Large pericardial effusion induced by minoxidil

Minoksidilin neden olduğu ciddi perikart efüzyonu

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Summary– A 53-year-old male admitted with increased shortness of breath. In the physical examination, he had dyspnea, tachycardia and tachypnea. An echocardiogram showed large pericardial effusion (PE) as well as significant pulmonary hypertension. He had been started recently on minoxidil for blood pressure control. PE was reported to occur with minoxidil treatment both in patients undergoing dialysis and those with normal renal function. Pulmonary hypertension has been reported to affect the cardiac tamponade physiology. Because of significant pulmonary hypertension in our patient, a right heart catheterization was also done, which prevented cardiac tamponade. He was treated conservatively without any intervention, and PE resolved spontaneously after discontinuation of minoxidil.

Özet– Elli üç yaşında erkek hasta artan nefes darlığı şikayetiyle başvurdu. Fizik muayenesinde dispne, takipne ve taşikardi olduğu izlendi. Ekokardiogramında bűyűk miktarda perikart efüzyonu (PE) ve pulmoner hipertansiyon (PH) vardı. Yakın zamanda hipertansiyonu için hastaya minoksidil başlanılmıştı. Minoksidile bağlı gelişen PE, diyaliz ya da diyalizde olmayan hastalarda daha önceden bildirilmiştir. PH'nin kalp tamponadı fizyolojisini etkilediği literatürde bildirilmiştir. Hastamızdaki ileri derecedeki pulmoner hipertansiyondan dolayı, kardiyak tamponadı daha iyi araştırmak için sağ kalp kateterizasyonu yapıldı. Bulgular kardiyak tamponadı desteklemedi, hasta konservatif olarak takip edildi, minoksidilin kesilmesinden sonra PE kendiliğinden azaldı.

Minoxidil is a direct-acting arterial vasodilator. Pericardial effusion is reported with minoxidil treatment both in patients undergoing dialysis and those with normal renal function. PE can be large and result in cardiac tamponade in some cases.[1]

Herein, we report a large PE caused by minoxidil treatment that was resolved after discontinuation of minoxidil in a patient who has also underlying pulmonary arterial hypertension.

Abbreviations:

PE	*Pericardial effusion*
PAH	*Pulmonary arterial hypertension*

CASE REPORT

A 52-year-old male with a past medical history of hypertension and stage 2 chronic kidney disease presented to the emergency department with complaints of dyspnea on minimal exertion and epigastric pain. In a physical examination, his blood pressure was 90/60 mmHg, his heart rate was 90 beats/min, and his respiratory rate was 20 breaths-min. His jugular venous pressure was elevated, his cardiac auscultation revealed a soft 1/6 systolic murmur at the left lower sternal border with accentuation of physiologically split of S2, he had a palpable right ventricle (RV) heave as well as a third heart sound.

Trace pitting edema was present in both legs. Pulsus paradoxus of 18 mmHg was also noted upon presentation. The patient was started on minoxidil 10 mg a day by his nephrologist two months prior to admission because of resistant hypertension. His other medications were metoprolol XL 50 mg, Amlodipine 10 mg, lisinopril 40 mg, and aspirin 81 mg orally once a day. An EKG showed diffuse T wave inversions and a chest X-ray showed globular enlargement of cardiac silhouette and vascular congestion, which was new compared to a chest

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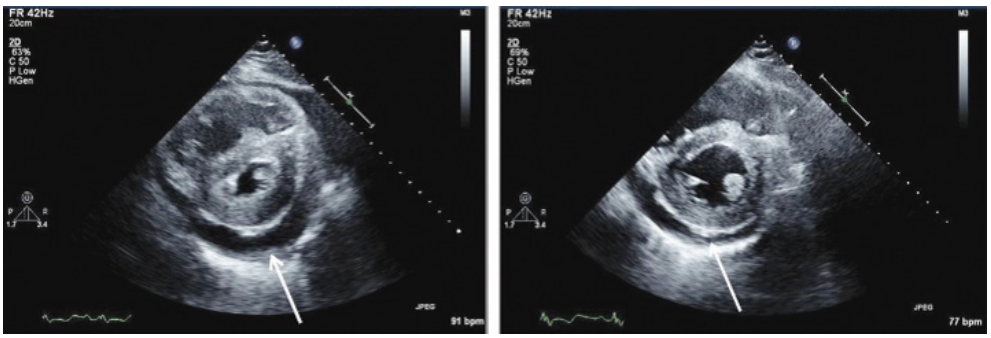

Figure 1. Transverse view by TTE showing large posterior effusion at baseline and 12 days after minoxidil therapy is discontinued with significant reduction in the amount of pericardial effusion (white arrows).

X-ray taken 3 weeks ago. A transthoracic echocardiogram (TTE) (Figs. 1, 2, 3) showed normal left ventricular (LV) systolic function as well as a large PE with swinging motion of the heart without right atrial (RA) or RV free wall collapse. Findings consistent with RV pressure overload were present as well enlarged RV and RA. There was about a 16% respiratory variation in transmitral flow velocity with a Doppler study. The inferior vena cava (IVC) was dilated, but was still collapsing more than 50% by a sniff. Pulmonary hypertension was also present with an estimated pulmonary artery systolic pressure of 73/28 mmHg. There was a concern that the echocardiographic findings of tamponade were masked due to the pulmonary hypertension.

The patient's laboratory work up revealed creatine to be 1.9, BUN to be 21, he had a sedimentation rate of 15, and a CRP of 1.64. A work-up for collagen vascular diseases including ANA, anti-Histone antibodies, cardiolipin antibodies, and anti Ds-DNA antibodies were all negative. A therapeutic pericardiocentesis was being planned. A pre-pericardiocentesis right heart catheterization (RHC) showed an RV pressure of 72/11 mmHg, a mean RA pressure of 14 mmHg, and a pulmonary artery pressure of 74/37 mmHg with a wedge pressure of 14 mmHg and an LV pressure of 145/8 mmHg. He also had an LV end diastolic pressure of 8 mmHg, consistent with PAH without cardiac tamponade physiology.

He was taken off the minoxidil for a few days with close follow-up. The patient's symptoms improved over the next few days. He was discharged with a close outpatient follow-up and a repeat echocardiogram (Figs. 1, 2, 3) after twelve days. On follow up, the patient's PE was significantly reduced, while his RA, RV enlargement, and PAH remained unchanged. After discharge he

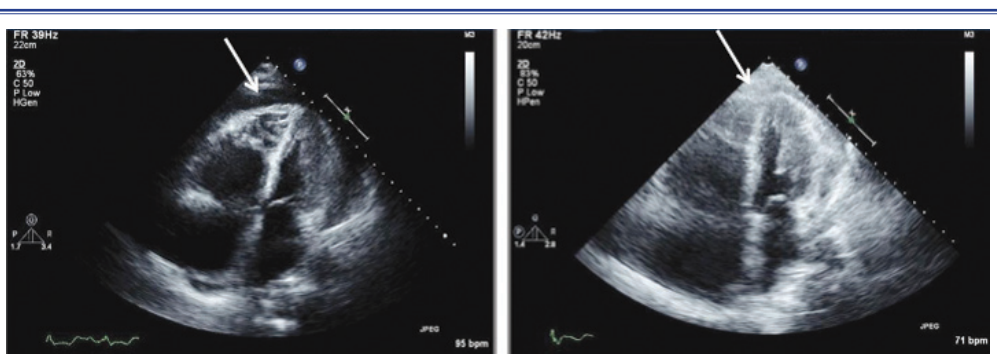

Figure 2. Apical 4 chamber view by TTE showing large anterior pericardial effusion at baseline and 12 days after minoxidil therapy is discontinued with significant reduction in the amount of pericardial effusion (white arrows).

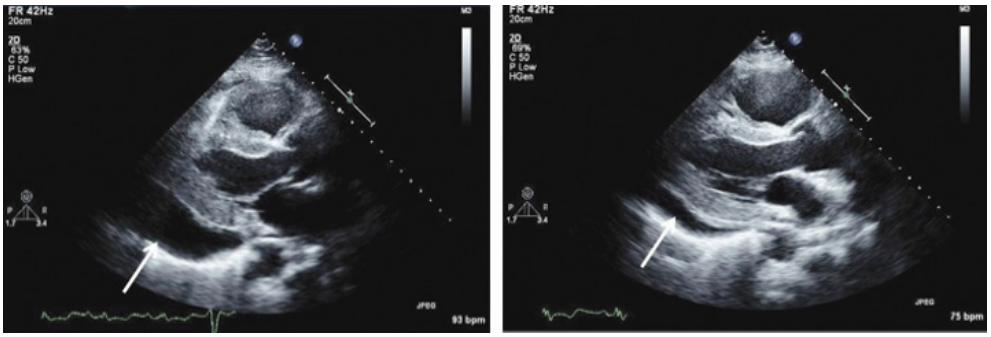

Figure 3. Parasternal view by TTE showing large pericardial effusion at baseline and 12 days after Minoxidil therapy is discontinued with significant reduction in the amount of pericardial effusion (white arrows).

was evaluated by a pulmonologist and was tested negative for HIV and performed normally on all pulmonary function tests. He was diagnosed with primary PAH, and phosphodiesterase inhibitor treatment is being considered. During the last eight months of follow-up he has not had any recurrence of symptoms.

DISCUSSION

Minoxidil (U-10,858), an orally active arterial vasodilator, was introduced for human studies as early as 1969. The molecular structure was noted to be 6-amino-1, 2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine. Minoxidil was unique in the way it was introduced because there was no control group and the majority of patients were treated in an open label study.[1] The hypotensive effects of minoxidil were noted to be related to the interference of intracellular calcium activity, which caused peripheral vasodilation. Side effects observed with the drug were reflex tachycardia, increased cardiac output and decreased peripheral resistance mediated by baroreceptor stimulation,[2] salt and water retention, and hypertrichosis. Minoxidil also caused increased flow to the normal myocardium and decreased flow to the ischemic areas, which can result in angina and EKG abnormalities.[1] In the literature, PE is reported in up to 3% of patients taking minoxidil. Patients with renal impairment were at higher risk of developing PE, although it has also been seen in patients with normal renal function. The mechanism of minoxidil-induced PE is still unclear. In a review by Martin et al.[1] it was reported that out of 1869 patients on minoxidil, 73 had PE. Cardiac tamponade occurred in 14 patients who were on dialysis and in 7 that were not. In this retrospective cohort study there was an identifiable cause for effusion, including systemic lupus erythematous, tuberculosis pericarditis, severe renal failure and congestive heart failure, which was seen in only one of cardiac tamponade patients and in 8 of the remaining effusions. Minoxidil was discontinued in 16 of the 21 patients who experienced cardiac tamponade.[1] PE has been frequently reported in patients undergoing dialysis use of minoxidil further increased the risk of PE, but even among this group PE was more significantly associated with the use of minoxidil (81% on minoxidil versus no minoxidil 23% $p<0.0005$).[3] Since this large study, several more case reports have been published attributing PE to minoxidil therapy.[2,4-7] In one case,[2] when the dose of minoxidil was decreased from 30 mg to 20 mg, PE was resolved, while in 3 other cases.[5-7] PE was resolved after discontinuation of minoxidil treatment, and these patients were not re-challanged with minoxidil. In one patient[4] that was re-started on minoxidil, PE recurred even after initial pericardial drainage, resulting in its discontinuation.

Although pericardiocentesis is required in patients with hemodynamic compromise, most cases of PE resolve spontaneously upon cessation of minoxidil therapy. There is also concern for an adverse outcome for pericardial drainage in patients with PAH.[8] Hemnes et al.[8] reported outcomes in 6 patients with PAH and large PE who underwent

pericardial drainage. Three of these patients died within 13 hours of drainage. Dunne et al.[9] also reported poor outcomes after pericardial drainage in 2 systemic sclerosis patients with PAH and significant PE.

The other issue is poor correlation of ECHO findings of cardiac tamponade with RHC in patients with pulmonary hypertension. In a study of 12 patients by Plotnick et al.[10] IVC plethora was found to be the best predicting ECHO finding for tamponade. There is also a report of diastolic LA collapse in ECHO, which is typically a late sign of tamponade with no collapse of RA or RV. This is usually an early sign of tamponade in patients with PAH and large PE that do not have any signs of cardiac tamponade physiology in RHC.[11]

Having PAH with high RV and RA pressures, or the slow accumulation of pericardial fluid over weeks might have prevented cardiac tamponade in our patient. Discontinuation of minoxidil resulted in the resolution of PE and prevented unnecessary pericardial drainage, which may carry higher risk in this subgroup of patients with PAH. Right heart catheterization should also be considered in settings of severe PAH for confirmation of cardiac tamponade physiology, prior to pericardiocentesis.

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Key words: Adult; cardiac tamponade; heart failure; hypertension; kidney; minoxidil; pericardial effusion; renal dialysis.

Anahtar sözcükler: Erişkin; kardiyak tamponat; kalp yetersizliği; hipertansiyon; böbrek; minoksidil; perikart efüzyonu; böbrek diyalizi.