A new hope in the treatment of coronary vasospasm: bosentan

Koroner vazospazm tedavisinde yeni bir umut: Bosentan

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Summary– Atherosclerosis is the most important cause of acute coronary syndromes. The mediators that trigger vasospasm, including endothelin and serotonin, are synthesized and secreted into circulation from atherosclerotic plaques and surrounding tissues. A 68-year-old man was hospitalized due to acute coronary syndrome four times in a one-year period. The patient presented to emergency service again with heartburn and a pressure-like pain in his upper abdomen in February 2012. He was admitted to the coronary care unit with the detection of a more than three-fold increase in troponin values and ischemic changes on electrocardiography. By decision of the cardiology council, the endothelin receptor antagonist, bosentan was added to the treatment. There were no contraindications to this medication according to his blood and hepatic indicators. After confirmation of the Social Security Institution, bosentan was started as 62.5 mg twice a day. After the first month, the dose was increased to 125 mg b.i.d. As of completion of the eighth month of treatment with bosentan, the patient had not been hospitalized due to angina attack or acute coronary syndrome.

Özet– Akut koroner sendromların en önemli nedeni aterosklerozdur. Aterosklerotik plaklardan ve bunların çevresindeki endotelden endotelin ve serotonin gibi vazospazmı tetikleyici aracıların sentez edilip dolaşıma salgılandıkları bilinmektedir. Altmış sekiz yaşında erkek hasta son bir yıl içerisinde akut koroner sendrom tanısı ile dört kez hastaneye yatırıldı. En son Şubat 2012'de göğüste yanma ve üst batında baskı tarzında ağrı ile merkezimiz acil servisine başvurdu. Troponin değerlerinde üç kattan fazla artış ve elektrokardiyografisinde iskemik değişiklikler saptanması üzerine koroner yoğun bakıma yatırıldı. Hastanın tedavisine kurul kararı ile endotelin reseptör antagonisti olan bosentan eklenmesine karar verildi. Hastanın kan ve hepatik göstergelerine göre bu tedaviye engel herhangi bir kontrendikasyon saptanmadı. Sosyal Güvenlik Kurumu'ndan onay alındıktan sonra başlangıç dozu olarak günde iki kez 62.5 mg bosentan başlandı. Birinci aydan sonra günde iki kez 125 mg dozuna çıkıldı. Bosentan tedavisinin sekizinci ayı dolan hastanın anjina atağı veya akut koroner sendrom nedeniyle hastaneye yatışı olmadı.

Atherosclerosis is the most important cause of acute coronary syndromes. Atherosclerosis starts as an intimal lesion and eventually evolves into an occlusive lesion.[1] Small atherosclerotic plaques may trigger vasospasm in the coronary arteries. The mediators that trigger vasospasm, including endothelin and serotonin, are synthesized and secreted into circulation from atherosclerotic plaques and surrounding tissues.[2] Vasospasm may be extensive, affecting the entire coronary bed. However, vasospasm is a rare finding in the left main coronary artery.[3,4] Nitrates and calcium channel blockers are used most commonly in the treatment of vasospastic angina pectoris.

Herein, we present a case in whom high-dose calcium channel blockers and nitrates were used due to coronary vasospasm. However, the increased frequency of attacks and hemodynamic severity of the side effects led us to search for new treatments. For this purpose, some limited data were reviewed that indicated endothelin receptor antagonists may be effective as an alternative therapy.[5,6] There are only two case reports about this new treatment protocol in the literature. The first case was a 46-year-old man with severe and resistant coronary vasospasm. At 16 weeks after bosentan treatment in this patient, he was free of chest pain and had good coronary flow reserve on

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oxygen 15-labelled carbon monoxide positron emission tomography (PET).[5] The second case in the literature was an approximately 55-year-old woman. She had recurrent crushing central chest pain radiating to both arms and jaw. There was extensive vasospasm in the right coronary artery on her coronary angiography. During the six-month follow-up period under bosentan therapy, she was asymptomatic without any admission to the clinic.[6]

CASE REPORT

A 68-year-old man was hospitalized due to acute coronary syndrome four times in a one-year period. At his most recent admission to the hospital, the patient was diagnosed with vasospastic angina pectoris. He was discharged with a treatment of diltiazem (90 mg/day), nifedipine (30 mg/day), isosorbide-5-mononitrate (50 mg/day), ramipril (2.5 mg/day), and atorvastatin (20 mg/day). The patient presented to the emergency service again with heartburn and a pressure-like pain in his upper abdomen in February 2012. He was admitted to the coronary care unit with the detection of a more than three-fold increase in troponin-I values and ischemic changes on electrocardiography. In the intensive care unit, intravenous (*iv*) nitroglycerin, heparin and other anti-ischemic treatments were administered. While the patient was under medical therapy, cardiogenic shock developed (arterial blood pressure, 50/30 mmHg), so dopamine infusion was started immediately. The ECG showed ST-segment depressions in anterior derivations and ST-segment elevation in AVR derivation (Fig. 1). The patient was taken to the catheter laboratory as his hemodynamic status did not improve in spite of the treatment. It was observed that the patient had a common vasospasm starting from the distal segment of his left main coronary artery (Fig. 2a). The follow-up angiography

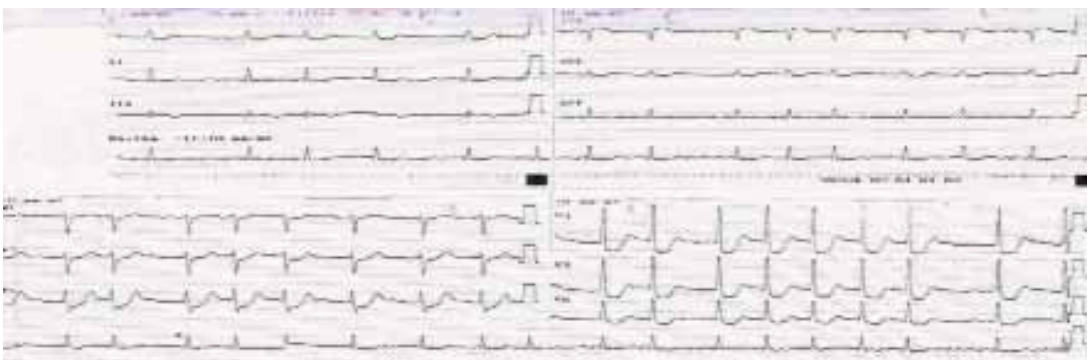

Figure 1. During the attack, electrocardiogram performed before angiography.

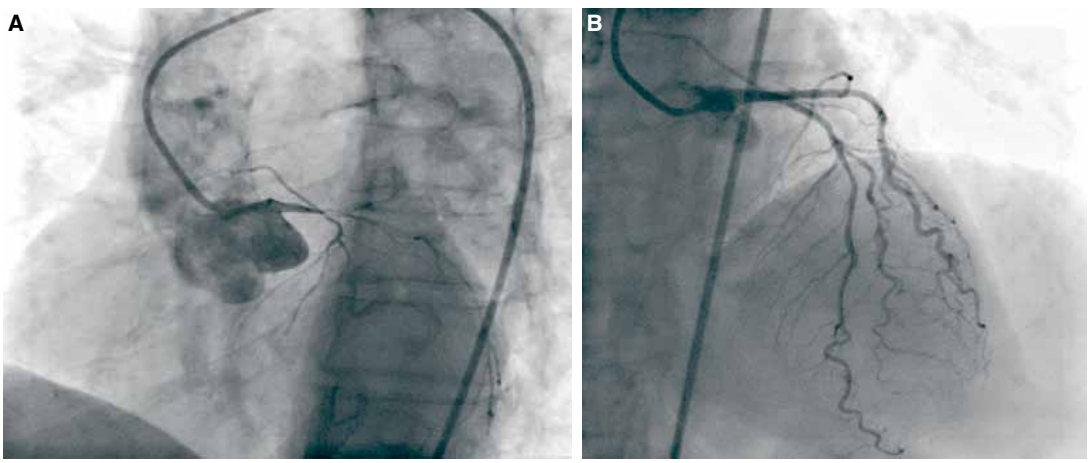

Figure 2. **(A)** The vasospasm view of the patient starting from the left main coronary artery after the first injection of contrast agent. **(B)** The patient underwent coronary angiography after intracoronary nitrate.

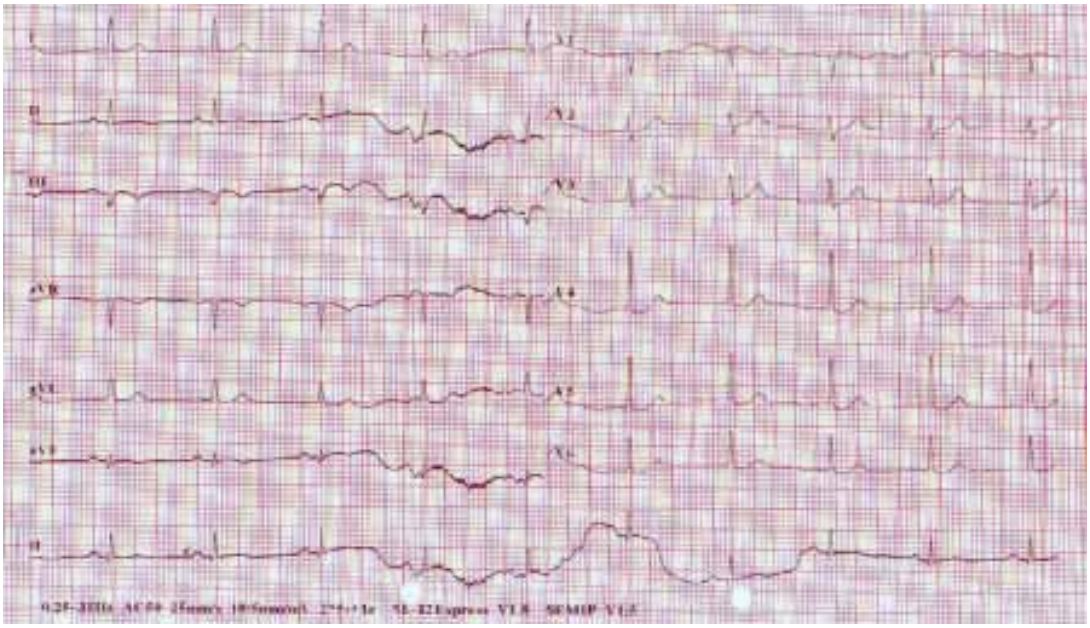

Figure 3. Electrocardiogram of the patient in intensive care follow-up after intracoronary nitrate.

showed reduction in vasospasm after the application of intracoronary nitroglycerin (Fig. 2b). Mild stenosis was observed in the patient's proximal left anterior descending artery, and atherosclerotic plaques causing mild-moderate stenosis were detected in his circumflex artery. As his hemodynamics had improved, the patient was transferred back to the intensive care unit. In his ECG performed after the application of coronary nitrates, improvement in ST-segment changes was observed (Fig. 3). The dose of *iv* nitroglycerin was increased. Diltiazem (120 mg/day), nifedipine (60 mg/day), atorvastatin (40 mg/day), acetylsalicylic acid (100 mg/day), and clopidogrel (75 mg/day) were prescribed in oral form. Intravenous nitroglycerin was stopped, and isosorbide-5-mononitrate (60 mg/day) was added to his treatment on the second day of hospitalization. The patient was transferred to service on the seventh day of his hospital admission as no vasospastic attacks were observed during his stay in intensive care. By decision of the cardiology council, the endothelin receptor antagonist bosentan was added to the treatment. There were no contraindica-

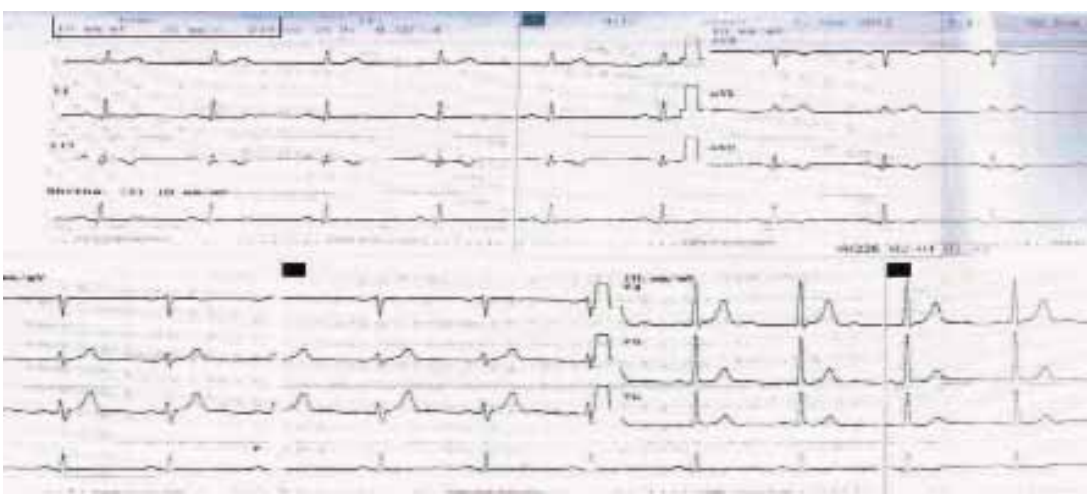

Figure 4. The seventh-month electrocardiogram of the patient receiving bosentan treatment.

tions to the use of bosentan according to his blood and hepatic indicators. After confirmation of the Social Security Institution, bosentan was started at a dose of 62.5 mg twice a day (b.i.d) (confirmation number: B.10.0.IEG.0.14.00.02) and increased to 125 mg b.i.d after the first month. Diltiazem was stopped in the second month of treatment with bosentan. In the third month, it was decided to terminate the nifedipine treatment. Electrocardiography of the patient in the follow-up period revealed no evidence of emerging ischemia (Fig. 4). Myocardial perfusion scintigraphy in the onset of the fifth month of his treatment detected a fixed defect without reversible ischemia in a small area in the apical zone. After this examination, oral isosorbid-5-mononitrate therapy was terminated since the patient had no complaints.

Bosentan 125 mg b.i.d, clopidogrel (75 mg/day), atorvastatin (20 mg/day), and ramipril (2.5 mg/day) were prescribed. As of the completion of the eighth month of treatment with bosentan, the patient had not been hospitalized due to angina attack or acute coronary syndrome (Fig. 4). Follow-up visits were scheduled as once every three months instead of monthly.

DISCUSSION

It has been many years since Prinzmetal et al. defined coronary vasospasm. Coronary vasospasm can be defined as focal or occasionally diffuse spasm of the coronary arteries and inability to meet the blood supply even in the absence of obstructive atherosclerotic coronary lesions. Over these years, there has been little improvement in new treatment options for this disease. Endothelin, having physiological and pathological effects, is a vasoactive peptide that is secreted from the vascular endothelium.[7] Endothelin is one of the most potent vasoconstrictor substances. The negative role of endothelin receptors in pulmonary hypertension is well known.

The endothelial system serves in one of the three major pathways that are responsible for the increase in pulmonary vascular resistance. For this reason, endothelin receptor antagonism plays an important role in the treatment of pulmonary hypertension. Apart from the pulmonary veins, it has been shown that endothelin A and B receptors also exist in coronary arteries. It is indicated that spontaneous phasic contractions that occur after the development of atherosclerosis in coronary arteries may cause vasospasm. During episodes of angina, blood and tissue levels of vasospastic mediators, such as endothelin and serotonin, are elevated. As a result of this increase, it is suggested that the violence and frequency of spontaneous phasic contractions are increased.[8,9] Spontaneous phasic contractions have been reported in patients with a coronary artery shown to be blocked by endothelin receptor antagonists.[10]

Despite the use of high-dose calcium channel blockers and nitroglycerin in patients having increased frequency and severity of vasospasm attacks, patients may benefit from the incorporation of endothelin receptor blockers.[5,6] Under treatment with bosentan, our patient had not been re-hospitalized due to vasospastic angina as of the eighth month of his follow-up. The patient's calcium channel blockers and isosorbid-5-mononitrate treatments were terminated. The patient has been followed with bosentan, statins, angiotensin converting enzyme (ACE) inhibitors, and antiplatelet therapies for nearly two months. This is the first reported case in our country to show a benefit of bosentan treatment following a diagnosis of vasospastic angina pectoris. Large-scale randomized researches will be needed in order to determine the role of endothelin receptor antagonists in the treatment of vasospastic angina pectoris.

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Key words: Acute coronary syndromes; bosentan; chest pain/etiology; coronary vasospasm.

Anahtar sözcükler: Akut koroner sendrom; bosentan; göğüs ağrısı/etyoloji; koroner vazospazm.