World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Changes in hemodynamic parameters and atrial fibrillation risk in patients after permanent pacemaker implantation

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World Journal of Advanced Research and Reviews, 2024, 22(01), 901–905

Publication history: Received on 18 February 2024; revised on 11 April 2024; accepted on 13 April 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.1.1171

Abstract

Data on the development of left ventricular dysfunction after permanent pacemaker implantation are available. According to data from the DAVID (The Dual Chamber and VVI Implantable Defibrillator) study, it was shown that DDDR-paced patients had significantly more fatal events and HF deterioration cases requiring hospitalization. Similar were the results of the MOde Selection Trial (MOST), which poses serious questions to the cardiology community. For that reason it is important to understand how PPM implantation changes the hemodynamic parameters of the heart and what consequences this may have. On the one hand, asynchronous contraction of the paced heart and increase in AF risk with advancing age require active screening of asymptomatic paroxysms of tachyarrhythmias to promptly adjust therapy. On the other hand, minimizing the rate of ventricular pacing through proper programming of the devices should not be overlooked. Recently, various biomarkers have been validated to select high-risk patients in which the therapeutic strategy can be modulated on time.

Keywords: Apical Pacing; Left Ventricle Dysfunction; Heart Failure; Asynchrony contraction

1. Introduction

In the second half of the 20th century, technological advances in the field of cardiology and cardiac pacing led to an increase in the number of patients with permanent pacemakers (PPM) to overcome existing rhythm-conduction pathologies [1]. This led to an increase in the duration and quality of life of affected patients [2].

In addition to the definite benefits of overcoming the conduction disturbance with PPM, indisputable evidence has been accumulated in recent decades for the negative consequences of apical right ventricular stimulation [3]. Abnormal ventricular activation by apical right ventricular stimulation leads to asynchronous contraction, reduced efficiency of LV pumping function, and LV remodelling. This raises the question of how PPM implantation changes the hemodynamic parameters of the heart and what consequences this may have.

2. Exposition

According to data from the DAVID (The Dual Chamber and VVI Implantable Defibrillator) study [4], it was shown that DDDR-paced patients had significantly more fatal events and HF deterioration cases requiring hospitalization. Similar were the results of the MOde Selection Trial (MOST), which poses serious questions to the cardiology community [5]. This was a six-year randomized prospective study, comparing sick sinus syndrome (SSS) patients and implanted single or dual-chamber pacemakers. The study tested the theory that ventricular asynchrony induced by apical right ventricular pacing leads to increased hospitalizations for decompensated HF and atrial fibrillation. The results showed that greater than 40% DDDR ventricular pacing was associated with a 2.6-fold increase in HF hospitalization risk

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compared to the group with less than 40% ventricular pacing. Data analysis also showed an increase in AF risk with an increasing rate of ventricular pacing in both DDDR and VVIR device groups. AF increased proportionally with increase in DDDR ventricular pacing percentage. These results require an active search for a way to overcome and minimize the negative consequences on cardiac function in PPM patients.

Data from another study suggested that apical right ventricular pacing led to an increase in left ventricular end-diastolic pressure, which led to an increase in left atrial pressure to ensure adequate diastolic filling [6]. This was followed by an increase in left atrial myocardial stress, structural remodelling, dilatation, and fibrosis, becoming in turn a substrate for AF onset. The relationship between AF and left ventricular apical stimulation was also demonstrated in the SAVE PACe study [3]. Persistent AF was found in 12.7% of patients with a conventional dual-chamber pacemaker and 7.9% in the LV pacing minimization algorithm group (P = 0.004). HF mortality and hospitalizations were comparable in both groups. Also, conduction restoration of the native conduction system was followed by reverse remodelling and AF recurrence reduction [7]. These data were confirmed by another study conducted in patients after PPM implantation. In it, an increase in LA volume was found for 6 months after implantation, and this was also associated with significant increases in NT proBNP serum levels [8].

It is important to note that myocardial remodelling is involved in the pathogenesis of both HF and AF [9]. In both diseases, there is an increased filling pressure of the cardiac cavities, corresponding with increased stress and increased fibrous deposition in the interstitium of the cardiac muscle [10]. This suggests the presence of similar pathogenetic mechanisms developing in the myocardium after sustained apical right ventricular stimulation. Over the years, quite a bit of data has been accumulated suggesting involvement of perfusion changes, abnormal humoral, cellular and molecular response in the heart muscle [11, 12]. These data provide the basis to search for the mechanisms influencing cardiac remodelling in PPM patients and how these changes affect myocardial function and structure.

In daily practice, pump parameters of the myocardium are evaluated with echocardiography, on the one hand, a widely available method, and on the other hand, not related to patient radiation exposure. Several studies point to the negative impact of left ventricular dysfunction on quality of life [13]. On the other hand, the increased filling pressure of the LV leads to an increase in LA volume [14]. LAVI is an independent predictor of AF, stroke, heart failure, and cardiovascular death [15]. Also, it is an important marker to assess LV diastolic dysfunction and correlated significantly with overall cardiovascular outcome and functional capacity in HF patients [16]. The left atrium is extremely sensitive to volume and pressure loading as a result of increased left ventricular filling pressure [17]. Also, disruption of LA function led to remodelling of the pulmonary vessels, as well as to a decrease in their compliance, which led to right ventricular pressure load and pulmonary hypertension. For these reasons, early LV dysfunction detection played an important role in the evaluation of many heart diseases [18] and LV asynchrony, which led to the development of left ventricular dysfunction and increased filling pressure [19]. Non-physiological activation of the myocardium caused asynchrony in the systole of the chamber, disrupted its relaxation, reduced the degree of longitudinal shortening and circular twisting [20, 21]. This led to structural remodelling of the atrial myocardium, increased collagen deposition in the interstitium, electrical inhomogeneity, which was a substrate for AF occurrence [22]. Additionally, right ventricular apical pacing induced left ventricular diastolic dysfunction and increased left atrial afterload [23]. This process increased atrial pressure and contributed to left atrial enlargement as early as the postoperative period, as shown by the results of the study by Xie et al.

Yoncheva and Negreva obtained similar results. They investigated the process of LV remodelling after PPM implantation by following echocardiographic parameters in 45 patients and connective tissue growth factor (CTGF) levels [24]. CTGF is a matrix protein that is expressed in cardiac fibroblasts and cardiomyocytes. It is involved in the regulation of many processes such as cell adhesion, structural remodelling and production of matrix proteins in the ECM, and is a proven biomarker for activated collagen synthesis. The results showed a significant increase in serum CTGF levels as early as 12 weeks after PPM implantation, and this increase was maintained until the end of the 24-week follow-up period. This was also accompanied by a statistically significant increase in LA volume, which occurred extremely early, as early as 6 weeks post-implantation and continued to increase toward the end of the follow-up period.

Left atrial load as a result of provoked asynchronous ventricular contraction in PPM patients was suggested as the main reason for the increased risk of AF paroxysms in this group of patients [25]. On the other hand, there are data on changes in various biomarkers, which were also associated with an increased risk of tachyarrhythmia in PPM patients. In a study of adult PPM patients on the occasion of CVS, it was found that increased values of red blood cell distribution width (RDW) and γ-glutamyl transferase (γGT) in the serum were associated with an increased risk of AF [26].

Data from an experimental animal study showed an increase in RDW, as well as oxidative stress markers superoxide dismutase (SOD) and malondialdehyde (MDA) in the rapid atrial pacing group [27]. The presence of oxidative stress

and inflammation resulted in reduced erythrocyte survival, which was followed by an increase in RBC [28]. On the other hand, the rise of oxidative stress markers was associated with an increased AF risk, and sinus rhythm (SR) restoration was followed by the normalization of these markers [29]. Similar results were also shown in a study in paroxysmal AF patients, where oxidative stress developed in the first hours of the clinical manifestation of the disease (between the second and the twenty-fourth hour), as a result of enhanced pro-oxidant processes and reduced non-enzymatic and enzymatic antioxidant mechanisms [30]. These changes were also reversed after SR restoration for 28 days.

From what has been said so far, it becomes clear that the presence of oxidative stress is associated with an increased risk of AF. On the other hand, there are data that in PPM patients, asynchrony caused by apical right ventricular stimulation was associated with provoking a proinflammatory and prooxidative state. According to data from a study by Marketou et al. after 15 days of DDDR pacing, a significant increase in interleukin-6 (IL-6) and lipid peroxides (LP) serum levels was observed, while in AAI mode these values were significantly lower [31].

As it became clear, the presence of oxidative stress in patients after PPM implantation on the one hand, and the provoked asynchronous contraction, followed by diastolic dysfunction and LV dilatation on the other, synergistically led to an increase in AF risk in PPM patients. AF is the most common arrhythmia and is associated with an increased risk of stroke and systemic embolism [32]. This necessitates the timely detection of AF paroxysms to start adequate treatment to minimize the risk of complications.

Estimating the burden of AF paroxysms is very often difficult [33]. The unclear relationship between symptomatology and the actual manifestation of the arrhythmia, as well as variations in the frequency and duration of episodes, make it difficult to judge whether a change in the patient's therapeutic plan is necessary. Data from implanted dual-chamber pacemakers can be used to detect AF paroxysms and estimate tachyarrhythmia burden. The results of such a study showed the presence of AF paroxysms in 68% of patients with an implanted dual-chamber pacemaker [34]. The researchers explained the high percentage by the fact that all episodes of atrial fibrillation lasting more than 6 min were included in the analysis, and the group of patients had concomitant cardiac pathology and an average age of more than 70 years. Also, all patients had their intracardiac electrogram (EGM) profile storage activated and a physician confirmed each reported episode. This avoided false positive episodes when the devices misinterpreted artifacts and other types of tachycardias, different from AF.

Similar results were reported by a study by Witkowski et al., with asymptomatic episodes occurring 13 times more often than symptomatic episodes [35]. They followed 50 patients with dual-chamber pacemakers, finding that asymptomatic AF episodes were more common in men and were associated with higher rates of atrial and ventricular pacing.

3. Conclusion

The increase in average life expectancy and the presence of concomitant pathologies in aging individuals leads to the implantation of more and more pacemakers. On the one hand, asynchronous contraction of the paced heart and increase in AF risk with advancing age require active screening of asymptomatic paroxysms of tachyarrhythmias to promptly adjust therapy. On the other hand, minimizing the rate of ventricular pacing through proper programming of the devices should not be overlooked. Recently, various biomarkers have been validated to select high-risk patients in which the therapeutic strategy can be modulated on time.

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