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Increased P wave dispersion in hypothyroidism: a sign of risk of atrial fibrillation

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Aim: As in hyperthyroidism, cardiac arrhythmias can be seen in hypothyroidism. In this study, we measured P wave dispersion among hypothyroid patients to evaluate atrial fibrillation risk.

Methods: 75 patients who received first time diagnosis of hypothyroidism and 40 normal control patients were included in this study. Each patient had echocardiographic and electrocardiographic studies were carried out. Groups were compared for statistically significant difference in P wave dispersion, minimum P wave duration and maximum P wave duration.

Results: The groups were similar in echocardiographic and electrocardiograpic features. P wave dispersion was significantly higher in the hypothyroid group compared to normal controls (31.9±9.3 ms vs. 26.5±9.4 ms, p= 0.003). Minimum P wave duration was significantly shorter in the hypothyroid group compared to controls (63.8±9.2 ms vs 68 ± 9.2ms, p= 0.026). Maximum P wave duration was not significantly different between groups (95.4±12.3 ms vs. 94.7±8.7 ms, p.0, 74).

Conclusion: P wave dispersion was increased in the first time diagnosed clinical hypothyroid patients. This is the first study to evaluate P wave dispersion in clinical hypothyroid patients. We believe that our findings have clinically important implications and provide insight into possible mechanisms of this morbid condition.

Key words: P wave dispersion, atrial fibrillation, and hypothyroidism

Hipotiridide artmış P dalga dispersionu: Atriyal fibrilasyon için bir risk göstergesi

Amaç: Hipertiroidide olduğu gibi hipotirodide de kardiyak ritim bozuklukları görülebilir. Bu çalışmada, hipotiridili hastalarda atriyal fibrilasyon riskini incelemek amacıyla P dalga dispersiyonunu hesapladık.

Yöntemler: Ocak 2008- Mayıs 2008 tarihleri arasında ilk kez hipotiroidi tanısı alan 75 hasta ve 40 kontrol hasta çalışmaya alındı. Her hastaya ekokardiyografi ve elektrokardiyografi incelemeleri yapıldı. Gruplarda istatistiki anlamdaP dalga dispersiyonu, Maksimum P Dalga süresi ve Minimum P Dalga süresi karşılaştırıldı.

Sonuçlar: Gruplar ekokardiyografi ve ekg bulguları benzerdi. P dalga dispersiyonu hipotiroidi grubunda kontrol grubuna göre anlamlı olarak daha yüksekti (31.9±9.3 ms; 26.5±9.4 ms, p= 0.003). Minimum P dalga süresi kontrol gurubuna göre hipotiroidi grubunda anlamlı olarak daha kısaydı (63.8±9.2 ms ; 68 ± 9.2, p= 0.026.). Maksimum P dalga süresi bakımından gruplar arasında anlamlı bir fark yoktu (95.4±12.3; 94.7±8.7, p.0, 74).

Sonuç: Yeni tanı konmuş klinik hipotiroidi hastalarında artmış P dalga dispersiyonu artmıştır. Bu çalışma klinik hipotiroidi hastalarında P dalga dispersiyonunu inceleyen ilk çalışmadır. Bizim bulgularımızın, bu önemli problemin olası mekanizmalarına anlamlı katkı sağlayacağına inanıyoruz.

Anahtar sözcükler: P dalga dispersiyonu, atriyal fibrilasyon, hipotiroidi

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Introduction

Hypothyroidism affects cardiac function by decreasing myocyte-specific gene expression in the heart (1). Decreased cardiac output, increased vascular resistance, diastolic hypertension, bradycardia and premature ventricular beats are well known cardiac effects of hypothyroidism (2, 5). Prevalence of atrial fibrillation of other cardiac arrhythmias is not well studied. Only a few studies on hyperthyroidism and arrhythmia association have reported data regarding prevalence of atrial fibrillation among hypothyroid patients. Interestingly, these studies reported higher prevalence of atrial fibrillation among hypothyroid patients compared to normal population (6, 7, and 8). Still, exact risk of atrial fibrillation or flutter associated with hypothyroidism is not known. Moreover, PWD has not been studied in hypothyroid patients.

This is the first study to compare PWD and P wave minimum and maximum durations in clinically hypothyroid patients and normal controls. We found significant increase in PWD and minimum P wave duration in hypothyroid patient group. As an independent risk factor for atrial fibrillation, increased PWD in clinical hypothyroidism have important clinical implications. First of all, atrial fibrillation, which has probably been studied more widely in hyperthyroidism as it usually takes considerably more time to achieve euthyroidism, has been underscored in hypothyroidism. Considering dare consequences associated with atrial fibrillation and easy treatability of hypothyroidism, our study indicates the importance of early recognition and treatment of hypothyroidism to avoid atrial rhythm disturbances.

Methods

Patients presented to Dışkapı Research and Education and Düzce University Research and Education Hospital cardiology and internal medicine outpatient clinics from Jan 2008 to May 2008 were included in the study. Electrocardiography, echocardiography evaluation and serum free T_4 (FT_4), free T_3 (FT_3) were measured in all patients. 75 patients diagnosed with clinical hypothyroidism and 40 age-matched normal controls were included in this study. Serum TSH values were >10 uIU/mL, FT_4 <11.6 ng/dL and FT_3 <2.8 ng/dL in all hypothyroid patients.

Exclusion criteria were as following: Having received previous treatment for hypothyroidism, history of myocardial infarction, cardiomyophaty; structural heart disease, valvular heart disease, increased left atrial dimensions, diastolic dysfunction, and abnormal segmental wall motion as documented by echocardiography, low left ventricular ejection fraction, use of anti-arrhythmic medication, uncontrolled diabetes mellitus and chronic renal or hepatic failure.

Transthoracic echocardiography (TTE) was performed by using GE Vivid 3 (GE Healthcare, Haifa, Israel). Left atrial dimension, diastolic dysfunction (E and A velocity, E/A ratio), ejection fraction and ascendant aortic dimension were evaluated in all patients. Left ventricular systolic and diastolic dimensions were measured by using M-mode echocardiography.

ECG was performed by using 12-leads with 10 mV amplitude and 50 mm/sec velocity. Starting and ending points of P waves were manually marked along the isoelectric line. Measurements were performed at least on 10 derivations in each patient. Patients whose P wave starting and ending points couldn't be measured were excluded from data analysis. P wave dispersion (PWD) was calculated by subtracting minimum P wave duration (min Pd) from maximum P wave duration (max Pd).

As parameters didn't show normal distribution, non-parametric Mann Whitney-U test was used to compare PWD, minimum and maximum P wave durations between groups. 95% CI was selected and $p<0.05$ was set for significance. SPSS 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical calculations.

Results

115 patients, 75 of whom were hypothyroid, and 40 healthy controls were included in this study and formed the basis for data analysis. Groups did not differ in age and other main characteristics as well as risk factors for atrial fibrillation (Table 1). Groups also did not differ in main electrocardiographic and echocardiographic characteristics (Table 2).

Table 1. Characteristics of study and control groups

	Clinical Hypothyroidism	Controls
Patients, n	75	40
Female	62	25
Male	13	15
Age,	42 (29 to 53)	40 (36 to 48)
(Median and interquartile range)		
Other medical problems, n		
Hypertension	6	4
Diabetes	none	none
Hyperlipidemia	6	2
(LDL-C >100, Tg-C>200)		
Heart Failure	none	none
Diastolic dysfunction	none	none
Smoking	3	1
Alcohol	none	none

Table 2. ECG and echocardiographic results

	C. Hypothyroidism (n=75)	Controls (n=40)	P Value
LVEF(%)	64.3 (3.8)	65.2 (3.7)	0.51
Heart rate	68±10	77±9	>0.10
Left atrial diameter (mm)	3.1(0.3)	3.18(0.28)	>0.10
E/A ratio	1.19(0.35)	1.22(0.34)	>0.10
P max duration(msec)	95.4(12.3)	94.7(8.7)	0.74
P min duration(msec)	63.8(9.2)	68(9.2)	0.026
P wave dispersion (msec)	31.9(9.2)	26.5(9.4)	0.003

We found that P wave dispersion was significantly higher in the hypothyroid group compared to normal controls (mean (SD) 31.9 (9.3) ms and 26.5(9.4) ms, p= 0.003, respectively). Minimum P wave duration was significantly shorter in the hypothyroid group compared to controls (mean (SD), 63.8(9.2) ms and 68 (9.2), p= 0.026, respectively). Maximum P wave duration was not significantly different between groups (mean (SD), 95.1(11.2) p.0,74. We couldn't find significant correlation between PWD and age, sex, smoking or hypertension.

Discussion

In this study, we found that P wave dispersion was significantly increased in clinical hypothyroid patients compared to normal controls. Interestingly, this increase was more due to shortened P wave duration rather than increase in maximum P wave dispersion, which is characteristic for hyperthyroidism. Increased PWD is an independent risk factor for atrial fibrillation. We believe that one of the reasons to carry out more studies about atrial fibrillation and hyperthyroidism association is the need for long duration to achieve euthyroidism in hyperthyroid patients. Thus, our findings indicate that association between hypothyroidism and atrial fibrillation/flutter is underscored. Our findings show the presence of this association and this might have important clinical implications. Hypothyroidism can be treated in a relatively easy way, in a short time. Thus, our results suggest the importance of early recognition and

treatment of hypothyroidism in the primary prevention of atrial fibrillation with its detrimental consequences.

This is the first study in the literature to evaluate PWD in hypothyroid patients. Our study brought the association between atrial fibrillation and hypothyroidism in light. One of our drawbacks was to make the analysis manually instead of computerized digital methods. Still, a single person who was blinded to the characteristics and groups of the patents performed the analyses. Another advantage of our study was to include the patients with the first time diagnosis of clinical hypothyroidism. None of the patients developed atrial fibrillation during our study.

P wave dispersion is accepted as an independent risk factor for AF even in people without obvious heart disease (8). Increased PWD and its association with atrial fibrillation have been shown in hypertension, hemodialysis, coronary artery by-pass, chronic obstructive pulmonary disease, children with atrial septal defect, early rejection period after heart transplantation and hyperthyroidism (9, 10, 11, 12, 13, 14, and 15). Increased PWD was mostly due to the increase in maximum P wave duration in all of these entities. Thus, calculated PWD was prolonged and accepted as an independent risk factor for atrial fibrillation.

Our study was the first to showe increased PWD in hypothyroidism. Moreover, minimum P wave duration significantly decreased while maximum P wave duration did not change significantly in our study and this was unique to our study as well. In fact exact prevalence of atrial fibrillation is not known. Similarly, we could make suggestions regarding the possible mechanisms causing PWD increase in clinical hypothyroidism and we obtained most of the data about this subject from the studies of association between atrial fibrillation and hyperthyroidism.

It has been shown in animal studies that factors leading to interstitial fibrosis in the heart like heart failure might cause AF by causing irregularities in the cardiac conduction system. Also a fibrotic or scarred tissue in the heart can be a focus triggering AF (16, 17). Fujimoto K et al and Okabe M et al showed interstitial fibrosis by endomyocardial biopsies in hypothyroid patients (18, 19). Moreover, development of fibrosis in other organs and tissues in hypothyroidism was shown and hypothyroidism was accepted as an independent risk factor for some of them (e.g., development of pulmonary fibrosis in systemic sclerosis) (20). Thus, we can suggest that hypothyroidism might lead to atrial fibrillation by causing interstitial edema and/or fibrosis in cardiac and especially intra-atrial conduction system, even before causing other clinical symptoms or signs and heart failure.

Another contributing factor might be aging process. It can itself cause increased connective tissue elements in atri which might in turn cause formation of scar tissue. In rats, glycolytic inhibition has been shown to disrupt intracellular calcium transport of the aged heart leading to development of spontaneous AF (17, 21). Apoptosis led by hypothyroidism (22) and especially by Hashimoto's disease can cause increase in the rate of aging which might in turn lead to increased AF in hypothyroid patients.

Finally, left ventricular diastolic dysfunction might cause increased PWD and hence AF. Gunduz H. et al. have shown the association of increased left ventricular dysfunction and increased PWD (23). In our study, we excluded the patients with diastolic dysfunction and showed increased PWD without the presence of left ventricular dysfunction.

Our study showed significant PWD increase in hypothyroidism. In contrast to hyperthyroidism, this increase was due to the decreased minimum P wave duration instead of increased P max duration. This finding of our study clearly demonstrated a difference between hyperthyroidism and hypothyroidism in causing PWD increase. In addition to providing new insights to the association of PWD increase and hypothyroidism, our findings have important clinical implications. We suggest that hypothyroidism is as important as hyperthyroidism in the pathogenesis of atrial fibrillation. Early recognition and treatment of hypothyroidism might help to prevent the development of atrial fibrillation of flutter with its dare complications.

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