学 位 論 文 の 要 旨

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学 位 論 文 名　　　Evaluation of Diabetic Neuropathy Using the Tone-Entropy
Analysis, a Non-Invasive Method to Estimate the Autonomic
Nervous Function.

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論 文 内 容 の 要 旨

INTRODUCTION

Diabetes mellitus (DM) is a serious health problem causing severe complications such as retinopathy, nephropathy as well as other macro- and microangiopathies. Among such complications, peripheral nerve disorders appears at the early stage of DM. Further, somatic nerve disorders, when advanced, lead to sensory paralysis and autonomic disturbance. To prevent such complications, it is important to diagnose the diabetic neuropathy at the early stage. Despite this, the diagnosis of the diabetic neuropathy is often difficult because the neuropathy progresses latently without distinct symptoms. In addition, as the measurement of the peripheral nerve conduction velocity (NCV), which is a standard method to evaluate the diabetic neuropathy, requires a skillful technique to obtain accurate data, it is not suitable for a screening examination. In this context, we explored the possibility to apply a non-invasive Tone-Entropy (TE) analysis of the autonomic function as a substitute for NCV. In this study, the TE analysis of electrocardiogram was performed on diabetic patients and compare the results with the NCV.

MATERIALS AND METHODS

Consecutive diabetic inpatients in Shimane University Hospital were invited to the study between September 2004 and November 2005. Patients with abnormal cardiac rhythms, atrial fibrillation or atrioventricular block were excluded. A hundred and two (46 males and 56 females) participants who

gave an informed consent were included in the study.   Of those, nineteen (9 males and 10 females) had either nephropathy or retinopathy as diabetic complications.   Total cholesterol (T-chol), high density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), and HbA1c were measured after 12 h of fasting. Electrocardiogram was obtained and analyzed for the tone and the entropy using a software developed previously.   TE data were obtained after at least 10-min rest at the spine position. Coefficient of Variation of R-R intervals (CVRR) was obtained with a software implemented in the electrocardiograph simultaneously when the TE data collection was performed.   Motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) were measured using an EMG/evoked potential measuring system.   MCV and SCV were measured as orthodromic and antidromic conduction, respectively, in the median nerve (Med-MCV, Med-SCV), the posterior tibial nerve (Tib-MCV), and the sural nerve (Sur-SCV).   The carotid-femoral pulse wave velocity (cfPWV) and the ankle-brachial pressure index (ABI) were measured using a mechanocardiograph.   The intima-media thickness (IMT) in the carotid artery was evaluated with a sonography equipped with a 7.5 MHz linear probe.   The maximal IMT (max IMT) was measured bilaterally in the common carotid arteries, the carotid bulbs, and the proximal internal carotid arteries.

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RESULTS AND DISCUSSION

When the subjects were divided into quartile classes according to each of the four NCVs, the tone and the entropy were significantly associated with Med-SCV, Tib-MCV and Sur-SCV (by ANOVA).   Even after the Bonferroni's correction (the significant level was $P=0.004$), the tone and the entropy showed significant association with Sur-SCV. On the other hand, neither the tone nor the entropy was significantly associated with Med-MCV though the tendency similar to other NCVs was observed.   The CVRR was not significantly different among the quartile classes of any NCVs.

As Sur-SCV showed the most potent association with the tone and the entropy, various parameters potentially affecting Sur-SCV were evaluated in a univariate analysis and a multivariate analysis.   In a univariate analysis, the male/female ratio (p=0.007) and BMI (p=0.04) differed significantly among the quartile classes of Sur-SCV in addition to the tone (p=0.001) and the entropy (p=0.0006, by the non-parametric Kruskal-Wallis test). The parameters for DM (FPG and HbA1c) or for athero- and arteriosclerosis (T-chol, HDL-C, ABI, cfPWV and max IMT) did not correlate significantly with Sur-SCV.

A multivariate evaluation of the parameters contributing to the quartile classification of Sur-SCV was done using the ordinary logistic regression analysis including sex, BMI and the entropy as independent variables. The entropy remained to be the factor associated most strongly with Sur-SCV even after adjustment with sex

and BMI (β=1.14$\pm$0.32, p=0.0004).   When the tone was substituted for the entropy, a similar result was obtained.   In addition, similar results were observed when Med-MCV, Med-SCV or Tib-MCV was substituted for Sur-SCV though the significant level was much lower

It is quite interesting that the entropy, a parameter for the balance between the sympathetic and parasympathetic nerves regulating the heart rate, showed a highly significant correlation with a NCV in a peripheral sensory nerve in the leg, i.e., the sural nerve.   As it is believed that diabetic neuropathy first involves both autonomic and sensory nerves, the cardiac autonomic nerves may be one of the earliest targets for diabetes along with the sural nerve.   In this study, the CVRR was not correlated with NCVs.   This was probably due to respiratory fluctuation of heart rate that was a nuisance not in the TE analysis but in the CVRR analysis, which suggested an advantage of the TE analysis.

CONCLUSION

The TE analysis of electrocardiogram is a sensitive method to evaluate the peripheral neuropathy.   As it is simple and non-invasive, repeated use of the TE analysis may aid the diabetic patients to impede the progress of the neuropathy.   Larger clinical studies to evaluate the potential usefulness of the TE analysis are warranted.