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Holt-Oram syndrome

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Abstract. – BACKGROUND: Holt-Oram syndrome (HOS) is a rare genetic illness, which concerns disturbances in the appearance of the upper limbs, congenital heart malformations, and cardiac conduction diseases. HOS usually requires the implantation of a pacemaker, because of cardiac conduction disturbances.

CASE REPORT: We present the case of a patient with HOS qualified for pacemaker implantation due to overt bradycardia. To prevent the development of heart failure in the future, the His-bundle pacing technique was used. The implantation was successful. In the control, after one year, the man remains in good condition. The pacing was over 90%, and the left ventricular ejection fraction (LVEF) was stable (60%).

CONCLUSIONS: So far, there are no reports on which methods of stimulation are required when it comes to patients with HOS. His-bundle pacing technique is a new type of physiological pacing, which can avoid heart failure.

Key Words:
Holt-Oram syndrome, Pacemaker, His-bundle pacing.

Introduction

Holt-Oram syndrome (HOS) is a rare genetic illness, which concerns disturbances in the appearance of the upper limbs, congenital heart malformations, and cardiac conduction diseases. The disease is inherited in an autosomal dominant manner. Sequence alteration of the *TBX5* gene located on chromosome 12 is associated with HOS[1]. The incidence of the illness is reported at 0.95/100,000 births with no predilection for male or female sex[2]. Holt-Oram syndrome usually requires the implantation of a pacemaker because of cardiac conduction disturbances such as sinus bradycardia and atrioventricular block[1]. We present the case of a patient with HOS qualified for pacemaker implantation due to overt bradycardia. To prevent the development of heart failure in the future, the His-bundle pacing technique was used. So far, there are no reports on which methods of stimulation are required when it comes to patients with HOS. Our knowledge is barely based on very few case reports[2].

Case Presentation

A 52-year-old patient was admitted to the Cardiology Department for the diagnosis of arrhythmia in the course of the Holt-Oram syndrome. Having a hereditary burden of Holt-Oram syndrome on his father's side, the patient was diagnosed with the syndrome in early childhood. At the time of admission to the hospital, the main problem of the patient was symptomatic bradycardia. So far, he has not been treated for chronic diseases. In childhood, he underwent atrial septal defect (ASD) closure. Despite symptomatic cardiac conduction disturbances, a pacemaker was not implanted in the past due to the patient's refusal of informed consent for the procedure. The patient was explaining the lack of consent with the fear of worsening heart function caused by ventricular pacing and his father's history (multiple hospitalizations and device replacements).

At the time of admission to the hospital, the patient was in good general condition. His blood pressure was 144/83 mmHg. Temperature and oxygen saturation were normal. The heart rate was 41 beats/min. Moreover, a physical examination revealed distortions of the upper limbs and a chest – typical for Holt-Oram syndrome (Figures 1 and 2). Abnormal laboratory results included a slightly elevated level of N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), a slightly decreased level of platelets (PLT), and an abnormal lipid profile. Electrocardiography (ECG) showed atrial flutter (AFI) and third-degree atrioventricular block (complete heart block) with a heart rate of about 40 beats/min (Figure 3A-B). In echocardiography (ECHO), normal systolic left ventricle function with left ventricular ejection

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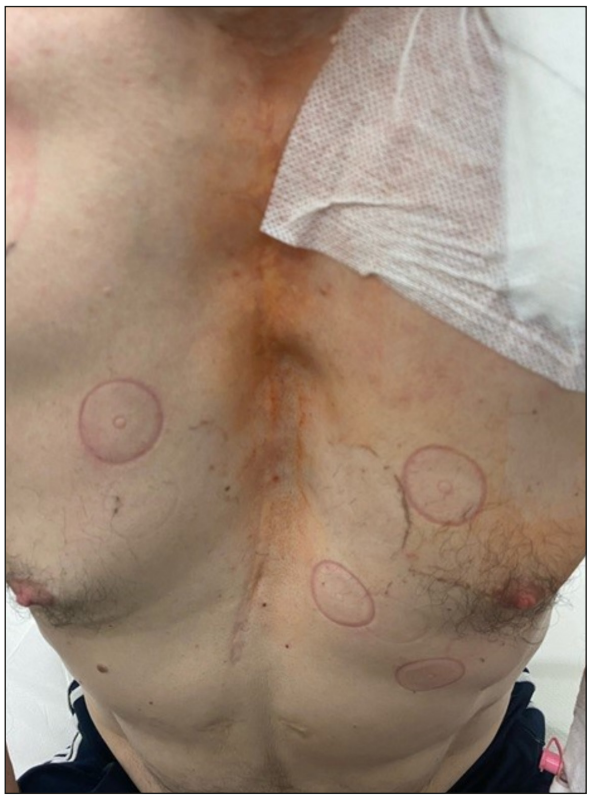

Figure 1. The chest abnormality characteristic of Holt-Oram syndrome.

fraction (LVEF) about 60%, enlargement of a left ventricle and enlargement of both atria [left ventricular end-diastolic dimension (LVEDd) about 6.1 cm, left atrial dimension (LAD) about 4.9 cm, left atrial area (LAAr) about 53 cm^2, right atrial area (RAAr) about 54 cm^2] were stated. In the Cardiology Department, Holter's EKG confirmed AFI and complete heart block. The patient was qualified for the implantation of a pacemaker. The computed tomography angiography (CTA) did not reveal new heart malformations, but the radiologist suggested the presence of an abnormal structure in the auricle of the left atrium. Transesophageal echocardiography (TEE) did not confirm the presence of a thrombus in the left auricle. Based on the CHA_2DS_2-VASc score, the patient did not get any points, so he was not qualified for anticoagulation therapy.

During the next hospitalization, it was decided to implant the His-bundle pacemaker (HBP), giving the patient a chance for electrotherapy using the physiological conduction pathway (Figure 4A-B). The implantation was successful, and the patient left the Cardiology Department in good condition. Accurate presentation of the indications for the procedure, as well as its course allowed to obtain informed consent from the patient for implantation of the pacemaker.

After one year, the man remains in good condition. The pacing was over 90%, and a LVEF was stable (60%).

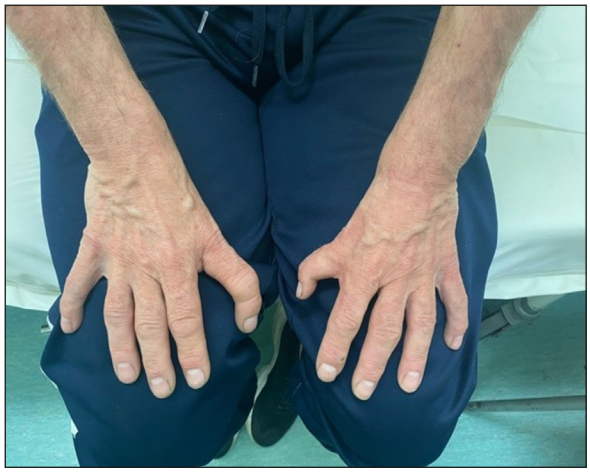

Figure 2. The upper limbs typical abnormality of Holt-Oram syndrome.

Discussion

Holt-Oram syndrome, also known as the heart-hand syndrome, first described in 1960 by Holt and Oram, is a rare disease[1]. The incidence of HOS is reported at 0.95/100,000 births with no predilection for male or female sex[2]. The syndrome is an autosomal dominant disorder, caused by a mutation in the *TBX5* gene on chromosome 12q24.1. Over 85% of people with Holt-Oram syndrome carry the mutated *TBX5* gene. However, most cases of the disease are sporadic and occur as a result of *de novo* mutation[1]. In the case of our patient, the syndrome was inherited, because the same illness occurred in the man's father.

Holt-Oram syndrome is characterized by upper limb defects, congenital heart malformations, and cardiac conduction disturbances.

Upper-limb malformations typically affect the bones of the hands, forearms, and humerus. They can be unilateral or bilateral and symmetric or asymmetric. General abnormalities are aplasia, hypoplasia, and anomalous development of bones. It might also occur in distortions of a

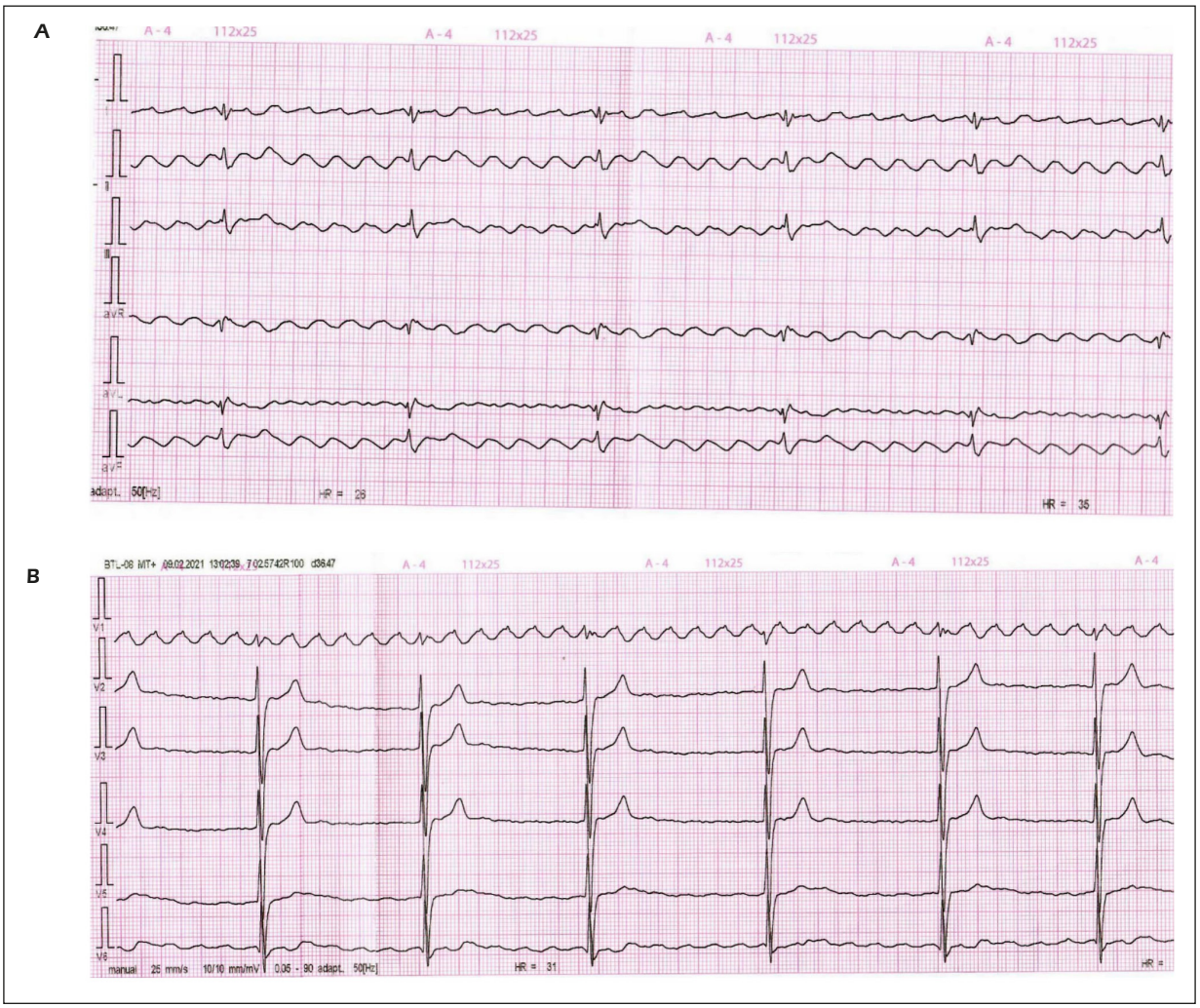

Figure 3. ESG with atrial flutter (AFI) (**A**) and third-degree atrioventricular block (complete heart block) (**B**) with a heart rate of about 40 beats/min.

chest[3,4]. In our patient, the abnormalities mainly concerned – fingers and chest – he had bilateral, symmetric deviations of fingers and pectus excavatum (Figures 1-2).

The most common congenital heart malformations are ASD and ventricular septal defect (VSD), as well as patent ductus arteriosus, hypoplasia of the left ventricle, and pulmonary stenosis, although they are not as common as septal defect[5]. Our patient developed ASD – he was operated on, in his childhood. The ASD was properly closed – it was checked by an ECHO in the Cardiology Department. CTA did not show other heart malformations.

The most common cardiac conduction disturbances for HOS are sinus bradycardia, atrioventricular block, and atrial fibrillation[6]. In our patient, the typical conduction problem appeared in the form of bradycardia (a heart rate of about 40 beats/minute), atrioventricular block (complete heart block), and atrial flutter. Despite the heart rhythm disorders that have been observed for years, the patient has not been treated with cardiac muscle stimulation so far. It resulted from reluctance to hospitalizations and battery replacements in the device. Moreover, he was afraid of heart failure caused by ventricular pacing. However, the patient reported it to our department due to the weaker exercise tolerance. He used to be a sportsman and was jogging regularly, so bad physical performance was a crucial problem for him. Due to the patient's concerns about decreasing the ejection fraction, he was proposed the bundle pacemaker. This method is an alternative

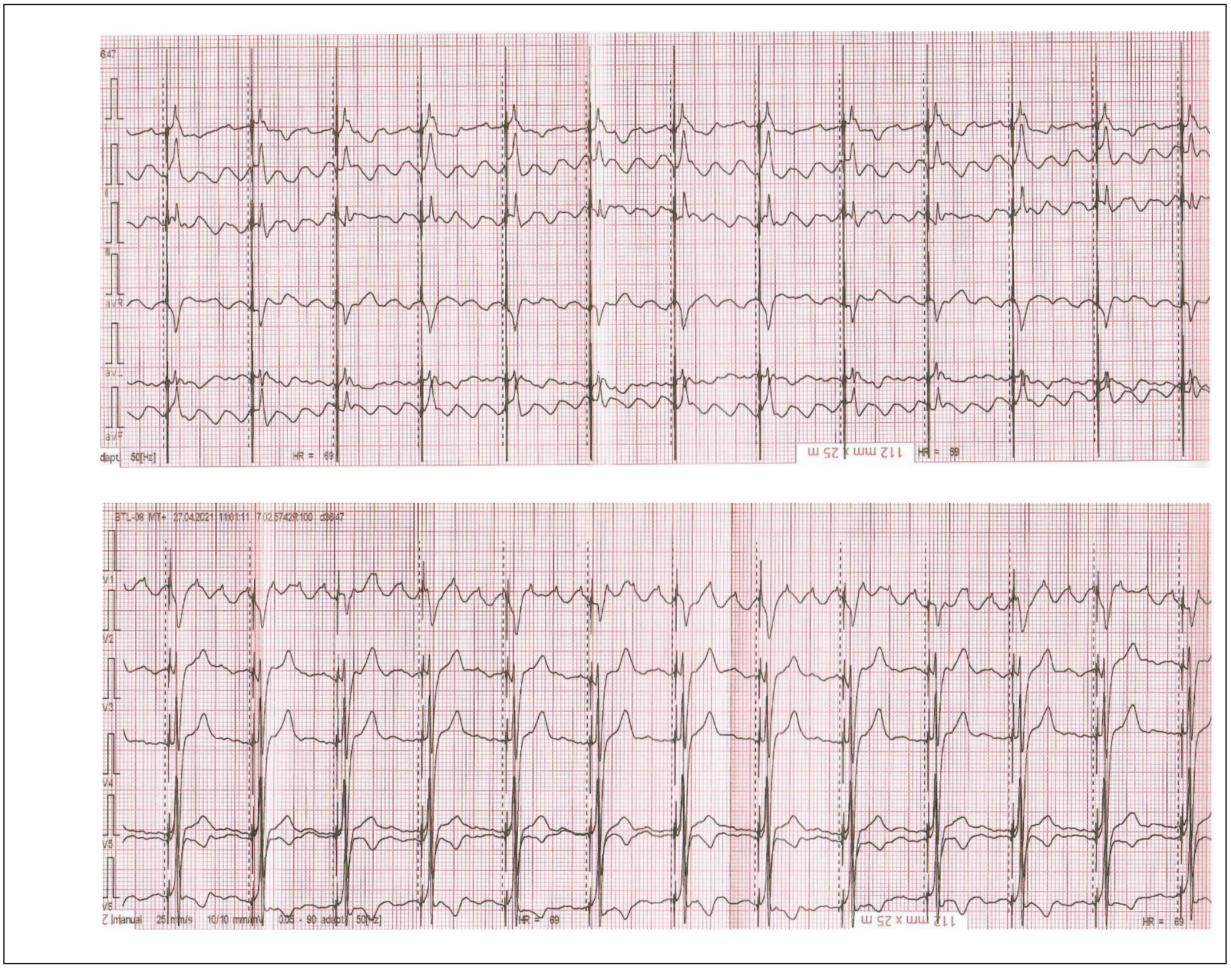

Figure 4. ECG after His-bundle implantation.

to traditional pacing techniques. HBP requires precise placement of the lead on the bundle in order to capture the cardiac conduction system directly. The implantation is guided by an electrogram (EGM) and pace mapping and anatomy of a heart[7]. It uses the His-Purkinje conduction to produce more physiological beats, specifically as a form of cardiac resynchronization therapy[8]. Right ventricular pacing, which is associated with the muscle conduction of electrical impulses, may induce electromechanical dyssynchrony[9]. Physiological pacing reduces the risk of heart failure. HBP enables the preservation or restoration of electromechanical synchrony, which makes this method particularly interesting for patients with systolic heart failure and congenital heart disease (CHD)[10]. There are numerous studies[6-9] that suggest that pacing-induced cardiomyopathy (PICM) can be reversed by selective or nonselective his-bundle stimulation in the adult patient population, but little is known about the use of this type of therapy in CHD. We learn how the incidence of PICM can be underestimated from studies such as Khurshid et al[11]. A retrospective study[11] of 257 patients meeting the criteria of the study with a pacemaker, normal left ventricular ejection fraction (LVEF) at baseline, and a repeat ECHO ≥1 year after implantation. The PICM was defined as a ≥10% decrease in LVEF, resulting in a <50%. 50 patients (19.5%) developed PICM, with a decrease in mean LVEF from 62.1% to 36.2% over a mean follow-up of 3.3 years. The risk of PICM started below the commonly accepted threshold of 40%. In the aforementioned study and others, similar patients with alternative causes of cardiomyopathy, such as CHD, were excluded. In the literature, we have case reports[12] in the group of pediatric patients and patients with tetralogy of Fallot. They show the possibility of reducing PICM in this group of patients. Due to

the young age, the patient will have to go through a few stimulator replacements. It is also likely that the electrodes may be exchanged. However, the parameters obtained during the implementation (low threshold of stimulation) provide a projected lifespan.

Additionally, His-bundle pacing seems to have more benefits than biventricular pacing. Cardiac resynchronization therapy (CRT) in patients with symptomatic heart failure and left bundle branch block (LBBB) can be achieved with His-bundle pacing by correcting the bundle branch block (His-CRT). According to a Danish study[13] published in 2021 comparing cardiac resynchronization therapy by His bundle pacing (His-CRT) and biventricular pacing (BiV-CRT), LVEF was significantly higher after 6 months (48±8% *vs*. 42±8), and the systolic end volume was lower (65±22 ml *vs*. 83±27 ml) in patients with his bundle pacing compared with patients with biventricular pacing. Pacing thresholds were higher for His-CRT compared with BiV-CRT both at implantation (1.8±1.2 V *vs*. 1.2±0.8 V) and at 6-month follow-up (2.3±1.4 V *vs*. 1.4±0.5 V).

After the implantation, the patient's heart rate increased to 70 beats/minute. The 1-year follow-up observation of the patient showed much better physical condition. The pacing was over 90%, and the LVEF was stable (60%). The patient is still under observation.

Conclusions

Holt-Oram syndrome is a rare disease, and it usually requires the implantation of a pacemaker, because of cardiac conduction disturbances. HBP is a new type of physiological pacing, which can avoid heart failure. This makes it especially attractive to young people. In the future, it may become a mainstream approach for patients undergoing cardiac electronic device implants. Due to the rare occurrence of the HOS, we do not have the management guidelines or any randomized studies. Further research is needed in order to optimize this kind of stimulation to enhance the prognosis of patients with HOS.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Informed Consent
The patient signed the informed consent form.

Ethics Approval
The ethical approval was not required. In any case, the Helsinki guidelines were followed.

Authors' Contribution
Conception and design: Aneta Skwarek-Dziekanowska. Acquisition of data: Aneta Skwarek-Dziekanowska, Agnieszka Wójtowicz-Ściślak. Analysis and interpretation of data: Aneta Skwarek-Dziekanowska. Drafting the article: Aneta Skwarek-Dziekanowska, Agnieszka Wójtowicz-Ściślak. Supervision: Grzegorz Sobieszek. Validation and final approval: all authors.

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