Noninvasive Electrocardiographic Findings and Plasma Norepinephrine Levels in Patients with Post-Myocardial Infarction Receiving Anti-anginal Agents

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Objective: The aim of this study was to investigate the effects of anti-anginal agents on plasma norepinephrine (NE) levels and the autonomic nerve functions evaluated by advanced noninvasive electrocardiographic (ECG) tests in post-myocardial infarction (PMI) patients.

Methods: The subjects were 89 PMI patients who had suffered myocardial infarction (MI) at least 2 months before they participated in this study, and who had been taking anti-anginal agent mono-therapy (typical Japanese doses) for at least 6 months. Subjects were classified into the following 3 groups, based on type of anti-anginal agent: calcium antagonists (n=31, 60 ± 12 years), nitrates (n=29, 56 ± 11 years) and β-blockers (n=29, 63 ± 14 years). Left ventricular late potentials (LP), heart rate variability (HRV), T wave alternans (TWA), QT dispersion (QTd), and plasma NE levels of all subjects were assessed. There were no significant differences in age, gender, MI location or coronary risk factors between the 3 groups.

Results: There were no significant differences in the number of subjects who satisfied criteria for LP, TWA, and QTd between the 3 groups. Mean high frequency power of HRV of the calcium antagonist group was significantly ($p<0.05$) lower than those of the nitrate and β-blocker groups. All 3 groups had similar LF/HF, TWA microvoltage and QTd values, but mean plasma NE level of the calcium antagonist group was significantly ($p<0.01$) higher than those of the nitrate and β-blocker groups.

Conclusions: These results indicate that calcium antagonist therapy in PMI patients lowers parasympathetic tone and elevates plasma NE levels. However, in the present study, these values remained within normal ranges. *(Anadolu Kardiyol Derg, 2003; 3:43-7)*

Key Words: Myocardial infarction, anti-anginal therapy, norepinephrine, noninvasive electrocardiographic markers

Introduction

Calcium antagonists have been widely used in Japan to treat post-myocardial infarction (PMI) patients, especially those with hypertension and angina pectoris. However, recent studies of calcium antagonists in PMI including meta-analysis study indicate that the use of calcium antagonists (particularly those that are short-acting) for control of blood pressure and secondary prevention of cardiac events in PMI patients can have undesirable effects (1-4). Recently developed noninvasive electrocardiographic (ECG) tests such as signal averaging (SA) (5), repolarization analyses (6) , heart rate variability (7) and T wave alternans (8) have improved our ability to evaluate autonomic nerve function and arrhythmogenic states. Also, these tests can serve as powerful risk stratifiers of arrhythmogenic states, thus helping to prevent sudden cardiac death in coronary artery disease (9). In this study, we used new ECG technologies to study the mode of action of 3 classes of anti-anginal agents in PMI patients, in order to obtain data that may be of use in preventing adverse effects.

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Materials and Methods

From January 1996 to December 2000, 89 PMI patients were examined. All patients were in sinus

rhythm and none had bundle branch block. They have had routine coronary angiography and left ventriculography. None of these patients were receiving digitalis or diuretics during this time. All patients were brought to the laboratory in the morning, where the procedure was explained.

Fasting venous blood samples were taken for measurement of serum catecholamine levels and lipids. Electrocardiogram for heart rate variability (HRV) analysis was then recorded for at least 20 minutes using a Marquette Electric two-channel ECG system. A fast Fourier transformation algorithm was used to analyze tape recordings. Spectral power results were obtained from a 2-minute segment and measured on a 128-point total spectrum (TS) for 0.01- to 1.0-Hz frequency bands. Bandwidth area and power values of the low-frequency (LF) band (0.04 to 0.40 Hz) and high-frequency (HF) band (0.15 to 0.40 Hz) were then calculated using the Marquette software (version 5.8, 0.02A) (7).

Left ventricular (LV) SA-ECG (LV SA-ECG) was obtained using the Case system described by Simson (5), and was recorded according to the guidelines of the ESC/AHA/ACC Task Force (10). The ECG was recorded using standard bipolar orthogonal X, Y and Z leads. Signals derived from 256 QRS complexes were averaged, amplified, digitized and then filtered using a bi-directional high band pass Butterworth filter with a high pass cut off of 40 Hz. The LV SA-QRS vector magnitude was calculated as the square root of X2 + Y2 + Z2. Recordings with a noise level ≥ 0.6 mV were rejected. The mean noise level was 0.2 ± 0.1 mV. Bi-directional high pass filtering was repeated 3 times. Left ventricular SA-ECG results are presented for 40 Hz, which we have been previously found to have high-cut sensitivity for predicting arrhythmia (11). Left ventricular SA-ECG activity was determined to be abnormal if 2 of the following 3 criteria were satisfied: 1) filtered QRS complex >114 ms; 2) root mean square voltage of the terminal 40 ms of the QRS≤20 μV; 3) duration of low-amplitude (<40 μV) signals at the end of the filtered QRS > 38 ms (10).

The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as its return to the T-P bioelectric baseline, using a Marquette QT reading system. Because QT intervals were recorded using a Marquette QT guard system, they were obtained without bias and the value of >80 ms was regarded as positive (12).

T wave alternans (TWA) was assessed using the Cambridge Heart 2000 system (Hi-Res TM, Cambridge Heart Inc., Cambridge, Massachusetts, USA), using the spectral method for detecting TWA microvoltage (7). After skin preparation, 7 silver chloride electrodes were positioned for ECG recording using the Frank orthogonal configuration and 7 standard with 12-lead position for recording ECG. We measured TWA at rest and during controlled bicycle ergometer testing.

After 20 min of recording with an ambulatory Holter ECG for analysis of HRV using the Marquette 8000 T system, all patients performed exercise on a bicycle ergometer, maintaining a minimum heart rate (HR) of 105 bpm. The ergometer pedaling rate was maintained at two-thirds of HR using a metronome. A sequence of 256 consecutive beats, occurring during a period of exercise with HR ≥ 105 bpm and with the lowest noise level and number of premature beats, was chosen for analysis.

The magnitude of TWA was represented as power spectra by calculating the square of the magnitude of the fast Fourier transformation of beat-to-beat fluctuations in amplitude of the sequence of 256 beats. The alternans was measured at a frequency of 0.5 cycles per beat, and was expressed as alternans voltage and alternans ratio. The alternans rate reflects the number of standard deviations (SDs) by which the peak at 0.5 cycles per beat exceeds the mean noise level in an adjacent frequency band (0.44 to 0.49 cycles per beat). The level of electrical alternans was considered significant if either of the following 2 sets of criteria were satisfied: at rest, alternans (alt) voltage ≥ 1 μV and alternans ratio > 3.0; during exercise at HR ≥105 bpm, alt ≥ 1.9 mV and alternans ratio > 3.0. Patients with VM noise levels > 2 μV were categorized as being of an indeterminate rest or exercise state (7,13).

Blood samples were transferred immediately into ice, and were later centrifuged before being assayed in duplicate simultaneously. Plasma samples used for catecholamine assays were kept frozen at -70°C. Plasma norepinephrine (NE) levels were measured using the method of Peuler and Johnson (14), which involves enzymatic transfer of tritium from a methyl-donor to the plasma NE to be assayed.

Subjects were studied in the supine position in a quiet room, without discontinuation of anti-anginal

agents. First, subjects gave blood samples and underwent LV SA-ECG recording. Then, ECG recordings were taken for 20 minutes in the supine position, using an ambulatory Holter ECG. Next, using a standard 12-lead ECG apparatus and the Cambridge 2000 system, TWA microvoltage was recorded in the sitting position just before exercise on the bicycle ergometer, during exercise at a heart rate ≥ 105 bpm, and for 10 min after exercise. In Figure 1, 68 years old male with inferior infarction showed positive TWA , because eZ lead was 9.38 μV (normal range: ≤ 1.9 μV) during exercise at a heart rate ≥ 105 bpm. His 12 lead ECG was revealed to be inferior myocardial infarction because of Q wave in LII, L III and aVF with inverted T wave.

All parameters are expressed as mean ± standard deviation. Pairs of related samples with continuous variables were compared using the Wilcoxon signed rank test. The Mann-Whitney U-test was used to compare unrelated samples. Associations were assessed using least square linear regression analysis. Patients were divided into 3 groups according to the class of anti-anginal drug they were receiving: calcium channel blockers, nitrates and β-blockers. The Bonferroni method was used for comparison between these 3 groups. A p value < 0.05 was considered to indicate statistical significance. All data were analyzed using Stat View software 4.5 (Abacus Concepts Inc. Berkeley, Ca).

Results

Clinical Characteristics

The clinical characteristics of the subjects are shown in Table 1. As shown in Table 1, there were no significant differences in age, cardiac-thoracic ratio, blood pressure or serum lipid levels between the 3 groups. Also, there were no significant differences in the values of left ventricular ejection fraction between the 3 groups.

Table 1: Clinical characteristics

	Age	Sex	BP(mmHg)	CTR (%)	TC (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	LVEF(%)
Ca^{++} antagonist group	65±8	6/25	120±16/83±9	49±6	236±52	64±13	146±28	46±18
Nitrate group	63±10	6/23	123±14/78±8	51±6	214±47	57±23	155±21	52±10
β-blocker group	65±14	7/22	136±12/80±13	50±7	205±44	61±13	139±25	49±15

(mean ± SD), (BP= blood pressure, CTR = cardiac-thoracic ratio, TC = total cholesterol,
HDL = high density lipoprotein, LDL = low density lipoprotein, LVEF = left ventricular ejection fraction)

Table 2: ECG findings and plasma NE levels

	LP	TWA	QTd	HF (ms^2)	LF/HF	TWA (.V)	QTd (ms)	NE (pg/ml)
Ca++ antagonist group	7/31	7/31	3/31	3.4±2.5*	2.3±1.5	2.4±2.6	54±27	621±341**
Nitrate group	11/29	11/29	2/29	5.0±1.8	2.8±1.9	2.4±2.0	63±39	461±273
β-blocker group	14/29	10/29	1/29	5.3±3.1	2.0±2.0	2.4±2.0	78±42	450±273

(mean ± SD, * : p<0.01, ** : p<0.01), (LP = late potential, TWA = T wave alternans, QTd = QT dispersion,
HF = high frequency spectra, LF = low frequency spectra, NE = norepinephrine)

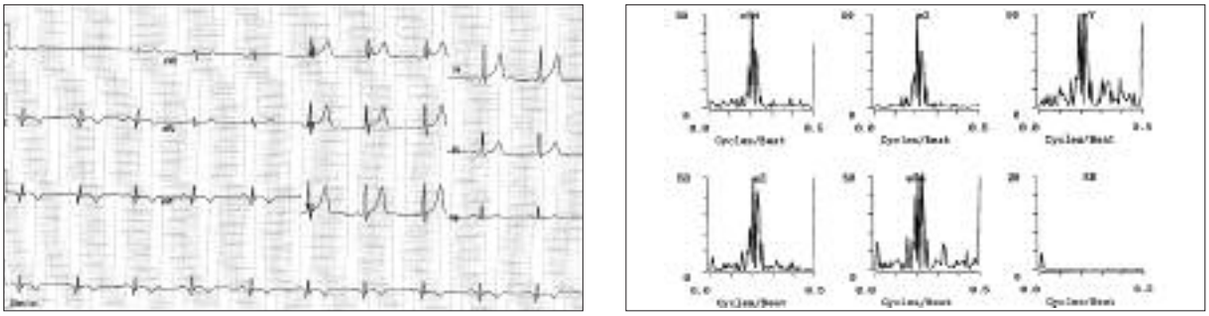

Figure 1: 68 years old male with old inferior myocardial infarction. His 12 leads ECG showed Q wave in leads II ,III and aVF with inverted T wave. His microvolt TWA was positive because microvoltage in eZ was 9.38 μV and the alternans ratio was 226.13 which satisfied both TWA microvoltage as well as alternans ratio.

Noninvasive ECG Findings

The ECG findings of the 3 groups are shown in Table 2. There were no significant differences in the number of subjects that satisfied the criteria for LV-SA-ECG, and TWA abnormality or QT dispersions between the 3 groups. However, the value of high frequency power of HRV in the calcium antagonist group (3.4 ± 2.5 ms^2) was significantly ($p < 0.05$) lower than those of the nitrates group (5.0 ± 1.8 ms^2) and β-blocker group (5.3 ± 3.1 ms^2), although all 3 values were within the normal range. There were no significant differences in LF/HF ratio between the 3 groups. Also, there were no significant differences in TWA among the 3 groups; all 3 groups had a TWA value of about 2.4 mV. The QTd value of the β-blocker group (78 ± 42 ms) was longer than those of the calcium antagonist group (54 ± 27ms) and nitrate group (63 ± 39 ms), but differences in QTd among the 3 groups were not statistically significant. The serum NE level of the calcium antagonist group was 621 ± 341 pg/ml, which was significantly higher than those of the other 2 groups (nitrate group, 461 ± 273 pg/ml; β-blocker group, 450 ± 273 pg/ml).

Discussion

The major findings of the present study are as follows. First, the calcium antagonist group had the lowest HF value. Second, the calcium antagonist group had a significantly higher plasma NE value than the other 2 groups. Third, all 3 groups had similar QTd and TWA values.

In 1984, Muller et al. (15) reported for the first time that nifedipine capsules did not reduce the size of MI and did not prevent MI in patients with threatened MI. They found that patients with threatened MI who received nifedipine capsules had a higher 2-week mortality (7.5%) than the placebo group (2.3%). Ishikawa et al. (16) reported that, in PMI patients, short-acting nifedipine and diltiazem were associated with a 24% higher cardiac event rate, but this adverse trend was not statistically significant, probably due to the small study populations. Results of meta-analysis studies suggest that short-acting calcium channel blockers are involved in rapid hemodynamic effects associated with rapid changes in peripheral vascular resistance, such as increased heart rate and decreased blood pressure following activation of sympathetic tone (1-4). In the present study, we demonstrated that HRV can serve as an index of autonomic activity. Although LF/HF may be useful as an indicator of sympathetic modulation or sympathovagal balance, the significance of LF in this context is not very clear. Compared to LF/HF, HF appears to more specifically reflect parasympathetic tone (7,17). Thus, our findings suggest that the higher NE values of the calcium antagonist group, compared to the other 2 groups, are primarily due to reduction of parasympathetic tone and modulation of sympathetic tone. It has been reported that the number of patients with vasospastic angina in Japan is greater than in Europe or North America (18). The Ministry of Health and Welfare in Japan has approved the use of calcium channel blockers in PMI patients with vasospasm and hypertension. The fact that we found no statistically significant differences in LV SA-ECG, TWA or QT dispersion values, as well as re-attack of MI nor arrhythmic episodes between the 3 groups in the present study suggests that calcium antagonists can be used for relief of transient hypertensive and vasospastic episodes in PMI patients. However, in PMI patients receiving routine, long-duration treatment with calcium channel blockers, calcium antagonists may accelerate sympathetic tone, resulting in adverse effects.

There were several limitations in the present study. First, each group contained a small number of patients. Second, we did not measure the serum concentration of medications. Third, the HRV values were obtained from short-duration recording. A recent study (19) has found that short-term (10 minutes) HRV R-R interval data is very similar to data obtained from 24-hour recordings, in both healthy subjects and old MI patients. Thus, short-term HRV recording could be used to predict approximate effects of autonomic nerve tone. However, HRV data obtained from longer recordings is probably more reliable for analysis of parasympathetic tone. The fourth limitation is that blood samples were drawn from a peripheral vein, rather than from the coronary sinus; the plasma NE levels we obtained may not accurately reflect cardiac sympathetic activity.

In spite of the above-mentioned limitations of this study, we can reasonably conclude that calcium antagonists produce lower parasympathetic tone than the other 2 classes of anti-anginal agents.

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