

Successful use of ivabradine in a case of exaggerated autonomic dysfunction

Aşırı otonomik disfonksiyonlu bir olguda ivabradin ile başarılı tedavi

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We present a 30-year-old male with complex and predominantly cardiovascular autonomic dysfunction. He had frequent syncopal attacks and paroxysmal atrial fibrillation (PAF). Physical, electrocardiographic, and echocardiographic findings were unremarkable. Syncopal attacks were precipitated by emotional stress, upright position, and micturition. Electrocardiograms obtained immediately after syncopal events revealed PAF with a low ventricular rate, which spontaneously returned to sinus rhythm without any medication. Syncopal events were suggestive of postural orthostatic tachycardia syndrome (POTS), were induced during upright position, and were associated with a sudden increase in heart rate to approximately 140 beats per minute and a sudden drop in blood pressure. Syncope was also induced during carotid sinus massage (CSM) in the upright position. It was thought that cardiac autonomic dysfunction, with POTS as the main component, was responsible for this clinical condition. Syncopal episodes increased in frequency during treatment with metoprolol. Treatment with ivabradine (5 mg twice a day) resulted in disappearance of syncopal episodes both during upright position and CSM. During six months of follow-up, the patient remained asymptomatic without syncope or atrial fibrillation.

Key words: Atrial fibrillation; autonomic nervous system diseases; benzazepines; postural orthostatic tachycardia syndrome/complications; syncope/etiology.

Postural orthostatic tachycardia syndrome (POTS) refers to the presence of orthostatic intolerance associated with increased heart rate from baseline by 30 beats per minute (bpm) or exceeding 120 bpm, which occurs within 10 minutes of standing in the absence of other precipitating factors such as drug use or prolonged bed rest. Peripheral autonomic neuropathy is one of the

Bu yazıda, karmaşık ve temel olarak kardiyovasküler otonomik disfonksiyon bulguları sergileyen 30 yaşında bir erkek hasta sunuldu. Hastada sık senkop atakları ve paroksizmal atriyal fibrilasyon (PAF) vardı. Fizik muayene, elektrokardiyografik ve ekokardiyografik incelemelerde bir anormallik saptanmadı. Senkop atakları duygusal stres, dik durma ve idrar çıkarma ile birlikte artmaktaydı. Senkop ataklarından hemen sonra çekilen elektrokardiyogramlarda düşük ventrikül hızlı ve herhangi bir tedavi olmaksızın sinüs ritmine dönüşen PAF görüldü. Senkop atakları postural ortostatik taşikardi sendromunu (POTS) düşündürmekteydi; ayakta dik durma sırasında oluşmakta, bu sırada kalp hızı ani bir artışla yaklaşık 140 vuru/dakikaya ulaşmakta ve kan basıncı düşmekteydi. Bu ataklar, ayakta dikilme sırasında yapılan karotis sinüs mesajı (KSM) ile de oluştu. Bu klinik duruma, ana bileşeni POTS olan kardiyak otonomik disfonksiyonun neden olduğu düşünüldü. Uygulanan metoprolol tedavisi sırasında senkop ataklarının sıklığı daha da arttı. Bunun üzerine, günde iki kez 5 mgr dozda ivabradin tedavisine başlandı. Bu tedaviyle hem dik pozisyonda hem de KSM ile oluşan senkop atakları kısa zamanda kayboldu. Altı aylık takip sırasında hastada senkop ve atriyal fibrilasyon görülmedi.

Anahtar sözcükler: Atriyal fibrilasyon; otonomik sinir sistemi hastalığı; benzazepin; postural ortostatik taşikardi sendromu/komplikasyon; senkop/etyoloji.

main features of this disease and is characterized by failure of peripheral vasculature to maintain vascular resistance during the upright position. It is suggested that loss of effective blood volume results in a compensatory increase in heart rate and myocardial contractility. We present a male patient with complex and predominantly cardiovascular autonomic dysfunction.

Received: February 28, 2009 Accepted: August 8, 2009

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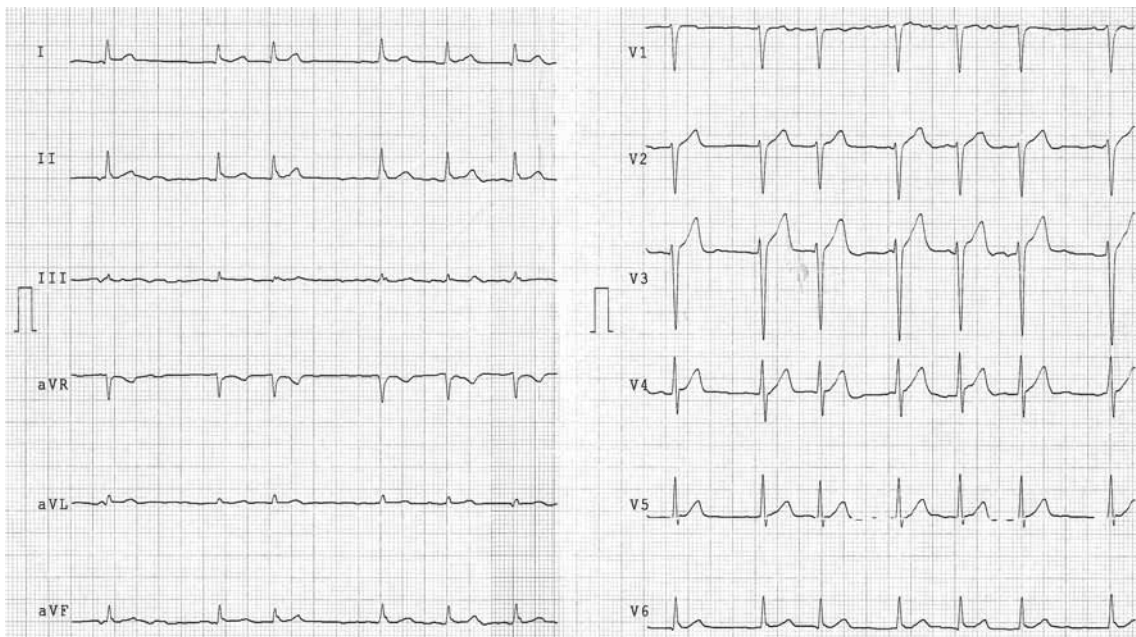


Figure 1. Paroxysmal atrial fibrillation. Electrocardiogram obtained 30 minutes following a syncopal episode. Note decreased ventricular rate, suggesting increased vagal tonus.

CASE REPORT

A 30-year-old male patient with frequent syncopal attacks and paroxysmal atrial fibrillation (PAF) was admitted to our hospital for diagnostic and therapeutic evaluation. His physical, electrocardiographic, and echocardiographic examinations were unremarkable. Syncopal attacks were precipitated by emotional stress, upright position, and micturition. Electrocardiograms obtained immediately after several syncopal events revealed PAF with a ventricular rate of low than expected, which spontaneously returned to sinus rhythm without any pharmacological intervention (Fig. 1). Some of the syncopal events were suggestive of POTS and were observed as reproducible syncopal episodes between the 4th and 7th minutes of upright standing position (Fig. 2). All syncopal episodes were associated with sudden increases in heart rate to approximately 140 bpm accompanied by a sudden drop in blood pressure. Syncopal events were also reproducibly induced during carotid sinus massage (CSM) performed in the upright position, which were characterized by a sudden drop in blood pressure with only minimal change in heart rate. Supine CSM was unremarkable. In view of these findings, it was thought that the presence of pure cardiac autonomic dysfunction, with POTS as the main component, was responsible for this clinical scenario. Syncopal episodes were reproducible with increased frequency during treatment with metoprolol. Then ivabradine (If current inhibitor) was administered at a dose of 5 mg twice a day, and

all the above-mentioned maneuvers were repeated five days after the initiation of therapy. This short-term treatment with ivabradine resulted in disappearance of syncopal episodes both during upright position and CSM (Fig. 2). The same findings were obtained at the end of the first month. During six months of follow-up, the patient remained asymptomatic without syncope or atrial fibrillation and he was scheduled to receive ivabradine for a longer period of time.

DISCUSSION

The clinical features of the patient described here may be interpreted as a reflection of inappropriately functioning autonomic system resulting in autonomic imbalance (hypo- and hyperactivity).

Postural orthostatic tachycardia syndrome and vasovagal syncope were the main factors responsible for syncopal episodes in our patient. Primary and secondary forms of POTS have been described. Subgroups of primary POTS include partial dysautonomic and hyperadrenergic forms.^[1] Partial dysautonomic form, possibly present in our patient, is an autoimmune disorder that may occur after various clinical conditions such as acute febrile illness, viral infections, pregnancy, surgery, sepsis, and trauma.^[2,3] Relationship of POTS with syncope and migraine have also been reported.^[4,5] The mechanism of POTS in the setting of migraine has been attributed to nociceptive activation of dura mater, which triggers an inhibitory reaction from the ventrolateral periaqueductal gray substance

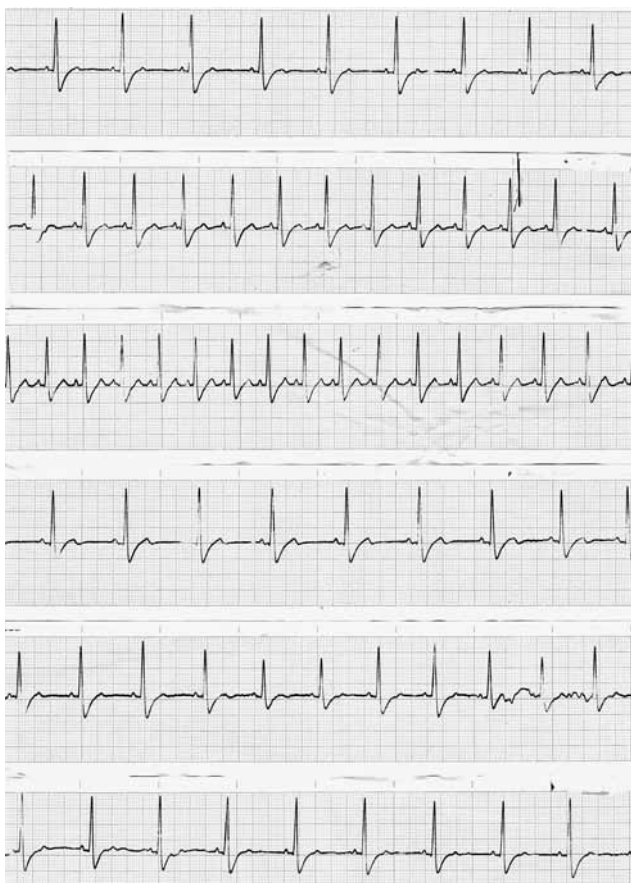


Figure 2. The first three ECG strips were obtained during supine position, and at 2 and 7 minutes of upright position, respectively, before treatment with ivabradine. The latter three strips were obtained during treatment with ivabradine. Note considerable decreases in postural change of heart rate during treatment with ivabradine.

to the trigeminal nucleus caudalis, resulting in secondary sympathoinhibition.^[4] We successfully treated symptoms of POTS with ivabradine. Although the beneficial effect of ivabradine in a patient with POTS has been reported,^[6] the mechanism of this effect has yet to be clearly defined. We suggest that the If current inhibition prevents sudden increase in the heart rate, but more importantly, it may prevent vigorous left ventricular contraction in the presence of relative hypovolemia due to pooling of blood in peripheral and mesenteric vasculature.

Paroxysmal atrial fibrillation observed in our patient always occurred during nighttime, immediately after a syncopal episode, which was generally associated with micturition. This type of PAF was suggested to be vagally mediated. This form of arrhythmia differs from sympathetically driven atrial fibrillation (AF) with respect to underlying mechanisms, precipitating factors, time of occurrence, and response to

pharmacological treatment. It is well-known that both parasympathetic and sympathetic stimulations may cause AF. Parasympathetic stimulation shortens atrial effective refractory period, increases its heterogeneity, and augments the ability of single atrial premature beats to induce AF, while sympathetic hyperactivity results in enhancement of abnormal automaticity, triggered activity, and microreentry.^[7,8] Vagally mediated PAF is generally observed in young patients in the absence of an underlying structural cardiac disease and precipitated by several factors, resulting in increased vagal drive particularly during nighttime or relaxation period. Cough, nausea, postprandial state, swallowing, ingestion of cold foods and drinks are among the factors that may precipitate vagally mediated PAF.^[9-11] Conversion to sinus rhythm is commonly observed in the morning, when sympathetic drive is higher.^[12] We noted high ventricular rate in previously reported patients with parasympathetically driven PAF,^[11,13] which is inconsistent with the presence of increased vagal tonus. In contrast, relatively slow ventricular rate during AF in our patient may be explained by the presence of exaggerated vagal drive, which results in inhibition of atrioventricular conduction. Treatment of vagally induced AF also differs from sympathetically driven AF. Antiarrhythmic treatment with disopyramide, procainamide, or ibutilide can be advised in the setting of vagally mediated AF, while treatment with beta-blockers, digoxin, or other antiarrhythmic drugs may be either ineffective or even harmful as was observed in our patient.^[14] Because of its more pronounced vagolytic properties, flecainide may be more effective than propafenone.^[15] Nonpharmacological treatment strategies also shows some differences because these two forms of AF have diverse anatomical localization of triggers. It was reported that pulmonary vein isolation had lower efficacy in vagally mediated AF than that in adrenergic form of AF.^[16] Ivabradine effectively suppressed episodes of AF in our patient. It is difficult to exactly explain this effect of the drug. Based on current data on the mechanisms of AF, we can speculate that ivabradine may suppress local firing of automatic foci originating from pulmonary veins or prevent both sympathetically and parasympathetically driven AF by several hypothetical mechanisms. Inhibition of adrenergic AF with ivabradine may be related to inhibition of the If current responsible for ectopic activity arising from pulmonary veins. However, it is still not well-established and contradictory information exists about the presence of If current in these ectopic foci.^[17-21] Inhibition of vagally mediated AF by ivabradine is an unexpected observation. At

this moment, it is not possible to explain this effect, but it is also possible that this drug may have no effect on vagatonic AF. In our opinion, explanation of this finding needs further clinical investigation.

Importance and clinical value of hypotensive response to CSM is not well established. We routinely perform CSM both in the supine and upright positions for the evaluation of syncope. It is our observation that young patients with mixed type response during tilt-table testing show hypotensive response during CSM in the upright position (unpublished data). In our opinion, isolated hypotensive response during upright CSM is also a reflection of autonomic imbalance similar to peripheral neuropathy observed in patients with POTS. The finding that ivabradine treatment resulted in complete resolution of upright CSM-induced syncope in our patient needs explanation.

The patient presented here has very interesting and challenging clinical features, because he had interchanging episodes of increased and decreased heart rate, which was difficult to treat with specific pharmacological drug regimens. For example, calcium channel blockers and beta-blockers are not appropriate and may even be harmful in this setting, and treatment with beta-blockers was ineffective and harmful in our case. Other antiarrhythmic drugs such as disopyramide and flecainide could be used for the prevention of PAF episodes, but these drugs are not expected to influence POTS and other types of vasovagal conditions and additionally their side effects could limit long-term treatment. Ivabradine is a selective If current inhibitor with no significant side effects and causes selective reduction in heart rate. Moreover, it has no effect on other electrophysiologic parameters such as AH, HV, PR, QTc intervals, and QRS duration.^[22,23]

Our experience shows that selective inhibition of the If current with ivabradine may be of value in patients with syndromes of cardiac autonomic dysfunction, but this should be confirmed by large scale clinical trials.

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