P wave duration changes and dispersion

A risk factor or autonomic dysfunction in stroke?

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ABSTRACT

الأهداف: لقياس الموجة P والتشتت في المرضى المصابين بالجلطات، ومقارنتها بالمرضى الأصحاء.

الطريقة: قمنا بقياس الفترة القصوى والدنيا للموجة P، والشتت على تخطيط القلب الكهربائي للسطح-12، لدى 67 مريضاً يعانون من أعراض عرضية مع أول جلطة افتقارية حادة، و58 يمثلون (مجموعة التحكم)، في جناح طب الأعصاب – كلية الطب – دوزك – تركيا، خلال الفترة مابين مايو 2005م وحتى أكتوبر 2006م. لم يتم شمول المرضى ممن لديهم تاريخ مرضي بالرجفان الشرياني، مشكلة قلبية، أو المستخدمين لعقاقير ذات صلة بأمراض الجهاز القلبي الوعائي أو مشاكل نفسية.

النتائج: كانت فترات موجة P والتشتت متشابهتين لدى المرضى المصابين بالجلطة ومجموعة التحكم. أظهر التحليل المتصل وجود علاقة إيجابية بين العمر وفترة موجة P الدنيا (p=0.03). كانت قيم الفترة الدنيا للموجة 63.85±22.55 في الذكور و 76.43±26.84 في الإناث على التوالي، وكان هذا الفرق ملحوظاً من الناحية الإحصائية (p=0.04). كانت العلاقة بين فترات موجة P وحضور عامل الخطر، نقاط نتائج الجلطة، ووفاة المرضى خلال ستة أشهر غير ملحوظة من الناحية الإحصائية.

خاتمة: على الرغم من وجود تقارير مسبقة حول تغيرات تخطيط القلب الكهربائي بما في ذلك موجات P في الجلطة الحادة، فقد وجدنا أن فترات موجة P والتشتت كانا متشابهين لدى المرضى المصابين بالجلطة الحادة ومجموعة التحكم. قد يكون لذلك صلة لدى فئة اختيار المرضى لهذه الدراسة. لم نشمل المرضى الذين لديهم شذوذية سابقة في القلب في هذه الدراسة. نختتم دراستنا بأن تعطل الجهاز العصبي المستقل يسبب شذوذية قلبية في الجلطة وتحتاج إلى المزيد من الفحوصات الطبية.

Objectives: To investigate the P wave duration and P wave dispersion in stroke patients, and to compare those with healthy subjects.

Methods: We measured maximum and minimum P wave durations, and dispersion on the 12-lead surface ECG in 67 consecutive patients with first ever-acute ischemic stroke and 58 controls at the neurology wards of the Medical School, Düzce, Turkey, between May 2005 and October 2006. The subjects were not included if there were a history of atrial fibrillation, cardiac problem, and using drugs related to cardiovascular diseases or psychiatric problems.

Results: P wave durations and dispersion were similar in stroke patients and controls. The correlation analysis revealed a positive relation between age and Pmin duration (p=0.03). The mean Pmin values were 63.85±22.55 for male and 76.43±26.84 for female patients, and this difference was statistically significant (p=0.04). The correlations between P wave durations, and the presence of risk factors, the stroke outcome scales, and death of patient within 6 months were not statistically significant.

Conclusions: Although there were some previous reports on ECG changes including P waves in acute stroke, we found that P wave durations and dispersion were similar in acute stroke patients and controls. This may be related to the patient selection criteria of this study, as we did not include patients with any previous cardiac abnormality. We concluded that the autonomic nervous system dysfunctions causing cardiac abnormalities in stroke need more investigation.

Neurosciences 2009; Vol. 14 (1): 14-18

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Received 31st May 2008. Accepted 16th September 2008.

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Electrocardiography (ECG) changes are common in patients with acute ischemic stroke. Frequency of new onset cardiac arrhythmias in both ischemic and hemorrhagic stroke patients without underlying cardiac disease is reported as 25-40%.[1] Although the coronary heart disease and ischemic stroke share the same risk factors and may coexist in the same patient, there is no evidence of ECG changes following acute stroke.[2-4] The effects of acute cerebral infarction on the heart are temporary, but associated with higher mortality.[2-5] Previous studies have shown that the frontal lobe, insular cortex, and amygdala play an important role in the regulation of the heart via the sympathetic and parasympathetic systems and cardiac involvement is more common in patients with cerebral lesions involving these areas.[6-8] Abnormalities in heart rate variability and autonomic regulation in this population suggest that a significant number of acute stroke patients show evidence of autonomic dysfunction.[9,10] Atrial fibrillation (AF) is one of the most common serious cardiac rhythm disturbances observed in routine clinical practice and it displays striking age dependent increase.[11] The principal causes of AF are hypertension, structural heart diseases, ionic disturbances, and autonomic dysfunction. The patients suffering from AF have longer intra-atrial and inter-atrial conduction times of sinus impulses.[12] P wave duration lengthening and P wave dispersion (PWD) calculated on a standard 12-lead surface ECG are simple ECG markers that could be used to identify the patients with idiopathic paroxysmal AF. Some recent reports revealed that the measurement of P wave duration and PWD in sinus rhythm might be a useful noninvasive clinical tool to identify patients at risk of developing atrial electrical instability and AF.[13-16] Patients with frequent episodes of paroxysmal AF are prone to develop permanent AF and thromboembolic complications that lead to a permanent functional impairment.[7,14] As AF and its hazards are difficult to control once established, a preventive approach to the problem is required. Previous studies have suggested that a variety of cardiac conditions such as stable coronary artery disease, myocardial ischemia, and acute coronary syndromes and valve diseases as well as autonomic disturbances could affect P wave dispersion.[11-13,17] Therefore, we particularly excluded the patients with concomitant disease. Our intention was to determine whether there is a relationship between PWD and stroke itself. Although some ECG abnormalities have been shown in the acute stroke period, P wave duration and dispersion has not previously been studied in acute stroke.[17] We hypothesized that cardiovascular autonomic impairment may affect P wave duration and PWD in patients with acute stroke. Therefore, this study was planned to investigate the P wave duration and PWD in stroke patients and to compare those with healthy subjects.

Methods. Sixty-seven consecutive patients with first ever-acute ischemic stroke admitted to the neurology wards of the Medical School, Düzce, between May 2005 and October 2006 were included in the study. Cranial CT and/or MRI established the diagnosis of cerebral infarction in all the patients. Patients with hemorrhagic strokes, and strokes related to trauma were not included in the study. Detailed history, systemic examination, stroke risk factors, and neurologic findings were recorded in all the patients. The patients were excluded from the study if there were a history of one of these, namely, atrial fibrillation, coronary artery disease, coronary by-pass operation, angina, myocardial infarction, acute coronary syndrome, severe mitral or aortic valvular disorder, subsequent ECG abnormalities (branch block, pathologic Q wave and left ventricular hypertrophy), using drugs related to cardiovascular diseases (beta blockers, nitrates, calcium channel blockers, digoxin) or psychiatric problems (neuroleptics), embolic infarction, subarachnoid bleeding, brain tumor, severe electrolyte problems, or thyroid problems. All patients that met the inclusion criteria were evaluated for cardiac disease by detailed history and clinical examination. The ECG carried out on the day of admission (first 24 hours of stroke) was considered for the analysis. Two experienced cardiologists who were unaware of the clinical details analyzed the findings. The study was approved, and the Local Ethical Committee of Düzce Medical School granted a waiver of consent. Fifty-eight gender and age matched healthy subjects admitted to a cardiology center for cardiology check-up served as a control group. They had no previous cardiac or cerebrovascular diseases. All patients were examined during the acute stage. The disability of patients was evaluated using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (RS). Brain CT or MRI revealing the characteristics of lesions were also evaluated. The patients were classified into 2 groups according to the presence of cortical involvement. As another classification, they were grouped as patients with anterior circulation problems, and patients with posterior circulation problems. In addition, the patients were classified according to the presence of aphasia and if present, aphasia type. The side differences (left or right hemiparesis) were taken into consideration and the relationship between the side of brain involvement and P wave durations was evaluated. Follow-up data regarding death was collected from the relatives of the patients either by personal interview in the clinic or by telephonic interview. Mortality rates within 30 days of the onset of stroke and also at 6 months were collected.

Table 1 - Clinical characteristics of stroke and control subjects.

Variable	Stroke patients (mean ± SD)	Control subjects (mean ± SD)	*P*-values
Male/Female	39 / 28	32 / 26	0.73
Age (years)	64.82±12.89	61.67±7.58	0.11
Heart rate (beats/minute)	79±11	78±10	0.86
Minimum P wave duration (ms)	69.11±25.0	70.86±10.48	0.61
Maximum P wave duration (ms)	114.78±31.35	114.05±11.22	0.86
P wave dispersion (ms)	45.67±20.54	43.19±12.27	0.42

At the end of the sixth month, we could not reach 8 patients. These patients were excluded from the analysis for mortality, and we analyzed the data of 59 patients. Twelve-lead ECG was recorded for each subject at a rate of 50 mm/s in the supine position (Hewlett Packard page writer 300pi, USA). Measurement of P wave duration was carried out manually using a caliper. To improve accuracy, measurements were performed with magnifying lenses for defining the ECG deflection. All measurements (PMI, Pmax and PWD) were performed in duplicate during the first 24 hours, and by 2 independent observers who were unaware of the order of ECG. The third observer verified agreement between observers. The onset of P wave was defined as the point of the first visible upward departure of the trace from the bottom of the baseline for positive waves, and as the point of first downward departure from the top of baseline for negative waves. The return to the baseline of the bottom of trace in positive waves, and of the top of the trace in negative waves were considered to be the end of the P wave. The difference between the maximum and minimum P wave duration was calculated from the 12-lead ECG. This difference was defined as the PWD.

Intra and inter-observer coefficients of variation (standard deviation [SD] of differences between 2 observations divided by the mean value and expressed in percent) were found as 4.1% and 4.2% for P wave dispersion. Intra and inter-observer coefficients of variation were found to be less than 5%. All data were presented as mean value ± SD. Comparison of clinical variables between 2 groups was performed with paired Student t test for numeric variables and chi-square test for categorical data. A p-value <0.05 was considered to be statistically significant. The SPSS version 11.0 package was used statistical analysis.

Results. The clinical characteristics of the 2 groups are shown in **Table 1**. There was no significant difference between the 2 groups with regard to gender, age, or heart rate. In stroke patients, the mean degree of disability of the patients was 8.19±5.60 according to the NIHSS and 3.18±1.59 according to RS. The number of the leads in which P wave duration could be measured was similar in both groups (range 8 to 12 leads). There was no significant difference in Pmin, Pmax, and PWD values between the patients and controls (**Table 2**). The correlation analysis revealed a positive

Table 2 - The factors affecting mortality during the follow-up period.

Variable	Patients alive (mean±SD)	Patients died during the first month (mean±SD)	Patients died during the first 6 months (mean±SD)	*P*-value
Male/Female	27 / 19	5 / 3	3 / 2	0.98
Age (years)	62.93 ± 13.19	73.63 ± 5.58	71.20 ± 11.15	0.03
Pmin (ms)	71.30 ± 24.46	70.00 ± 29.77	72.00 ± 33.47	0.98
Pmax (ms)	116.96 ± 27.96	120.00 ± 46.60	124.00 ± 45.61	0.88
PWD (ms)	45.65 ± 18.70	50.00 ± 29.76	52.00 ± 26.83	0.73
Aphasia				
No aphasia	37	4	2	0.002
Global aphasia	4	4	1	
Motor aphasia	5	0	1	
Sensorial aphasia	0	0	1	
Risk factors				
Single	30	3	1	0.01
Multiple	16	5	4	
Cortical involvement				
Present	20	6	2	0.21
Not present	26	2	3	

relation between age and Pmin duration (p=0.03). The average Pmin values were 63.85±22.55 ms for males and 76.43±26.84 ms for female patients (p=0.04). We found no statistically significant relation between Pmax and PWD values and gender. The correlations analysis showed no correlation between p wave durations and the other variables including gender, risk factors, the stroke outcome scales, and death rate. The correlation analysis also revealed no relation between the p wave values and the stroke characteristics, namely, anterior or posterior circulation involvement, side of infarction, cortical involvement, and aphasia. During the follow up period; 8 patients died within one month, and 5 patients within 6 months. The mortality positively correlated with age (p=0.010), the presence of aphasia (p=0.015), and the presence of multiple risk factors (p=0.012), **Table 2**).

Discussion. Cortical and lower brain level control mechanisms play a role in cardiovascular regulation.[18] The hypothalamus, insula, amygdala, cingulate gyrus, and brain stem are the important areas in the control of autonomic function.[19-23] Some ECG abnormalities showing electrophysiological dysfunction of the heart may be observed in neurological disorders. The most commonly recorded ECG changes in stroke are the P wave variations, ST changes, prolonged QT interval, T wave inversion, and pathologic Q waves.[24] Autonomic nervous system dysfunction characterized by altered sympathetic and parasympathetic output and increased catecholamine levels causes cardiac abnormalities.[25,26] Usually, subarachnoid hemorrhage patients with high concentrations of plasma catecholamine and hypokalemia may be more susceptible to life-threatening arrhythmia in comparison with other stroke types.[27] Previous studies reported a variety of ECG changes in stroke patients, however, to our knowledge no studies compared P wave duration and PWD in patients with stroke and controls. As the relation between AF and stroke is well known, we hypothesized that P wave duration and PWD, the marker of AF, could be increased in stroke. Therefore, we attempted to investigate the P wave duration and PWD changes in patients with acute stroke and to compare those with control subjects. We found that P wave durations and PWD were similar in stroke patients and controls. However, we found that there was a statistically significant relationship between Pmin duration, age, and gender. The Pmin was lower in male than female patients. These findings were in accordance with previous reports.[17,28]

In contrast, patients with hemispheric lesions have a higher incidence of cardiac arrhythmias when compared to patients with brain stem infarction.[29] Accordingly, it is well known that those with insular involvement, right-sided stroke, advanced age, coexisting hypertensive or coronary heart disease, and those expressing intense emotional stress are prone to development of cardiac arrhythmia and therefore these patients need monitoring in the intensive care unit.[17,23,29] However, in the present study we failed to show any tendency towards the development of AF during acute stroke.

In conclusion, despite the other ECG manifestations, acute stroke patients have no prolonged P wave duration and increased PWD compared to healthy controls. Thus, our findings suggest that P wave duration and PWD cannot be used as a marker to predict AF development during acute stroke or as a risk factor in stroke. Obviously, measurement errors performed during manual evaluation may be one limitation of the study. However, manual measurement of PWD has been well accepted and has been used in several studies mentioned above, and our inter and intra-observer measures yielded minimal variability. As another criticism, the endpoints that might be of greater interest would include atrial fibrillation and stroke rather than mortality. In the present study, to minimize the effect of confounding factors on ECG parameters we particularly excluded the patients with concomitant diseases and none of the study subjects were using medication affecting the atrial conduction. However, lack of the Holter recordings may be another potential limitation of the study. In this study, we aimed to investigate the potential relationship between p wave dispersion and stroke. However, whether the patients with acute stroke are prone to development of atrial conduction abnormalities should be established by further large scale studies.

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ETHICAL CONSENT

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed. Research papers not involving human or animal studies should also include a statement that approval/no objection for the study protocol was obtained from the institutional review board, or research ethics committee.