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Diabetic cardiac autonomic dysfunction: parasympathetic versus sympathetic

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Background: Diabetic cardiac autonomic dysfunction often causes lethal arrhythmia and sudden cardiac death. ^{123}I-Metaiodobenzylguanidine (MIBG) can evaluate cardiac sympathetic dysfunction, and analysis of heart rate variability (HRV) can reflect cardiac parasympathetic activity. We examined whether cardiac parasympathetic dysfunction assessed by HRV may correlate with sympathetic dysfunction assessed by MIBG in diabetic patients.

Methods and Results: In 24-hour electrocardiography, we analyzed 4 HRV parameters: high-frequency power (HF), HF in the early morning (EMHF), rMSSD and pNN50. MIBG planar images and SPECT were obtained 15 minutes (early) and 150 minutes (late) after injection and the heart washout rate was calculated. The defect score in 9 left ventricular regions was scored on a 4 point scale (0 = normal ~ 3 = severe defect). In 20 selected diabetic patients without congestive heart failure, coronary artery disease and renal failure, parasympathetic HRV parameters had a negative correlation with the sum of defect scores (DS) in the late images ($R = -0.47 \sim -0.59$, $p < 0.05$) and some parameters had a negative correlation with the washout rate ($R = -0.50 \sim -0.55$, $p < 0.05$). In a total of 64 diabetic patients also, these parameters had a negative correlation with late DS ($R = -0.28 \sim -0.35$, $p < 0.05$) and early DS ($R = -0.27 \sim -0.32$, $p < 0.05$).

Conclusions: The progress of diabetic cardiac parasympathetic dysfunction may parallel the sympathetic one.

Key words: diabetic mellitus, autonomic nervous system, metaiodobenzylguanidine, heart rate variability

INTRODUCTION

PATIENTS with diabetes mellitus frequently have autonomic neuropathy, which often limits their lives by causing arrhythmia and sudden cardiac death.[1,2] The progression of diabetic cardiac autonomic dysfunction may be intervened by using intensive insulin therapy and some medication.[3] It is therefore important to detect cardiac autonomic nervous system dysfunction in diabetic patients as early as possible. Many investigators have assessed diabetic autonomic neuropathy by means of heart rate variability (HRV)[4] and myocardial scintigraphy with ^{123}I-metaiodobenzylguanidine (MIBG).[5]

Some investigators[6,7] have reported that myocardial MIBG uptake predicts autonomic dysfunction in diabetic patients and is related to sympathetic neural modification of HRV such as low-frequency power (LF). In addition, one[6] of them reported that MIBG scintigraphy is the most accurate quantitative measurement of diabetic autonomic dysfunction and that subjects with clinical autonomic dysfunction had the same values in HRV parasympathetic parameters as those without autonomic dysfunction. Because of this fact, they concluded that the parasympathetic component of HRV is less affected by diabetes than the sympathetic component, but LF reflects both sympathetic and parasympathetic influences, indicating that a decrease in LF does not necessarily imply a reduction in sympathetic activity.[8] Earlier studies[9,10] also demonstrated that defects in parasympathetic innervation were more

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Table 1 Patient characteristics

	Total population (n = 64)	Selected population (n = 20)
Male/Female	36/28	12/8
Age	60 ± 13 y.	53 ± 12 y.
Hypertension	37 (58%)	11 (55%)
CAD	32 (50%)	0
CHF	11 (17%)	0
CRF on Dialysis	10 (16%)	0
α blocker	6 (9%)	2 (10%)
β blocker	6 (9%)	2 (10%)
ARI	10 (16%)	4 (20%)
ACEI	9 (14%)	3 (15%)
Insulin	25 (39%)	10 (50%)

CAD, coronary artery disease; CHF, congestive heart failure; CRF, chronic renal failure; ARI, aldose reductase inhibitor; ACEI, angiotensin converting enzyme inhibitor.

Table 2 Correlation coefficients between MIBG and HRV parameters

Total Population	Washout Rate	Early DS	Late DS
ln(EMHF) (ln ms^2)	−0.04	−0.32*	−0.33*
ln(HF) (ln ms^2)	−0.07	−0.32*	−0.34*
ln(rMSSD) (ln ms)	−0.11	−0.31*	−0.35†
ln(pNN50) (ln %)	−0.02	−0.27*	−0.28*
Selected Population	**Washout Rate**	**Early DS**	**Late DS**
ln(EMHF) (ln ms^2)	−0.28	−0.36	−0.47*
ln(HF) (ln ms^2)	−0.42	−0.43	−0.59†
ln(rMSSD) (ln ms)	−0.55*	−0.40	−0.54*
ln(pNN50) (ln %)	−0.50*	−0.46*	−0.58*

*$p < 0.05$; $^\dagger p < 0.01$, EMHF, early morning high-frequency power (from 2 a.m. to 5 a.m.); HF, high-frequency power; rMSSD, root-mean square of difference of successive RRs; pNN50 = proportion of adjacent normal RRs more than 50 msec different; DS, sum of defect scores.

frequent and occurred relatively earlier in diabetes mellitus and that defects in sympathetic innervation were less frequent and occurred later. If diabetic autonomic parasympathetic dysfunction precedes or parallels a sympathetic one, it would be wise to examine HRV at first to evaluate diabetic autonomic dysfunction because HRV has some advantages over MIBG in costs and irradiation.

The purpose of our study was to examine how the parasympathetic component of HRV may relate to myocardial MIBG washout and distribution and whether cardiac parasympathetic dysfunction assessed by HRV may follow a sympathetic one assessed by MIBG in diabetic patients.

MATERIALS AND METHODS

Study population. Of 598 consecutive patients who underwent myocardial scintigraphy with MIBG as a routine clinical examination in our laboratory from January, 1993 to July, 1997, 65 had diabetes mellitus and underwent a 24-hour ambulatory electrocardiographic recording. Since one of the 65 patients was excluded because of frequent extrasystoles (> 5% of all beats), the study population comprised the remaining 64 patients (age 60 ± 13 years, 28 females and 36 males). The median between HRV and MIBG studies was 18 days. None of the patients had tricyclic-antidepressants. Other characteristics including medications are summarized in Table 1. We further studied a subgroup of 20 patients (age 53 ± 12 years, 8 females and 12 males) in whom complications such as coronary artery disease, heart failure and renal failure on dialysis were excluded. Coronary artery disease was defined by history, stress perfusion scintigraphy and/or coronary angiography. Heart failure and renal failure on dialysis were defined by history, medical records and laboratory examinations. The subgroup characteristics are also summarized in Table 1.

MIBG. Myocardial scintigraphy with MIBG was performed by a previously reported method.[11,12] Anterior images of 180 seconds acquisition were obtained over the whole thorax 15 and 150 min after 111 MBq MIBG injection. We measured mean counts per pixel in the heart (H) and upper mediastinum (M) in the early and late images. The washout rate (%) from the heart was calculated with the following formula: [(early H − early M) − (late H − late M)] × 100/(early H − early M).

Immediately after the early and late planar imaging, single-photon emission computed tomography (SPECT) was acquired by using a three-headed SPECT system (PRISM3000, Picker International, Inc., Ohio) equipped with low-energy, general purpose, parallel-hole collimators and interfaced with a computer (Odyssey, Picker International, Inc., Ohio). Twenty projections over 120° per head were acquired in a 64 × 64 matrix for 30 sec per projection. No attenuation or scatter correction was used. Transverse slices were reconstructed with a filtered backprojection algorithm after pre-processing of the projection images with a low pass filter. Vertical long-axis, short-axis and horizontal long-axis tomograms were reconstructed from the transverse slices. The MIBG defect score of was visually determined for each of a total of 9 myocardial segments (basal anterior, basal septal, basal inferior, basal lateral, apical anterior, apical septal, apical inferior, apical lateral walls and apex) according to a 4-point scoring system: 0 = normal, 1 = mildly reduced, 2 = moderately reduced and 3 = greatly reduced. Early and late defect scores (DS) were defined as the sum of the defect scores for the 9 segments in the early and late images, respectively.

HRV. We performed 24-hour ambulatory electrocardiographic recording with Marquette 2-channel recorders (Marquette Electronics, Milwaukee, WI).[11] With a fast

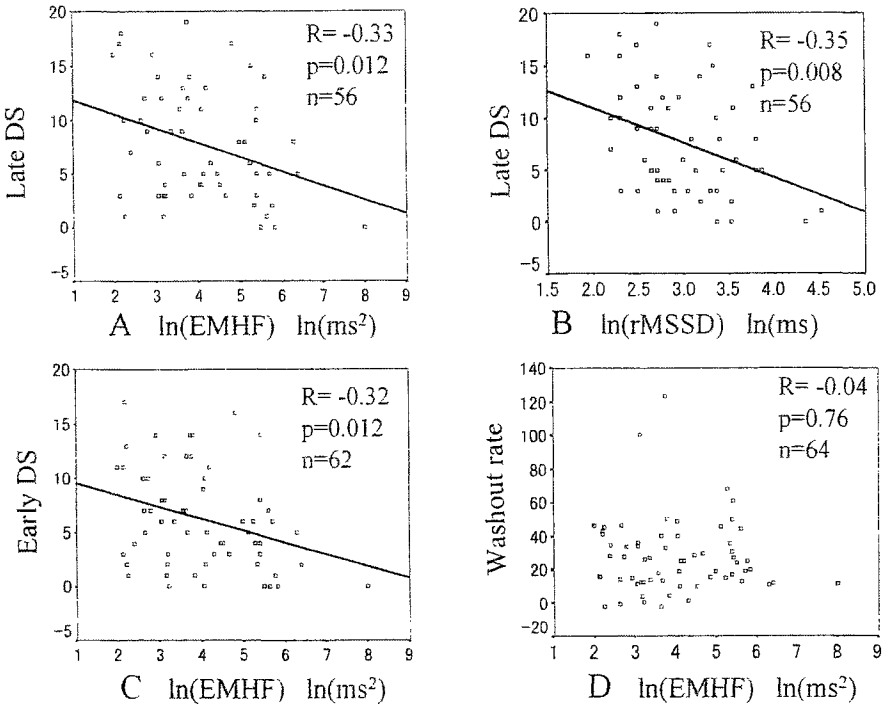

Fig. 1 In the total population the relation between sympathetic parameters of MIBG and parasympathetic parameters of HRV. A: the relation between late DS and EMHF in the total population. B: the relation between late DS and rMSSD in the total population. C: the relation between early DS and EMHF in the total population. D: the relation between washout rate and EMHF in the total population. EMHF, early morning high-frequency power (from 2 a.m. to 5 a.m.).

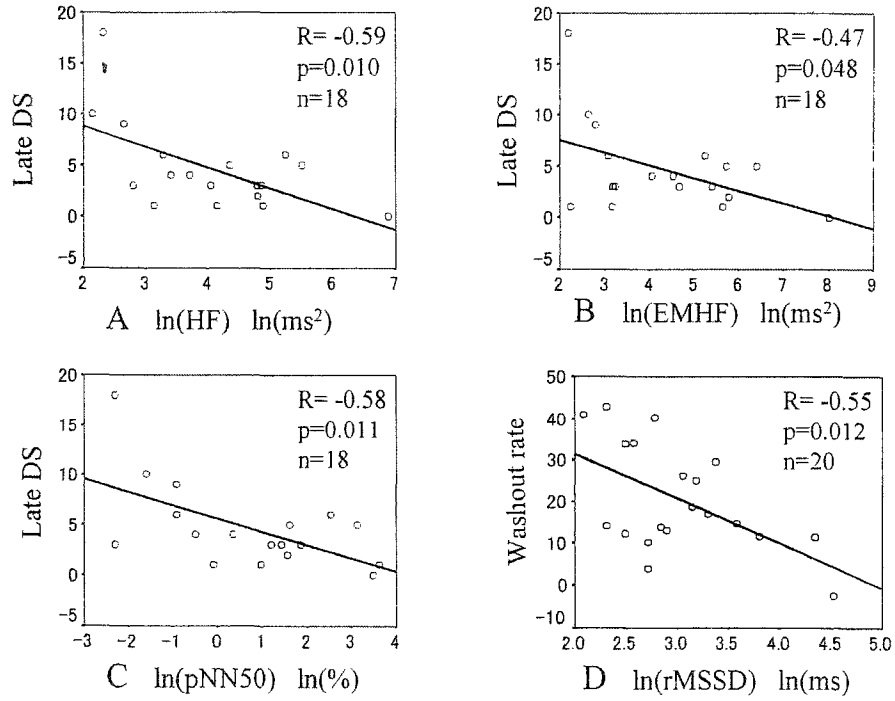

Fig. 2 In the selected population the relation between sympathetic parameters of MIBG and parasympathetic parameters of HRV. A: the relation between late DS and HF in the selected population. B: the relation between late DS and EMHF in the selected population. C: the relation between late DS and pNN50 in the selected population. D: the relation between washout rate and rMSSD in the selected population. EMHF, early morning high-frequency power (from 2 a.m. to 5 a.m.); HF, high-frequency power; pNN50, proportion of adjacent normal RRs more than 50 msec different; rMSSD, root-mean square of difference of successive RRs.

Table 3 Normal ranges reported previously, Freeman's data and our selected population

	Number of subjects	Age (y.o.)	ln(HF) (ln[ms^2])	rMSSD (ms)	pNN50 (%)
Chakko et al.[20]	11	54 ± 10	—	—	13.6 ± 8.9
Counihan et al.[21]	16	23 ± 11	—	45 ± 21	19 ± 16
Bigger et al.[22]	274	57 ± 8.2	5.05 ± 0.83	27 ± 12	9 ± 7
Our laboratory's normal data	20	50 ± 16	5.26 ± 0.70	34 ± 12	10.8 ± 9.2
Diabetic patients without autonomic dysfunction in Freeman et al.[6]	15	50 ± 14	4.31 ± 0.81	22 ± 6	4.0 ± 3.0
Our diabetic patients without complications	20	53 ± 12	3.92 ± 1.3	26 ± 22	6.8 ± 11

EMHF, early morning high-frequency power (from 2 a.m. to 5 a.m.); HF, high-frequency power. pNN50, proportion of adjacent normal RRs more than 50 msec different; rMSSD, root-mean square of difference of successive RRs.

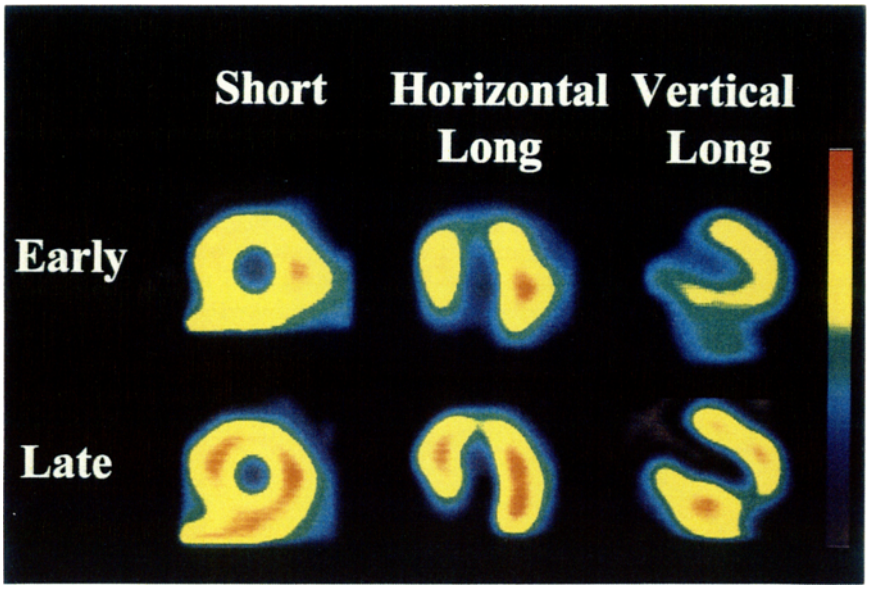

Fig. 3 A representative case with discrepancy between MIBG and HRV. The early and late MIBG images of a 66 year old male with diabetes mellitus for 13 years showed only a minimal defect in the apex and the washout rate was not increased (3.9%).

Fourier transform algorithm, we analyzed the time series of normal RR intervals for the entire 24 hours. High-frequency power (HF, ms^2) was computed for the 0.15–0.40 Hz band with a Marquette HRV program (version 002A). We calculated HF in the early morning (EMHF, ms^2), that is, from 2 a.m. to 5 a.m. to assess a parasympathetic component in the relatively stationary state. In addition, we calculated the square root of the mean of the squared differences between adjacent normal RR intervals (rMSSD, ms), and the proportion of adjacent normal RRs more than 50 ms different (pNN50, %). We considered HF, EMHF, rMSSD and pNN50 to be parasympathetic parameters.

Data analysis. All measures were expressed as the mean ± SD. Comparisons of continuous data in the two series were made by unpaired Student's t-test. Correlation between two variables was examined by linear regression analysis. Logarithm transformation was used before statistical analysis of some variables to make them normally distributed. Statistical significance was defined as $p < 0.05$.

RESULTS

The late defect score could not be evaluated because of greatly reduced myocardial MIBG uptake in 2 of 20 selected patients as well as in 8 of the total of 64 patients. In the total population, HF, EMHF, rMSSD and pNN50 had no significant correlation with the MIBG washout rate, but had a significant negative correlation with both the early and late DS (Table 2). Representative figures are shown in Figure 1. In the 20 patients selected, there was a significant negative correlation of the washout rate with rMSSD and pNN50, of late DS with HF, EMHF, rMSSD and pNN50, and of early DS with pNN50 (Table 2 and

Figure 2). As a result, HF and EMHF similarly correlated with MIBG parameters in both the selected population and the total population in this study.

A representative case with a discrepancy between MIBG and HRV is shown in Figure 3. The early and late MIBG images showed only a minimal defect in the apex and the washout rate was not increased (3.9%), although HRV was greatly decreased; for example, ln(HF) and rMSSD were 3.13 ln(ms^2) (normal range 5.26 ± 0.70) and 15 ms (normal range 34 ± 12), respectively.

DISCUSSION

This study demonstrated that HF, EMHF, rMSSD and pNN50 negatively correlated with MIBG late DS in diabetic patients and that rMSSD and pNN50 negatively correlated with the MIBG washout rate in diabetic patients without coronary artery disease, heart failure or renal failure on dialysis. In all the diabetic patients, HF, EMHF, rMSSD and pNN50 negatively correlated with MIBG early and late DS.

Both rMSSD and pNN50 have been accepted as parasympathetic measures, but 24-hour HF is inappropriate for the evaluation of cardiac parasympathetic activity since the physiological interpretation of the spectral components calculated over 24 hours is difficult.[8] Therefore EMHF (HF from 2 a.m. to 5 a.m.) is more suitable for assessing parasympathetic modification than 24-hour HF because of its stationariness.[8] In this study, however, the same tendency was obtained with HF and EMHF. On the other hand, MIBG scintigraphy may reflect cardiac sympathetic innervation.[13] Some investigators have reported that diabetic patients with autonomic dysfunction generally show low late myocardial uptake of MIBG with rapid washout, which is prominent in the inferior wall in the early stage and progresses to the adjacent areas of the ventricle.[14–16] An increased washout rate was assumed to be related to increased noradrenaline activity in the sympathetic nerves of diabetic patients with autonomic neuropathy.[15,17,18] In our study, the increased washout rate of MIBG correlated closely the impairment of parasympathetic nerves. Some investigators[14,15,19] showed that the ratio of heart to mediastinum (H/M) correlated with sympathetic impairment in diabetic patients. Although it is not shown in this paper, however H/M did not correlate with parasympathetic parameters of HRV in our study. The insignificant correlation may be due to the fact that sympathetic impairment begins with a local area which is indicated by a defect score and progresses to the whole heart, as indicated by H/M. Hattori et al.[15] reported that H/M showed less sensitivity than the indices of regional uptake in evaluating diabetic autonomic neuropathy by MIBG. Our observations therefore suggest that cardiac parasympathetic neuropathy assessed by HRV may parallel the sympathetic one assessed by MIBG in diabetes mellitus.

Some studies[6,7] reported that LF had a negative correlation with the late MIBG defect score. One[6] of them also reported that 24-hour HF, rMSSD and pNN50 were similar but MIBG defect size and LF in diabetic patients with and without clinically evident autonomic dysfunction were significantly different, and it suggested that parasympathetic nerves are less affected by diabetes than sympathetic ones. There are, however, some limitations to their suggestion. First, LF is a parameter that includes both sympathetic and parasympathetic influences, indicating that a decrease in LF does not necessarily imply a reduction in sympathetic activity.[8] Second, diabetic patients "without autonomic dysfunction" in the study[6] were likely to already have parasympathetic neuropathy, since their HF, rMSSD and pNN50 decreased compared to normal subjects (Table 3).[20–22]

The plots in Figure 2A, B, C, and D are fitted linearly, suggesting that sympathetic neuropathy may deteriorate at the same rate as parasympathetic neuropathy. Earlier studies[9,10] demonstrated that defects in parasympathetic innervation were more frequent and occurred relatively earlier in diabetes mellitus than defects in sympathetic innervation. In fact, the plots in Figure 2A, B and C may be fitted to a concave curve, and it is therefore possible that sympathetic neuropathy develops slowly in the early stage and accelerate in the late stage, whereas parasympathetic neuropathy may develop early and deteriorate gradually. Nevertheless, the number of plots in these figures is not enough to support this hypothesis because one or two data points would easily change an apparent concave curve into a linear relationship. Diabetic cardiac parasympathetic neuropathy may therefore not follow a sympathetic one, but may parallel or precede it. In other words, HRV analysis can detect cardiac autonomic neuropathy at least as early as MIBG scintigraphy, although these methods evaluate different aspects of autonomic neuropathy.

Comparing HRV and MIBG, HRV has some advantages over MIBG. First, the cost of HRV is cheaper than that of MIBG. In Japan the cost of ambulatory electrocardiographic recording is $115 (¥15,000), but that of MIBG scintigraphy is $507 (¥65,922). Second, HRV can be undergone without irradiation, but MIBG cannot. On the other hand, HRV has a disadvantage: it cannot be evaluated in the patients with frequent extra beats and atrial fibrillation.

Although we demonstrated a significant correlation between MIBG and HRV parameters, the correlation is not very close. We should bear in mind that HRV cannot replace MIBG and that these methods evaluate different aspects of autonomic neuropathy.

Study limitations

First, our study population was relatively small but a consistent tendency was obtained. Second, medications capable of interfering with the assessment of autonomic function were administered to some patients in this study,

but all medications were withheld on the day of the examination. Third, the prognostic studies are strictly necessary to elucidate whether cardiac parasympathetic dysfunction assessed by HRV may follow cardiac sympathetic dysfunction assessed by MIBG in diabetic patients; for that reason further studies are needed in the future.

Clinical implication

Our study demonstrated that HRV analysis can detect cardiac autonomic neuropathy at least, as early as MIBG scintigraphy, and HRV analysis also has some advantages over MIBG, such as costs and irradiation. In patients without frequent arrhythmia, therefore, the examination of HRV parasympathetic parameters can be the gatekeeper of an MIBG study.

Conclusion

In summary, a reduction in HRV may parallel or precede abnormalities in myocardial MIBG uptake in patients with diabetic mellitus.

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