Original Paper

Association between Dual-Chamber (DDD) Pacemakers and Plasma Level of Soluble Suppression of Tumorigenicity-2 (Sst2). A Case-Control Study in A Sample of Iraqi Patients

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Abstract

Background: Although dual-chamber pacemakers are more physiological, they can negatively impact cardiac function due to the dyssynchrony caused by right ventricular pacing, affecting left ventricular function.
Soluble suppression of tumorigenicity-2 (sST2) is an isoform for the ST2, and the second isoform is called transmembrane ST2 (ST2L). After a cardiac insult, IL-33 interacts with ST2L to counteract the adverse effects of that insult. sST2 acts as a decoy receptor for IL-33 competing with ST2L preventing it from binding to IL-33, limiting cardioprotective measures of ST2L/IL33.
Objective: This study aimed to investigate the effect of a dual-chamber pacemaker on sST2 levels in patients with preserved ejection fraction.
Methods: a case-control study with 52 dual-chamber pacemakers patients, 68% were males, together with 52 controls. Participants were divided into patients and control groups. Exclusion criteria were heart failure, recent acute coronary syndrome, uncontrolled hypertension, left ventricular hypertrophy, uncontrolled diabetes, pulmonary hypertension, right bundle branch block, and atrial fibrillation. sST2 was measured alongside ECG and echo to calculate the EF%, CO, SV, LVPEP, and RVPEP.
Results: sST2 was higher in patients (p = 0.0001), 95% CI [18.06, 25.22]. Patients had lower values of EF%, CO, and HR (p = 0.0001). The ΔVPEP was higher in patients (p = 0.0001), 95% CI [18.06, 25.22]. Both, SV and RVPEP showed no significant differences.
Conclusion: dual-chamber pacemakers cause elevated sST2 levels due to electromechanical dyssynchrony and minor fibrosis.
Keywords: sST2, Dual-chamber pacemaker, Dyssynchrony, Echocardiography, Remodelling.

Introduction

Dual-chamber (DDD) pacemakers are indicated for a variety of clinical situations. Recently, the aim for a more physiological pacing option was behind the increased use of such a pacing modality [(1)]. They involve two electrodes, one inserted at the right atrium and the other at the right ventricle [(2)]. The right ventricular apex (RVA) is the most convenient lead insertion site since it provides easy accessibility besides the high safety and stability profiles of such a pacing site [(3)]. As with any other pacemaker, dual-chamber pacemakers were associated with various adverse effects on cardiovascular function, including interventricular dyssynchrony. RVA results in an abnormal left ventricular activation inducing a widened QRS-complex and dyssynchronous left ventricular contraction [(4)]. With time, RVA pacing may progress into deleterious cardiac remodeling, cardiac fibrosis, and myocardial cell death [(5)].

In 1989, a new biomarker was introduced that is known as suppression of tumorigenicity-2 (ST2) which is an interleukin (IL-1) receptor family member that has a role in many autoimmune and inflammatory diseases [(6)]. The

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soluble suppression of tumorigenicity 2 (sST2) is one of the two isoforms for the ST2, the other being transmembrane ST2 (ST2L) [7].

Interleukin-33 (IL-33), on the other hand, is a cytokine molecule produced by a variety of cells like macrophages, dendritic cells, fibroblasts, endothelial and epithelial cells when they are being subjected to damage or insult [8, 9]. This interleukin acts as a ligand for ST2L; when they bind together, they form what is known as an ST2L/ IL-33 axis, which performs various protective actions protective to the heart by counteracting the fibrotic and hypertrophic actions of the insulting stimuli [10]. sST2, in turn, acts as a decoy receptor for IL-33, preventing it from binding to the ST2L isoform, thus sequestering it and preventing the protective effects of the ST2L/ IL-33 axis and culminating in fibrosis and hypertrophy. Cardiac fibroblasts, when enduring mechanical overloading, produce a marked level of sST2 which reflects ventricular remodeling and cardiac fibrosis. When vessels are engorged, vascular endothelial cells also express high levels of sST2 cytokine [11].

This study aims to determine if implanting a permanent dual-chamber pacemaker will impact the blood levels of the sST2 biomarker since the information connecting dual-pacemaker therapy with sST2 level is lacking or sparse.

Subjects and methods

Study population

This case-control study was designed and conducted at Karbala center for catheterization and cardiac surgery at Al-Hussain teaching center/ Karbala/ Iraq from the 15th of June 2018 to the 15th of November 2019. After obtaining informed consent from all participants and the approval of the medical research ethical committee at Karbala directorate of health/Iraq, A total of 52 patients with dual-chamber pacemakers were recruited for the study alongside 52 age and sex-matched, apparently healthy volunteers as controls.

Inclusion criteria: being an adult with a permanently implanted DDD pacemaker, a post-implantation period of not less than 3 months, and no recent change in his/her cardiovascular medication. Patients had right ventricle pacing events of not less than 40%, and their ventricular lead inserted in the right apical position as confirmed by a chest X-ray.

Exclusion criteria: the presence of symptoms of frank heart failure or depressed LV function (LVEF% less than 45 % as evidenced by transthoracic echocardiographic examination), recent acute coronary syndrome (ACS), uncontrolled hypertension, uncontrolled d9iabetes, left ventricular hypertrophy (LVH) evidenced by ECG based on Sokolow-Lyon criteria [12] or evidenced by transthoracic echocardiography (TTE), moderate to severe valvular disease, pulmonary hypertension, right bundle branch block (RBBB), and atrial fibrillation.

After obtaining a full medical history and thorough physical examination, an ECG was obtained from each participant (WELCH ALLYN CP 50 ECG unit/ USA). Checking for arrhythmias, especially atrial fibrillation, calculation QRS duration, measuring intervals (PR, QT, and RR), and examining the segments (PR and ST). Then, a TTE examination was performed using (Vivid 7, GE Medical Systems, Horton, Norway). Participants were divided into two groups:

- **Patients group:** included 52 patients with a permanent dual-chamber pacemaker. Their age ranged from 47 to 63 years (47.98 ± 5.9). 38 (68 %) of them were males.
- **Control group:** involved 52 volunteers with an age range of 48 to 62 years (49.81 ± 6.6). This group comprised 38 (68 %) males as well. The volunteers were members of the staff and their relatives alongside the relatives and acquaintances of the patients themselves.

Plasma level of sST2 estimation:

The assay was performed according to the manufacturer`s instructions (Elabscience Biotechnology Co., Ltd., Houston, Texas, USA). In brief, 5 ml of venous blood was drawn in EDTA tubes, of which diluted aliquots together with 100 µl of standard added into the well-containing plate. In the presence of Horseradish peroxidase (HRP) enzyme, sST2 yielded a colored compound the intensity of

which was read using spectrophotometer provided by (PD-3000 UV, APEL Co., Ltd. Japan), at a wavelength of 450 ± 2 nm, and extrapolated against a standard curve to Figure out the concentration of sST2.

Transthoracic echocardiography (TTE):

Calculating the stroke volume (SV):

The SV was calculated using the Doppler velocity time integral (VTI) method, which was found to correlate with the results of the thermodilution method in patients without significant left-sided valvular regurgitation [13, 14]. While in systole, the diameter of the left ventricular outflow tract (LVOT) was obtained using the left parasternal long-axis view (PLAX). Since the velocity time integral (VTI) of the LVOT reflects blood velocity during systole, the next step was calculating the VTI by obtaining an apical long-axis or 5 chamber view depending on which of the views is handier. The echocardiographic machine was then switched to pulsed-wave Doppler (PWD) to calculate the VTI. The SV was obtained after multiplying LVOT diameter by the VTI by using the built-in offline software of the echo machine. By echocardiographic estimation, a value of 60-100 ml/beat was regarded as the normal value for the stroke volume [15].

Calculating the cardiac output (CO):

For cardiac output calculation, the same Doppler VTI method was used, and its calculation was conducted after recording the heart rate since the cardiac output is the product of multiplying the heart rate by stroke volume. A reference range of cardiac output was set at 3.5-8.2 l/min [16].

Calculating the ejection fraction (EF %):

The ejection fraction was calculated using the modified Simpson`s method (biplane method of discs) [17]. Based on the American Society of Echocardiography (ASE) recommendations, the endocardial borders were traced to the end of diastole and systole. The tracing was conducted in the apical four-chamber view and then in the two-chamber view. After completion of trace out, the left ventricle was divided by the built-in automated feature of the device into 20 discs with perpendicular orientation concerning the long axis of the left ventricle. Each of these segment`s volumes was calculated as being a cylinder, and all 20 volumes were added up.

Assessment of inter-ventricular dyssynchrony:

Using PWD and while continuous ECG recording is enabled, a parasternal short-axis view was used to visualize the outflow tract of the right ventricle (RVOT). An apical 5-chambers view was used for the LVOT. At each outflow tract, time-lapse was calculated between the start of ventricular depolarization designated as a QRS-complex in the ECG trace out and the commencement of blood flow out of the ventricles as designated by the negative wave at the PWD as shown in Figure-1. The difference between the measurements is recorded as an index of interventricular dyssynchrony. Healthy individuals show a difference of 20 ±10 msec; a difference of >40 msec is considered evidence of significant interventricular dyssynchrony [18].

Statistical analysis

Statistical analyses were performed using EXCEL 2016 and SPSS® (Statistical Package for the Social Sciences) package (version 25.0, SPSS Inc., Chicago, IL, USA). Results are reported as means ± SD and 95% confidence interval (CI). A *p*-value of ≤ 0.05 was considered to indicate statistical significance. Comparisons were made using paired t-test.

Results

Table-1 shows the participant`s baseline characteristics. There was no statistically significant difference between groups concerning age (*P*= 0.27).

The results of this study, as depicted in both Table (1) and Figure (2), showed that there was no statistically significant difference between both groups concerning age, where it was (47.98 ± 5.9) years for the patients and (49.81 ± 6.6) years for the controls (p = 0.139), 95% CI [24.21, 59.94].

Table 1. Results of different parameters for both groups with statistical significance. All data are expressed as mean and standard deviation with a *p*-value level of significance < 0.05.

Studied parameter	Patients (n=52)	Controls (n=52)	*P*-value
Age (years)	47.98 ± 5.9	49.81 ± 6.6	0.139
Plasma sST2 level (pg/dl)	24.3 ± 8.7	19.32 ± 4.54	< 0.001
EF(%)	46.92 ± 1.47	50.36 ± 2.59	< 0.001
S.V. (ml)	58.53 ± 5.86	63.72 ± 5.39	0.339
C. O. (L/Min)	3.55 ± 0.32	4.85 ± 0.46	< 0.001
HR (beat/Min)	68.72 ± 5.39	79.98 ± 5.72	< 0.001
LVPEP (milliseconds)	143.1 ± 10.21	120.16 ± 5.76	< 0.001
RVPEP (milliseconds)	92.35 ± 2.29	90.24 ± 3.39	0.619
Δ VPEP (milliseconds)	55.8 ± 10.91	34.16 ± 6.58	< 0.001
QRS duration (milliseconds)	138.4 ± 65.40	85.98 ± 15.50	< 0.001

sST2= soluble suppression of tumorigenicity, EF%= ejection fraction, SV =stroke volume, CO = cardiac output, HR= heart rate, LVPEP= left ventricular pre-ejection period, RVPEP= right ventricular pre-ejection period, ΔVPEP = difference in PEP between the left and the right ventricles.

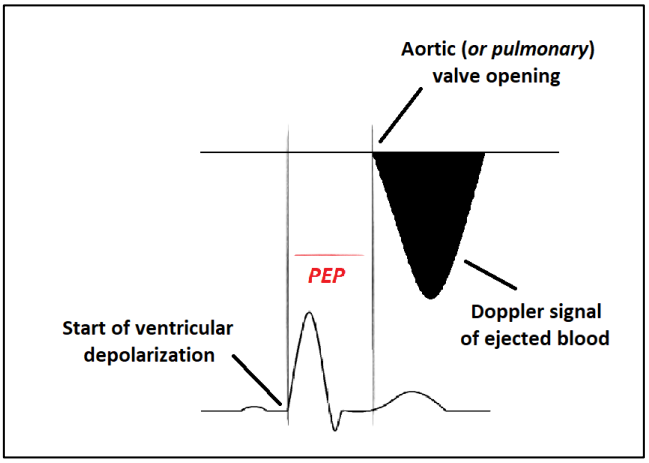

Figure 1. The echocardiographic basis for calculating the pre-ejection period (PEP) represents the time taken for the ventricle to eject blood after the onset of depolarization.

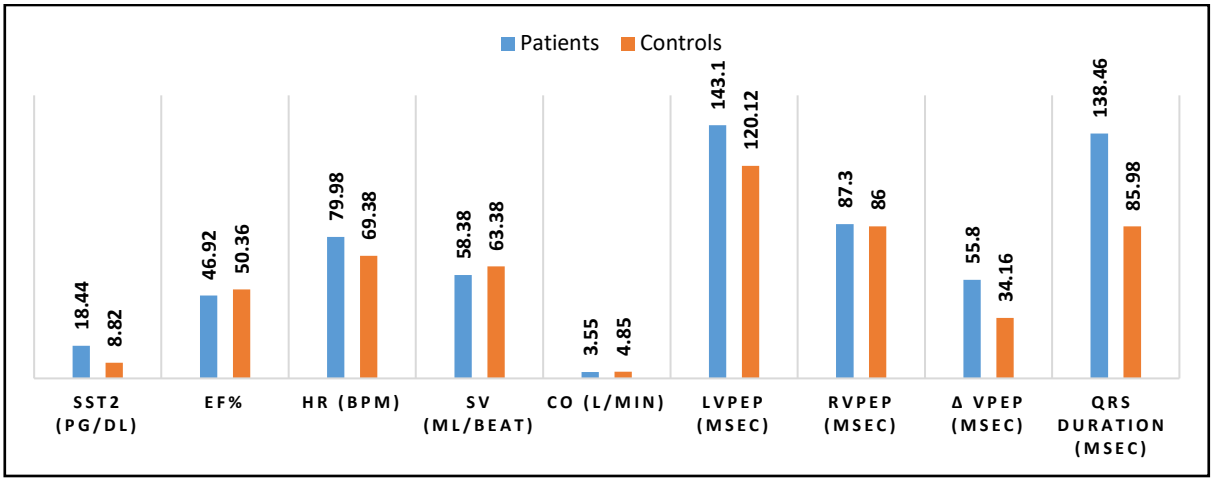

Figure 1. Comparison of different parameters between patients and controls. Values are reported as means. sST2= soluble suppression of tumorigenicity, EF%= ejection fraction, SV =stroke volume, CO = cardiac output, HR= heart rate, PEP= pre-ejection period.

Also, the results showed that patients had a significantly higher plasma level of sST2 (24.3 ± 8.7) vs (19.32 ± 4.54) pg/dl for the controls ($p < 0.001$), 95% CI [18.06, 25.22]. Additionally, they had generally lower values of left ventricular systolic function indices (i.e. SV, EF%, and CO) ($p < 0.001$) where the results showed a statistically significant difference in the EF% between patients (46.92 ± 1.47) and controls (50.36 ± 2.59) ($p < 0.001$), 95% CI [-4.27, -2.6]. Likewise, the CO was significantly lower in the patients group when compared to the control group (3.55 ± 0.32 vs 4.85 ± 0.46) l/ min respectively ($p < 0.001$), 95% CI [-0.43, 0.17]. But the SV didn't show statistically significant variation between both groups where it was (58.53 ± 5.86) ml/ beat for the patients and (63.72 ± 5.39) ml/ beat for the controls ($p = 0.339$), 95% CI [-21.17, 10.49].

This study also revealed that for RVPEP, both groups had no statistically significant difference in their mean values of RVPEP, which were (92.35 ± 2.29) and (90.24 ± 3.39) msec for the patients and the control groups respectively ($p = 0.619$), 95% CI [0.99,3.22]. On the other hand, the LVPEP showed a highly significant difference between both groups where it was (143.1 ± 10.21) msec in the patients' group and (120.16 ± 5.76) msec in the controls ($p < 0.001$), 95% CI [19.89, 26.3]. Moreover, there was a statistically significant difference in the ΔVPEP between both groups (55.8 ± 10.91 vs. 34.16 ± 6.58) msec for the patients and the control groups, respectively ($p < 0.001$), 95% CI [18.06, 25.22]. The QRS duration was higher in patients group compared to that of the controls (138.4 ± 65.4 vs 85.98 ± 15.5) msec respectively, ($p < 0.001$), 95% CI, [34.15,70.69].

Discussion

Patients with DDD-pacemakers showed a decline in the LV efficiency as evidenced by the relatively lower values of their CO and EF%, yet their SV values were comparable to those of the controls, as shown in Table (1). Therefore, having the same values of SV and yet having lower values for the CO and EF% may in part be explained by the fact that pacemaker patients mostly have their pacemaker programmed with the lowest possible and feasible heart rate to increase battery life. This claim is supported by the relatively higher heart rate values (HR) for the control group, as shown in Table(1). These results are consistent with those of other studies that concluded an overall negative impact of DDD-pacemakers on the LV function [19-21]. From the physiological point of view, this type of pacemaker, especially when the rate-response feature is activated, is regarded as a good choice when cardiac timing and output are concerned [21]. However, some degree of dyssynchrony (atrioventricular, inter-ventricular, and intra-ventricular) seems ineviTable even with this pacing modality [22]. Due to the atrioventricular dyssynchrony, there would be an out-of-time paced atrial kick that leads to blood being backfired into the venous side of circulation and resulting in venous congestion, together with lost atrial contribution, will attenuate cardiac output [23]. Some researchers reported that the right apical pacing would produce a situation mimicking LBBB "iatrogenic LBBB," resulting in a mistimed contraction of the LV free wall and the opposite interventricular septum. Thus, the left ventricular output is reduced [22, 24]. This study revealed that right ventricular pre-ejection time (RVPET) for the control group was (90.24 ± 13) msec; this was consistent with the reported values of several other studies [25]. The study reported evidence of such inter-ventricular dyssynchrony by finding that the difference between the LVPEP and the RVPEP was greater than the reference point of 40 milliseconds.

Although both group members showed within the reference range value of plasma sST2 level, those of the patient's group had a significantly higher level of that marker when compared to controls, as shown in Table-1. Radzik *et al.* had found similar results and even higher biomarker values when examined patients with DDD pacemakers [26]. This relatively higher sST2 level may be explained by the fact that permanent pacemakers import some fibrotic effect on the myocardium.

Several studies have shown that implanting a permanent pacemaker will cause fibrotic changes in the myocardium, especially at the leads contact sites [27-29]. According to Mase *et al.*, after a thorough postmortem examination of pacemaker patients, found that these fibrotic changes were in some cases more pronounced than they resulted in an extensive fibrous sheath formation around the tip of the leads, especially when they were implanted at the right ventricular apex [27].

sST2 is a good marker for left ventricular remodeling, and since permanent pacemakers will eventually result in remodeling, it would logically increase plasma levels of sST2.

The asynchronous left ventricular depolarization caused by the right ventricular apical pacing will eventually result in LV remodeling, which may ensue into LV failure [5, 30]. Several studies reported increasing morbidity and mortality secondary to heart failure in the adult pacemaker population, with such correlation being increased with the increase in the ventricular pacing events [31, 32]. It is well documented that pacemaker therapy is associated with LV remodeling in the long run, mainly through the disruption of atrioventricular, inter-ventricular, and intra-ventricular dyssynchrony [33, 34].

This study revealed that DDD-pacemaker patients showed evidence of LV dyssynchrony as indicated by the increased time difference in the pre-ejection periods (PEP) between the right and left ventricles. Also, the overall depressed LV function in this patient group may, in one way or another, be attributed to the dyssynchronous LV itself. SST2 levels correlate with hypertension mainly due to left ventricular remodeling after left ventricular hypertrophy [35, 36]. Nevertheless, the relatively higher plasma level of sST2 in the patients' group in the light of this study could not be explained by hypertension since we already excluded those with ventricular hypertrophy, evidenced by ECG or echocardiography. Also, since this study ruled outpatients with a history of myocardial infarction, it is safe to conclude that fibrotic scar after an infarct was responsible for such sST2 higher values.

Conclusions

Dual-chambers pacemakers, probably through their dyssynchrotic effects, which are minor compared to the other pacing modalities but yet are present, can result in cardiac remodeling and minor myocardial wall focal fibrosis apparent by the relatively higher plasma levels sST2. This remodeling may progress in the future into various clinical situations, including heart failure and arrhythmias.

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