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Randomized placebo controlled blinded study to assess valsartan efficacy in preventing left ventricle remodeling in patients with dual chamber pacemaker — Rationale and design of the trial

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ABSTRACT

Background: Dual chamber pacing is known to have detrimental effect on cardiac performance and heart failure occurring eventually is associated with increased mortality. Experimental studies of pacing in dogs have shown contractile dyssynchrony leading to diffuse alterations in extracellular matrix. In parallel, studies on experimental ischemia/reperfusion injury have shown efficacy of valsartan to inhibit activity of matrix metalloproteinase-9, to increase the activity of tissue inhibitor of matrix metalloproteinase-3 and preserve global contractility and left ventricle ejection fraction.
Purpose: To present rationale and design of randomized blinded trial aimed to assess whether 12 month long administration of valsartan will prevent left ventricle remodeling in patients with preserved left ventricle ejection fraction (LVEF ≥ 40%) and first implantation of dual chamber pacemaker.
Methods: A total of 100 eligible patients will be randomized into three parallel arms: placebo, valsartan 80 mg/daily and valsartan 160 mg/daily added to previously used drugs. The primary endpoint will be assessment of valsartan efficacy to prevent left ventricle remodeling during 12 month follow-up. We assess patients' functional capacity, blood plasma activity of matrix metalloproteinases and their tissue inhibitors, NT-proBNP, tumor necrosis factor alpha, and Troponin T. Left ventricle function and remodeling is assessed echocardiographically: M-mode, B-mode, tissue Doppler imaging.
Conclusion: If valsartan proves effective, it will be an attractive measure to improve long term prognosis in aging population and increasing number of pacemaker recipients. ClinicalTrials.org (NCT01805804).

1. Introduction

Dual chamber pacing is known to have detrimental effect on cardiac performance in the long run [1,2] and heart failure occurring eventually is associated with increased mortality [3].

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Right ventricle pacing results in an array of clinical, echocardiographic and laboratory changes. There are reports on deterioration of physical capacity [3,4], echocardiographic evidence of diastolic dysfunction, decreased systolic function, and significant mechanical dyssynchrony of left ventricle [3–7].

Paper by Hoffmann et al. [8] lends the evidence of detrimental effect of pacing in coronary artery disease patients on left ventricle diastolic function. Though, it is highly probable that the diastolic dysfunction, observed in this study, can be mainly attributed to rapid pacing-induced ischemia, and not to direct effect of pacing. Nevertheless, two animal experiments provide probable pathophysiologic explanation for the immediate relation of pacing and left ventricle dysfunction [9,10]. Garcia et al. [9] used piezoelectric sensors, that were located at pacing site and remote site, to assess myocardial contractility. Pacing caused significantly abnormal motion at the pacing site, and this pacing-induced dyssynchrony of left ventricle contraction was sufficient to stimulate matrix metalloproteinase-9 (MMP-9) activity. Lin et al. [10] have found increased interstitial fibrosis and fragmentation of myofibrils in the left ventricle lateral wall in the right ventricle apical pacing group. Moreover there was increased activation of MMP-2, MMP-9, tissue inhibitor of matrix metalloproteinase TIMP-1 and TIMP-3 in the same area.

There is an extensive body of literature that highlights the positive impact of the inhibition of the renin–angiotensin system on suppressing left ventricular remodeling in patients who suffered myocardial infarction or heart failure [11]. Studies on experimental ischemia/reperfusion injury have shown the efficacy of valsartan to inhibit activity of MMP-9, to increase the activity of TIMP-3 and to prevent left ventricle remodeling [12–14].

To date, no human study has prospectively examined the effects of proven heart failure drug, that is capable to prevent post-infarction remodeling, in prevention of pacing-induced left ventricle remodeling and symptomatic heart failure.

Given this background, we designed this study to assess whether 12 month long administration of valsartan will prevent left ventricular remodeling in patients with first implantation of dual chamber pacemaker and preserved systolic function of left ventricle.

2. Methods/design

2.1. Overview

This study is parallel 3-arm, randomized, placebo controlled, blinded clinical trial comparing two doses of valsartan for the prevention of left ventricle remodeling in patients with second and third degree atrioventricular block, scheduled for first time dual chamber pacemaker implantation. The study will be carried out in two Medical University of Silesia cardiology clinics in Zabrze, serving as referral centers — II Department of Cardiology and Department of Cardiology and Congenital Heart Diseases and Electrotherapy. Ethical approval has been secured from Medical University of Silesia Institutional Review Board (KNW/0022/KB1/147/12). Medical University of Silesia covers the patients' insurance throughout the study, but will not reimburse any expenses associated with study participation. Study is registered at Clinical Trials NCT01805804. Patients will be screened for eligibility criteria (Table 1) within 24 h from implantation. One hundred participants will be randomized in a 1:1:1 ratio to placebo, valsartan 80 mg/24 h, or valsartan 160 mg/24 h by drawing a consecutively numbered envelope. The consecutive envelopes contain pre-specified allocation generated on a basis of random digit generator. The recommended pacing site is right ventricle septum.

Table 1
Eligibility criteria.

Inclusion criteria
1. Written (signed) informed consent for a participation in the study
2. Age ≥ 18 years
3. Qualification to first implantation of dual chamber pacemaker due to II or III degree atrioventricular block
4. Left ventricle ejection fraction (EF) ≥ 40%
Exclusion criteria
1. Severe valvular heart disease
2. Ischemic heart disease requiring further revascularization treatment
3. Symptomatic hypotonia
4. Orthostatic disorders
5. Pregnancy, lactation, fertility (women)
6. Previous angiotensin II receptor blockers (ARBs) use
7. Known valsartan intolerance (hypersensitivity)
8. Severe hepatic disease
9. Severe renal disease, including renal artery stenosis
10. Hyperaldosteronism
11. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs)
12. Chronic use of lithium
13. Patient's reluctance to follow the protocol and to attend the control visits
14. Any severe disease decreasing life expectancy under 12 months
15. Participation in other clinical trial within 30 days before enrollment
16. Any condition increasing patient's risk

Study drugs (placebo, valsartan 80 mg, valsartan 160 mg), prepared and packed uniformly with unique identifying number are courtesy donated by Polpharma Pharmaceutical Company, Warsaw, Poland. Study staff (except BB, who is responsible for patient randomization, and study coordinator AT) will be blinded to treatment allocation. For the safety reasons, to avoid any unpredicted hypotonia or orthostatic reaction participants will be prescribed one half of a tablet and the dose will be uptitrated to one tablet daily on a visit 2 (2 weeks). Participants will be administered the study drug/placebo for 12 months. Study flow diagram is summarized in Fig. 1.

2.2. Study endpoints and measurements

The primary endpoint of the study is to assess the efficacy of valsartan to prevent left ventricle remodeling evaluated echocardiographically in patients with preserved left ventricle function and first time implantation of dual chamber pacemaker. Following endpoints are considered as secondary:

1. the assessment of correlation between left ventricle impaired diastolic function and its remodeling during dual chamber pacing;
2. the assessment of correlation between the structure and function of left ventricle during chronic pacing and the activity of matrix metalloproteinase, tissue inhibitor of matrix metalloproteinase, tumor necrosis factor alpha, and Troponin T;
3. the assessment of correlation between the changes of the echocardiographic parameters describing structure and function of left ventricle and the clinical indices of heart