands regarded as specific markers, but also their effects on heart-rate cyclic variability [7,8]. Previous studies have reported reducing MIBG accumulation and specific heart rate spectral components in PSA from patients with chronic renal failure and diabetes [9–12]. Only a few studies have, however, applied these
methods to quantitatively evaluate autonomic function from the point of DIH.

This report describes differences in autonomic insufficiency between diabetic and non-diabetic patients with and without DIH.

**Subjects and methods**

**Patients and dialysis prescription**

We investigated 44 chronic uraemic patients, aged 33–79 years (mean ± SD, 59 ± 12 years) who had been undergoing 3- to 4-h sessions of dialysis three times a week for periods ranging from 3 months to 25 years. None had severe heart failure, severe hypertension, ischaemic heart disease, amyloidosis, or bronchopneumopathy. For at least 48 h before each test, they refrained from taking any medication that affects the autonomic nervous system. In seven patients, however, since withholding all their anti-hypertensive drugs might have risks, we temporarily exchanged short-acting α- and/or β-blockers with other drugs (angiotensin-converting enzyme inhibitors or Ca²⁺ antagonists). All patients who had been taking long-acting α- and/or β-blockers were excluded. Each test was performed at 9.00 a.m. or 3.00 p.m. on a dialysis-free day.

We divided the patients into two groups according to presence of diabetes (DM(+)) and non-diabetes (DM(-)). The DM(-) group consisted of chronic glomerulonephritis (13 cases), medullary cystic disease (2 cases), nephrosclerosis (2 cases), chronic pyelonephritis (1 case), polycystic kidney disease (1 case), Alport syndrome (1 case), and unknown (4 cases). Each group was further divided into sub-groups, consisting of dialysis-induced hypotension (DIH(+) and no dialysis-induced hypotension (DIH(-))). DIH was defined as the presence of one or two of the following conditions on more than 30 occasions among 50 previous sessions of dialysis: (i) a fall of systolic blood pressure (BP) to less than 90 mmHg during dialysis, and/or (ii) a fall of systolic BP of more than 25% from the start of dialysis. Some patients without a fall of BP to less than 90 mmHg had been taking anti-hypotensive medications. Therefore, the second condition was applied to uncover possible false-negative DIH(+) patients. BP was measured by trained nursing staff, on the same arm, intermittently at 30-min intervals, with a mercury sphygmomanometer while the patients were seated in multi-adjustable chairs. The start and end positions were semirecumbent. Korotkoff sounds phases I and V were used to define systolic and diastolic BP respectively. BP values were estimated from the mean values of two readings. When sudden symptomatic hypotension (nausea, vomiting, dizziness, muscle cramps) occurred, BP measurements were repeated with the patients in the reverse Trendelenburg position, and isotonic saline boluses were given as needed.

Clinical characteristics of the each group are shown in Table 1. Ejection fraction evaluated by echocardiogram were 71.5 ± 10.9, 73.3 ± 10.3, 70.6 ± 8.2 and 69.5 ± 4.6% in the diabetic group with DIH, the diabetic group without DIH, the non-diabetic group with DIH, and the non-diabetic group without DIH respectively (means ± SD, P = n.s.). There were no statistical differences between the diabetic groups with and without DIH in terms of duration of diabetes (DIH(+) vs DIH(-); 18.5 ± 9.9 vs 16.0 ± 10.4 years), percentages of insulin therapy (45.5 ± 40.0%), HbA1c (6.0 ± 1.1 vs 5.6 ± 0.6%) and diabetic complications (diabetic retinopathy: 9 ± 8 patients, arteriosclerosis obliterans: 2 vs 2 patients). All patients provided informed consent before participation.

Dry weight was established by chest X-ray or vena cava collapse index. The ultrafiltration was linear and the ultrafiltration rate was regulated to achieve the dry weight of each patient. The dialysers used were Cupra-ammonium rayon in

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<th>Table 1. Characteristics of the four groups of patients*</th>
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*Plus-minus values are means ± SD. Start, start of dialysis; End, end of dialysis. The anti-hypertensive medications consisted of angiotensin-converting enzyme inhibitor, Ca²⁺ antagonist, central α₂-adrenergic agonists, peripheral α₂-adrenergic antagonists, and α₁-receptor antagonists. The anti-hypotensive medications consisted of etilephrine hydrochloride, glycerol, and aminezine metilsulphate. Each blood pressure, ultrafiltration volume, ultrafiltration rate, and ultrafiltration ratio was the average of the previous 50 sessions of dialysis. P < 0.05 vs DM(+) vs DIH(-). P < 0.05 vs DM(+) vs DIH(+).
22 patients, polysulphone in 11 patients, polyacrylonitrile in three patients, and polymethylmethacrylate in eight patients. The dialyser areas ranged from 1.0 to 1.5 m². The blood flow rates ranged from 200 to 250 ml/min, the dialysate flow rate was 500 ml/min and the dialysate temperature was 37°C. The dialysate composition was 140 mEq/l Na⁺, 2 mEq/l K⁺, 30 mEq/l HCO₃⁻, 110 mEq/l Cl⁻, 3.0 mEq/l Ca²⁺, 1 mEq/l Mg²⁺, and 100 mg/dl glucose.

[¹²³I]-MIBG myocardial scintigram

After a 30-min resting period, 111 MBq of [¹²³I]-MIBG (Daichi Radioisotope Laboratories, Tokyo, Japan) was injected intravenously. Early and delayed images were obtained 15 min and 4 h respectively after injection.

Planar scintigraphic images of the chest were obtained by a single-head gamma camera (GCA-901A/HG, Toshiba Co., Ltd, Tokyo, Japan), equipped with a low-energy general-purpose parallel-hole collimator. Images were recorded in the anterior view at an acquisition time of 3 min with the matrix size of 256 × 256. SPECT acquisition was performed by rotating the camera by 6° increments, collecting 30 views for 30 s each, with an acquisition matrix 64 × 64. Photopeak energy was centred at 160 keV with a 20% window. Image reconstruction was performed using a Shepp and Logan filter. No attenuation correction was performed. In the planar image, the heart-to-mediastinum (H/M) activity ratio was computed to quantify cardiac MIBG uptake. The H/M ratio, considered an index of global cardiac MIBG uptake [13], was calculated by use of the region of interest (ROI) positioned around the heart and the mediastinal area.

The MIBG washout rate was defined as the percentage change in activity from the early to the delayed image. The washout rate of the entire myocardium was calculated by the bull’s-eye polar map technique. This method permits the synthesis of three-dimensional information obtained from the single-photon emission computed tomography into a two-dimensional image.

Power spectral analysis of heart rate variability

An electrocardiogram (ECG) was obtained in the supine position for at least 15 min. The ECG monitor was simultaneously recorded on analogue tape using a magnetic-tape recorder (RD-135T DAT data recorder, TEAC Co., Tokyo, Japan). The recorded signals were then fed into the analogue-to-digital channels of a minicomputer (LRR-03, Arm Electronics Co., Tokyo, Japan). The time series of data was analysed by the maximum entropy method at high resolution (MemCalc, Suwa Trust Co., Tokyo, Japan). The PSA of a sequence of 500 R-R intervals was estimated. Ectopic beats or artefacts, which may affect the estimation of the power-spectral densities of the heart-rate variability, were automatically deleted from the data. The spectrum of the PSA was separated into a low-frequency (LF) band in the range of 0.04–0.15 Hz, and a high-frequency (HF) band in the range of 0.15–0.40 Hz. LF and HF components are regarded as specific markers of respectively sympathetic and parasympathetic activities [12]. Their ratio (LF/HF) is considered to reflect sympathovagal balance [14].

Additional measurements of autonomic function

We also evaluated the coefficient of variation of R-R intervals (CVR-R) and the existence of orthostatic hypotension (OH). CVR-R was measured using software (MemCalc, Suwa Trust Co., Tokyo, Japan) in the same manner as PSA analysis. A diagnosis of OH was made when the systolic BP fell by 20 mmHg or more, or when the diastolic BP fell by at least 10 mmHg within 10 min of standing [15].

Statistical analysis

Comparisons of continuous variables between the two groups were performed by Student’s unpaired t-test or Mann-Whitney U test, where appropriate. The mean differences between the four groups were analysed by two-factor factorial ANOVA. When a significant overall effect was detected, Scheffe’s F test was used for comparison of the mean values for the two groups. Proportions were compared by Fisher’s exact test and chi-square test. A P value of less than 0.05 was considered to indicate significance.

Results

[¹²³I]-MIBG myocardial scintigram

The H/M in early images were 1.54 ± 0.12, 1.99 ± 0.24, 2.09 ± 0.10, and 2.67 ± 0.18 in the DM(+) + DIH(+), DM(+) + DIH(−), DM(−) + DIH(−), and DM(−) + DIH(−) groups respectively. The H/M in delayed images were 1.46 ± 0.10, 2.09 ± 0.22, 1.90 ± 0.13, and 2.52 ± 0.20 in the DM(+) + DIH(+), DM(+) + DIH(−), DM(−) + DIH(+), and DM(−) + DIH(−) groups respectively. In both early and delayed images, the H/M of the DIH(+) groups were statistically lower than both of the DIH(−) groups. The H/M of the DM(+) groups were also statistically lower than both of the DM(−) groups in the DIH(+) groups. Moreover, in early images, the H/M of the DM(+) group was also statistically lower than that of the DM(−) group in the DIH(−) groups (Figures 1A and 1B).

Washout rates were 39.65 ± 13.21, 17.7 ± 10.40, 21.53 ± 5.61, and 5.48 ± 6.02% in the DM(+) + DIH(+), DM(+) + DIH(−), DM(−) + DIH(+), and DM(−) + DIH(−) groups respectively. They were statistically higher in the DM(+) + DIH(+) group than in the DM(+) + DIH(−) and DM(−) + DIH(−) groups. The difference between the DM(+) + DIH(+) and the DM(−) + DIH(+) groups did not reach statistical significance (Figure 1C).

Power spectral analysis of heart rate variability

The LF mean power values were 27.87 ± 8.3, 65.6 ± 42.8, 85.11 ± 23.67, and 160.30 ± 27.5 in the DM(+) + DIH(+), DM(+) + DIH(−), DM(−) + DIH(+), and DM(−) + DIH(−) groups respectively. There was a statistically significant difference between the DIH(+) and the DIH(−) groups without diabetes, but no difference between the two groups with diabetes. In the DIH(−) groups there was a significant difference between the DM(+) and the DM(−) groups, but there was no difference between the DIH(+) groups (Figure 2A).
The HF mean power values were 31.15 ± 10.09, 44.28 ± 20.10, 58.84 ± 16.42, and 110.2 ± 44.20 in the DM(+) + DH(+) group, DM(+) + DH(−) group, DM(−) + DH(+) group, and DM(−) + DH(−) group respectively. The LF/HF ratios were 1.40 ± 0.27, 1.42 ± 0.88, 2.48 ± 0.90, and 4.24 ± 1.48 in the DM(+) + DH(+) group, DM(+) + DH(−) group, DM(−) + DH(+) group, and DM(−) + DH(−) group respectively. There were no statistically significant differences (Figures 2B and C).

Additional measurements of autonomic function

CVR-R were 1.19 ± 0.12, 1.60 ± 0.34, 1.97 ± 0.18, and 3.12 ± 0.42 in the DM(+) + DH(+) group, DM(+) + DH(−) group, DM(−) + DH(+) group, and DM(−) + DH(−) group respectively. Although there was a significant difference between the DM(−) + DH(+) group and the DM(−) + DH(−) group, no differences were observed between the DM(+) + DH(+) group and the DM(+) + DH(−) group or between the DM(+) + DH(+) group and the DM(+) + DH(−) group (Figure 3).

OH was observed in six, two, and in one patient of the DM(+) + DH(+) group, DM(+) + DH(−) group, and DM(+) + DH(+) group respectively. No OH was observed in the DM(−) + DH(−) group. Significant differences were observed between the DM(+) + DH(+) group and the DM(−) + DH(+) group (P < 0.05) and between the DM(+) + DH(+) group and the DM(−) + DH(−) group (P < 0.05).

Discussion

The falls in BP accompanying certain symptoms during dialysis occasionally cause complications that, if they are severe, necessitate interruption of dialysis. Therefore, to prevent this, anti-hypotensive
medications have generally been used. In this study, DIH was defined by two conditions, so that patients who barely preserve their BP during dialysis by using anti-hypotensive medications would not be overlooked.

According to our definition of DIH, the present study demonstrated that patients with DIH have more severe autonomic insufficiency than those without DIH. In addition, the degree of autonomic insufficiency may be enhanced in diabetes; however, our diabetic patients were older than the non-diabetic patients. In general, both excessive ultrafiltration and excessive ultrafiltration rate are important factors causing DIH [3]. In this study, however, ultrafiltration volume and its rate did not differ statistically among the four groups. Thus, the patients with more severe autonomic insufficiency may be more susceptible to DIH.

A direct relationship between DIH and autonomic insufficiency has not been fully elucidated. Moreover, in one report, autonomic insufficiency was unrelated to the presence of DIH [11]. This, however, may result from the different method of autonomic function tests. Although many studies have evaluated autonomic function, the methods applied were usually not steady-state measurements (Valsalva manoeuvre, handgrip procedure, and so on) based on disturbances of the autonomic system, and the results were dependent on many factors [5]. In contrast, [123I]-MIBG myocardial scintigram and PSA of heart rate, which are steady-state measurements, can be performed without severe burden on the patient and may be easily applied as follow-up methods, since the results are quantitative. Previous reports showed that both chronic renal failure and diabetes mellitus could induce abnormal MIBG results [9,10] and that the heart-rate spectral components were reduced in patients with ischaemic heart disease [16], diabetes mellitus [10,12], or chronic renal failure [9,11].

Both the results from [123I]-MIBG myocardial scintigrams and LF components of PSA indicated that sympathetic neuropathy in patients with DIH is more severe than in the patients without DIH. According to the analysis of Barnas et al. [17], the initial response to hypovolaemia caused by ultrafiltration is activation of the sympathetic nervous system. Therefore we assume that this activation is insufficient to preserve the BP in patients with DIH.

However, the LF component in our PSA study was not different between the diabetic groups as was observed in the [123I]-MIBG myocardial scintigram study. Murata et al. [10] pointed out that PSA measures the indirect response, whereas [123I]-MIBG myocardial scintigrams allow the direct assessment of the integrity of the adrenergic cardiac innervation. According to another report, the LF component is also influenced to some degree by parasympathetic nerve activity [8]. Thus the [123I]-MIBG myocardial scintigram may constitute a more reliable method of evaluating sympathetic neuropathy.

Although the differences were not statistically significant, the mean systolic BP of the DIH(+) groups at the start of dialysis tended to be higher than those of the DIH(−) groups. This was probably not hypervolaemia because of inadequate setting of dry weight. We believe that this phenomenon results from insufficient anti-hypertensive medication. We did not reduce the BP of DIH(+) groups before starting dialysis because this may have caused severe reductions in BP during dialysis. Because we evaluated DIH by the degree of BP reduction, the patients with relatively high BPs were not always placed in DIH(+) groups. On the other hand, mean systolic BP of the diabetic group with DIH at the end of dialysis was higher than that in the non-diabetic groups. This may have been due to greater usage of anti-hypotensive medication during dialysis. In addition the BP at the end of dialysis was variable and may have been affected by various interventions such as isotonic saline infusion or the reverse Trendelenburg position.

The influences of age and duration of dialysis are also difficult to evaluate. Vita et al. [18] reported that these factors did not affect autonomic function. And according to their recent report, PSA values did not vary with patient age or with duration of dialysis, except for the LF component in the standing position, which correlated with age [11]. We believe that further studies are necessary to settle this issue.

In summary, our study suggests that DIH may be related to autonomic insufficiency. We should therefore pay special attention not only to dry weight but also to autonomic insufficiency in the management of DIH.

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References

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