R-R Interval Variability Analysis With Electromyography Detects Early Autonomic Neuropathy In Diabetic Children

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ABSTRACT

Purpose: Autonomic neuropathy may exist together with peripheral neuropathy, especially in diabetic patients and it is important to diagnose early autonomic neuropathy especially cardiac one because of their serious effects on mortality and morbidity rates. A decrement of R-R interval variability (RRIV) is a good marker for cardiac autonomic neuropathy. We analyzed RRIV with an alternative method using electromyography machine, and assessed the RRIV in diabetic children who have no clinical sign of cardiac autonomic neuropathy.

Method: 64 healthy (mean age 9.5±1.8) and 33 type 1 diabetic (mean age 10.2±2.8) children who have no peripheral neuropathy were included. Recording was made on EMG machine and RRIV was obtained during quiet and deep breathing. Two surface electrodes were placed on the chest, and using triggering mode and delay line, two QRS complexes displayed on the screen. Since the first QRS complex was triggering potential, variation in timing of the second QRS complex represented variation in the R-R interval. RRIV was expressed as a percentage of the average R-R interval.

Results: In healthy children, RRIV was 23.9±9.5% in rest and 25.6±10.2% in hyperventilation. In diabetic children, RRIV was 17,4±6.6% in rest, 22±8.9% in hyperventilation. Resting RRIV was lower in diabetic children than healthy children (p=0.001), but there was no difference between groups in hyperventilation (p=0.4).

Discussion: Our findings suggest that RRIV may have value to determine cardiac autonomic neuropathy in diabetic children who have no clinical sign of cardiac autonomic neuropathy.

Conclusion: The technique, we used is a non time consuming procedure, easily performed in EMG laboratory, and is a simple way of reflecting autonomic dysfunction of the heart.

Keywords: R-R interval variability, diabetes mellitus, autonomic neuropathy, electromyography

ÖZET

Diyabetik Çocuklarda Erken Dönemdeki Otonomik Nöropati Tespitinde R-R İnterval Değişkenliğinin Elektromiyografi İle Analizi

Amaç: Diyabetik hastalarda otonomik nöropati periferik nöropatiye eşlik edebilmekte, mortalite ve morbidite üzerine olan önemli etkilerinden dolayı özellikle de kardiyak otonomik nöropatinin erken tanısı önem kazanmaktadır. R-R interval değişkenliğindeki (RRID) azalma kardiyak otonomik nöropatinin önemli bir göstergesidir. Çalışmamızda RRID elektromiyografi (EMG) cihazı ile değerlendirilmiş, kardiyak otonomik nöropati klinik bulguları olmayan diyabetik çocuklarda RRID incelenmiştir.

Yöntem: Çalışmaya periferik nöropatisi olmayan 64 sağlıklı (yaş ortalaması 9.5±1.8) ve 33 tip 1 diyabeti olan (yaş ortalaması 10.2±2.8) çocuk alındı. Kayıtlamalar EMG cihazı ile yapıldı ve RRID hem sakin hem de derin solunum sırasında değerlendirildi. Göğüs ön duvarına iki yüzeysel elektrod yerleştirildi, tetik modu ve gecikme hattı kullanılarak iki QRS kompleksi ekranda görüntülendi. İlk QRS kompleksi tetik potansiyel olarak alındı ve ikinci QRS kompleksindeki zamansal varyasyon RRID olarak tanımlandı ve değerler oran cinsinden belirlendi.

Bulgular: Sağlıklı çocuklarda RRID istirahatte %23.9±9.5, hiperventilasyonda %25.6±10.2, diyabetik çocuklarda RRID istirahatte %17.4±6.6, hiperventilasyonda %22±8.9 olarak bulundu. RRID isti-

rahat değerleri diyabetik çocuklarda anlamlı olarak düşük bulunurken (P=0.001), gruplar arasında hiperventilasyon sırasında fark saptanmadı (P=0.4).
Tartışma: Bulgularımız kardiyak otonomik nöropati klinik bulguları olmayan diyabetik çocuklarda RRID ile kardiyak tutulumun tespit edilebildiğini göstermiştir.
Sonuç: Kullandığımız teknik zaman almayan, EMG laboratuarlarında kolaylıkla uygulanabilen, kardiyak otonomik tutulumun varlığını ortaya koyan bir tekniktir.
Anahtar Kelimeler: R-R interval değişkenliği, diyabetes mellitus, otonom nöropati, elektromiyografi

INTRODUCTION

Autonomic neuropathy may exist together with a peripheral neuropathy in patients with diabetes mellitus (Watahiki et al. 1989). Symptomatic autonomic dysfunction indicates the presence of diabetic autonomic neuropathy, however, early symptoms are usually very mild and nonspecific (Ewing and Clarke 1987). Also onset of cardiac autonomic neuropathy is gradual, clinical manifestations being delayed for many years by compensatory mechanism (Chessa et al. 2002). Diabetic cardiac autonomic neuropathy is associated with increased morbidity and mortality, thus, it is important to early diagnose cardiac autonomic neuropathy of diabetics (Chessa et al. 2002, Ewing et al. 1976, Ewing et al. 1991). Measurement of R-R interval variability (RRIV) is a sensitive test for detection of cardiac autonomic neuropathy (Ewing 1983).

Abnormalities in RRIV in diabetics have been extensively studied in type II diabetes but, there is a limited data for diabetic children (Bellavere et al. 1992, Bernardi et al. 1992, Hilsted 1984, Hilsted and Jensen 1979, Malpas and Maling 1990, Pagani et al. 1988, Yamasaki et al. 1991, Lindqvist et al. 1986, Akinci et al. 1993, Rollins et al. 1992, Wawryk et al. 1997, Young et al. 1986). Also in these studies, cardiac autonomic function was assessed in diabetic patients with QT interval analysis or by performing spectral analysis of heart rate variation.

In our study, we analyzed RRIV with alternative method using electromyography machine, which is non-time consuming procedure and assessed the clinical utility of this method in diabetic children who have no clinical sign of cardiac autonomic involvement.

METHOD

Subjects

Sixty-four healthy children (39 girls, 25 boys) -mean age 9.5±1.8 years (range 4-14 years)- and 33 type 1 diabetic children who have no clinical sign of peripheral neuropathy and cardiac autonomic dysfunction (20 girls, 13 boys) -mean age 10.2±2.86 years (range 4-14 years)- were included in the study. No patients with nephropathy, retinopathy was included in the study. The cardiologic and neurological examination of the healthy and the diabetic children were normal. Type 1 diabetic patients were diagnosed according to American Diabetes Association criteria (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997).

Methods

The study protocol was in accordance with the Helsinki declaration of human rights, and was approved by the local ethics committee and the written informed consent from each patient was obtained. Peripheral nerve conduction studies of the patients and the control subjects were done before determination of RRIV. Right median, ulnar, tibial motor nerves, right median, ulnar, radial, sural sensory nerves were studied (Oh 1993). Recordings were performed on Medelec Synergy EMG machine. Latency, amplitude and nerve conduction velocity values of the motor and sensory nerves were compared with the childhood reference values (Jones et al. 1996).

Measurement of R-R İnterval Variability

RRIV was obtained during quiet and deep breathing. For measurement of RRIV, two surface electrodes were placed on the chest, a ground electrode was placed around one wrist and recording was made on Medelec Synergy EMG machine. Patients rested before the procedure. The first run was obtained during quiet breathing, the next run during deep breathing. Sweep velocity was 100-200 msec/div, sensitivity was 200-500 micV/div, frequency band was 10-100 Hz. Using the triggering mode and delay line, the oscilloscope display was adjusted by the trigger sensitivity and sweep speed so that two QRS complexes displayed on the screen. Since the first QRS complex was the triggering potential, the variation in timing of the second QRS complex represented the variation in the R-R interval. Twenty traces were recorded and superimposed. Five groups of 20 sweeps were recorded during quiet breathing, and two during forced deep breathing at 6 breaths/min. The RRIV was expressed as a percentage of the average R-R interval using the following formula: (R-Rmax – R-Rmin) x 100 / R-Rmean

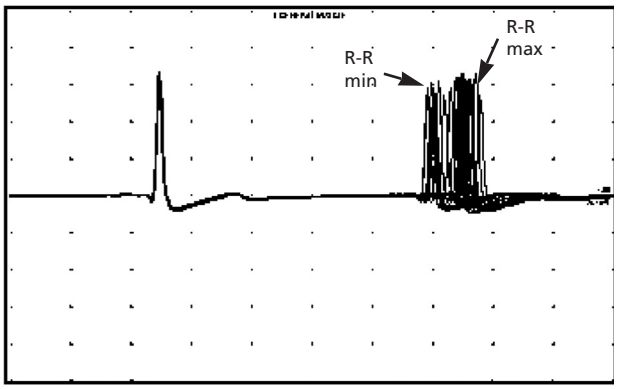

Figure 1: R-R interval variability in a healthy subject.

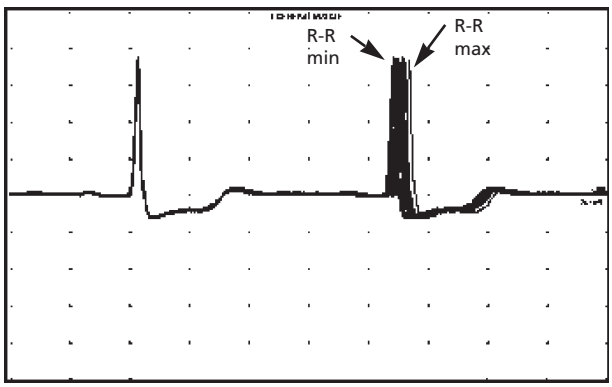

Figure 2: R-R interval variability in a diabetic child.

(the difference between the shortest and the longest R-R intervals during 1 minute given in percent of all maximal and minimal peaks) (Stalberg and Nogues 1989) (Fig. 1).

Statistical Analysis

The associations between means (age, RRIV, HbA1c etc.) were assessed using independent samples t test and proportions were assessed using chi-square test. All analyses were done using MINITAB Release 13.1 (license number: wcp 1331.00197). All values in the text and tables are given as mean±SD. The level of significance in all statistical analysis was set at $p<0.05$.

FINDINGS

There was no difference between the groups for age and gender (p=0,118, p=1). Clinical characteristics of the diabetic children were shown in Table 1.

Peripheral nerve conduction studies of the patients and the control subjects were done before determination of RRIV, and all of them demonstrated normal latency, amplitude and nerve conduction velocity values, when they were compared to childhood reference values.

Table 1: Clinical Characteristics Of The Diabetic Patients (N=33).

Subjects	Mean±SD
N (Male/Female)	13/20
Age (years)	10.2±2.8
Diabetes duration (years)	3.6±1.9
HbA1c (%)	8.7±2.1%
Total daily insulin dose (units/kg/day)	0.81±0.17

Table 2: RRIV In Healthy and Diabetic Children.

	Control (N=64)	Diabetics (N=33)	P
Age, years, mean+SD	9.5±1.8	10.2±2.8	0.1
Gender, N (Male/Female)	25/39	13/20	1
RRIV rest (%)	23.9±9.5%	17.4±6.6%	0.001
RRIV hpv (%)	25.6±10.2%	22±8.9%	0.4

The results of RRIV in control subjects and diabetic patients were compared in Table 2. The resting RRIV was lower in diabetic children than healthy children (p=0.001) (Fig. 2), but no statistically significant difference was founded between groups for RRIV in hyperventilation (p=0.4) (Table 2).

DISCUSSION

We measured RRIV in diabetic children with an alternative method that was demonstrated as an easy, reliable, and useful method for the assessment of cardiac autonomic function in patients with neuromuscular conditions (Nogues and Stalberg 1989). In this study, RRIV was significantly lower in diabetic children than healthy ones during resting but not during hyperventilation.

Peripheral neuropathy is a frequent complication appeared in diabetic patients (Dyck et al. 1993). Autonomic neuropathies frequently are together with peripheral neuropathy in diabetics but, sometimes they appear firstly (Watahiki et al. 1989). Clinical features can show autonomic neuropathy when the involvement is severe but electrophysiological tests have a important role for showing involvement if neuropathy is mild (Watahiki et al. 1989, Ewing and Clarke 1987). In various studies, electrophysiological autonomic

tests applied in diabetic patients were found to be sensitive to show neuropathy in the early period, also founded that cardiac autonomic neuropathy is correlated with disease duration and considered as a prognostic marker of microangiopathic complications (Ewing and Clarke 1987, Nogues and Stalberg 1989, Oka et al. 1995, Moridera et al. 1983, Valensi et al. 2003).

Type 1 diabetic patients has been evaluated for cardiac autonomic neuropathy in the several studies (Chessa et al. 2002, Akinci et al. 1993, Wawryk et al. 1997, Young et al. 1986, Lagi et al. 1994, Young et al. 1983). It has been founded that RRIV was significantly low in type 1 diabetic patients with and also without autonomic signs. In addition, it was demonstrated that cardiac autonomic neuropathy might appear without somatic neuropathy (Lagi et al. 1994). Makimattila et al. with a prospective study, investigated predictors of abnormal cardiovascular autonomic function in 83 type I diabetic patients. They evaluated heart rate variabiltiy two times of 10 years interval by frequency domain analysis and founded relationship between low heart rate variability and poor glysemic control, high BMI, female sex and late onset diabetes (Makimattila et al. 2000).

Cardiac autonomic neuropathy is associated with increased mortality in diabetic patients (Ewing et al. 1976, Ewing et al. 1991, Ewing et al. 1980, Ziegler 1994). Previous studies have shown that low heart rate variability is also predictive for sudden death (Maison-Blanche and Coumel 1997, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). It has been reported that cardiac autonomic function is often impaired early in the course of diabetes, even within the first 2 years following diagnosis (Valensi et al. 1997). Also we found that low RRIV in the diabetic children which have a median 3.5 years of duration of diabetes, some of these have 1 year duration. The chronic hyperglycemia causes nerve dysfunction and improved glysemic control reduces the development of neurological complication in type 1 diabetic patients (The Diabetes Control and Complications Trial Research Group 1994). Therefore, the analysis of RRIV in the patients with subclinical cardiac autonomic neuropathy may have a value in management and treatment of them (Chessa 2002).

In the previous studies, cardiac autonomic function was investigated with standard cardiovascular autonomic tests in diabetics, such as the response of the heart rate and blood pressure to maneuvers stimulating the autonomic nervous system, including deep breathing, Valsalva maneuver and standing. But the sensitivity of these tests in revealing an early impairment of cardiac autonomic function proved low (Hilsted 1984, Hilsted and Jensen 1979, Young et al. 1983, Ewing et al. 1985). RRIV analysis on 24-hour Holter recordings has been shown to be reliable and sensitive tool to assess the cardiac autonomic function (Chessa et al. 2002, Bellavere et al. 1992, Bernardi et al. 1992). Recently, Chessa et al investigated heart rate variability in diabetic children without clinical evidence of cardiac autonomic neuropathy. They performed 24-h heart rate variability analysis and obtained time-domain and frequency-domain variables from the entire 24-h analysis, and founded significant alterations of the heart rate variability in diabetic children. Also they founded autonomic impairment was significantly associated with disease duration, and poor metabolic control of diabetes (Chessa et al. 2002). In spite of its advantages, a 24-h holter recording is time consuming technique, requiring a long time analysis. In our study, we analyzed RRIV with alternative method using electromyography machine, which is non-time consuming procedure and we showed early cardiac autonomic neuropathy in diabetic children with this technique although age and disease duration of our cases were lower than the ones of Chessa et al were reported.

CONCLUSION

Consequently, in this study, RRIV was found as low in diabetic children in resting when compared healthy children. We confirmed that the analysis of RRIV is a sensitive test to show cardiac autonomic neuropathy in diabetic children in early period. Furthermore, the technique we used is a non-time consuming procedure, easily performed in the EMG laboratory, and is a simple way of reflecting the autonomic function of the heart.

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