

Mechanism of Pacemaker-Induced Left Ventricular Dysfunction: Study Protocol

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Abstract: A permanent pacemaker (PPM) is currently the definitive treatment for patients with a total atrioventricular block (TAVB). The number of pacemaker implantation has been increasing every year. However, PPM implantation increases the risk of developing left ventricular (LV) dysfunction and becoming pacemaker-induced cardiomyopathy (PICM). There has never been a published study on the cellular mechanism of LV dysfunction caused by PPM implantation. The mechanism of pacemaker-induced left ventricular dysfunction (PILVD) study is a multi-center, quasi-experimental, etiognostic study with a time-series design. This etiognostic study aims to investigate the mechanism of cellular level changes in TAVB patients who had PPM implanted. In particular, the difference in serum miR-155 levels and plasma levels of IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 in TAVB patients had LV dysfunction caused by right ventricular septal PPM implantation measured by global longitudinal strain (GLS) obtained from echocardiography. Blood samples and echocardiographic examinations will be performed on patients who satisfied the inclusion criteria prior to pacemaker implantation, one month after, and three months following pacemaker implantation. The ELISA method will be used to assess IL-6, sTNFR-2, MMP-9, ZO-1, and N-Cad from plasma samples. MiR-155 levels in serum will be determined using the reverse-transcriptase polymerase chain reaction (RT-PCR) technique. The main findings are a decrease in serum miR-155 levels and increased plasma IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 levels in TAVB patients who developed LV dysfunction due to right ventricular septal pacemaker implantation measured by GLS at 1 and 3 months.

Keywords: atrioventricular block, cardiac pacemaker, cardiomyopathy, global longitudinal strain, mechanism.

起搏器引起的左心室功能障礙的機制：研究方案

摘要：永久性起搏器目前是完全性房室傳導阻滯患者的最終治療方法。起搏器植入的數量每年都在增加。然而，永久性起搏器植入會增加發生左心室功能障礙和成為起搏器誘發的心肌病的風險。從未發表過關於永久性起搏器植入引起左心室功能障礙的細胞機制的研究。起搏器誘發左心室功能障礙的機制研究是一項多中心、準實驗性、時間序列設計的病因學研

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究。這項病因學研究旨在探討植入永久性起搏器的全房室傳導阻滯患者細胞水平變化的機制。特別是房室傳導阻滯患者存在右心功能不全引起的左心功能不全時，血清微核糖核酸155水平與血漿白細胞介素6、可溶性腫瘤壞死因子受體2、基質金屬蛋白酶9、N鈣粘蛋白和緊密連接蛋白1水平的差異。通過從超聲心動圖獲得的整體縱向應變測量的間隔永久起搏器植入。對符合納入標準的患者在起搏器植入前、1個月後、起搏器植入後3個月進行血樣和超聲心動圖檢查。酶聯免疫吸附測定法將用於評估血漿樣品中的白細胞介素6、可溶性腫瘤壞死因子受體2、基質金屬蛋白酶9、緊密連接蛋白1和N鈣粘蛋白。將使用逆轉錄酶聚合酶鏈式反應技術測定血清中的微核糖核酸155水平。主要發現是在因以下原因而發展為左心室功能障礙的全房室傳導阻滯患者中，血清微核糖核酸155水平降低，血漿白細胞介素6、可溶性腫瘤壞死因子受體2、基質金屬蛋白酶9、N鈣粘蛋白和緊密連接蛋白1水平升高。通過1個月和3個月的全局縱向應變測量右室間隔起搏器植入。

关键词：房室传导阻滞、起搏器、心肌病、整体纵向应变、机制。

1. Introduction

Permanent pacemaker (PPM) is currently the only therapy modality in patients with a total atrioventricular block (TAVB). PPM has also been proven to improve the quality of life of TAVB patients [1]. Unfortunately, the implantation of PPM also has several risks, including tricuspid regurgitation due to wire passing through the tricuspid valve. This condition can cause left ventricular (LV) dysfunction and may progress further to pacemaker-induced cardiomyopathy (PICM) [2]. The prevalence of PICM varies from 9% within one year to 15% within 25 years [3]. Another study concluded a different prevalence of 63.9% within six months [4]. One cohort study found that 40% of patients post PPM implantation had a left ventricular ejection fraction (LVEF) of less than 50% [5]. These high incidences of PICM underline the essentials of understanding in depth the mechanism of pacemaker-induced left ventricular dysfunction (PILVD). Up until now, the mechanism of PILVD at the cellular level remains uncertain [6]. Knowing the mechanism at the most basic level can be the basis in determining the etiology, diagnosis, therapy, and even prognosis of patients with PILVD.

PILVD is associated with Renin-Angiotensin System (RAS) changes, pro-inflammatory factors, proteolytic enzymes, and cell structure. RAS is a neurohormonal aspect that plays a vital role in cardiovascular pathological processes and can be found in the circulation and tissues [7, 8]. Stretching the cardiac wall will increase RAS activation, trigger remodeling, increase the inflammatory response and proteolytic enzymes. These three processes lead to changes in mechanotransduction and mechanosensors,

resulting in LV remodeling and dysfunction [9]. In the RAS system, the miR-155 level is essential in representing AT-1R [10]. Inflammatory factors that are thought to have a role in this process are sTNFR-2 and IL-6 [11, 12]. The increase in the proteolytic enzyme MMP-9 and the activation of the RAS system and the inflammatory response will affect the cell structures; ZO-1 is located in the tight junction, and N-Cad is located in the adherens junction [10, 13, and 14].

PICM can occur even within a year. Therefore, choosing a diagnosis method to detect heart failure as early as possible is crucial [9, 15, and 16]. The change initially occurred during LV dysfunction before the ejection fraction decreased. In determining the incidence of LV dysfunction, cardiac ejection fraction assessment is a common approach. However, global longitudinal strain (GLS) assessment is superior in assessing LV function than cardiac ejection fraction [17, 18].

Left ventricular GLS has shown a more sensitive and objective evaluation than ejection fraction in LV dysfunction [15-17]. GLS value was reported to detect LV dysfunction in patients implanted with PPM as early as one month in the Pacing and Ventricular Dysfunction (PAVD) study. This finding indicates that the process of LV dysfunction has occurred relatively quickly after the insertion of PPM [16]. In another study, 193 stable heart failure patients had changes in GLS during the sixth-month follow-up, and these changes were independently associated with clinical parameters such as patients' heart failure exacerbations [15]. Hence, GLS has an advantage over the ejection fraction in assessing PICM.

A study on the cellular mechanism of LV

dysfunction due to the insertion of PPM has never been published. This etiognostic research aims to examine the mechanism of cellular level changes in TAVB patients undergoing PPM insertion. In particular, the difference in serum value of miR-155, and plasma values of IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 in TAVB who experienced LV dysfunction due to right ventricular septal PPM implantation assessed with GLS.

2. Methods

2.1. Study Design

The mechanism of pacemaker induced LVD study (<https://www.thaiclinicaltrials.org>, identifier TCTR20210321003) is an etiognostic, quasi-experimental study with a time-series design. This study aimed to define the mechanism of PILVD by observing six biomarkers before, one month, and three months after pacemaker implantation on the right ventricular septum (Fig. 1).

2.2. Patients' Selection

All patients will undergo GLS examination using two-dimensional speckle tracking echocardiography (2D STE) to determine the patients' left ventricular function. A total of 240 patients consisting of 120 patients with left ventricular dysfunction and 120 patients without left ventricular dysfunction will be enrolled for IL-6 examination. 63 out of 240 patients who consist of 36 patients with left ventricular dysfunction and 38 patients without left ventricular dysfunction, will be enrolled for sTNFR-2, MMP-9, miR-155, N-Cad, and ZO-1 examination. The inclusion and exclusion criteria are presented in Table 1.

Table 1 Inclusion and exclusion criteria of PILVD study

Inclusion (A) and exclusion (B) criteria
A
1. Male or female aged >18 years old that was diagnosed with TAVB and will be implanted with a permanent pacemaker in the right ventricular septum
2. EF > 50% and TAPSE > 16 mm
3. Agree for follow up after pacemaker implantation
4. Written informed consent obtained from the patient
B
1. Pregnancy
2. Myocardial infarction or revascularization therapy in the last 3 months
3. Permanent AF
4. Heart valve disease with significant hemodynamic consequences
5. Abnormal heart structure changes including the right atrium, left atrium, right ventricle, or left ventricle dilation
6. NYHA function class III or IV
7. Significant respiratory disease
8. Carcinoma in the last 5 years
9. Autoimmune disease

In the Table 1: AF – atrial fibrillation; EF – ejection fraction; NYHA: New York Heart Association; TAPSE

– tricuspid annular plane systolic excursion; TAVB – total atrioventricular block

2.3. Blinding (Masking)

Both the patients and researchers will not be blinded during the clinical study.

2.4. Data Collection and Management

All patients' clinical data will be recorded in a specified form for research. The blood samples will be stored for further biomarker analysis. Raw data obtained from echocardiography, especially GLS, will be collected.

2.5. Echocardiography Examination

Echocardiography examination will be conducted before pacemaker implantation, one month and three months after. Transthoracic echocardiography examinations will follow standardized protocols. The elements that will be recorded:

1. Parasternal long axis (PLAX): Assessing left ventricle, right ventricular outflow tract (RVOT), and right ventricular inflow.
2. Parasternal short axis (PSAX): Assessing the global and regional function of the left ventricle.
3. Apical view: Assessing apex of left ventricle and atrium.
4. Subcostal view: Assessing right ventricular free wall.
5. Tricuspid annular plane systolic excursion (TAPSE): Assessing right ventricular longitudinal systolic performance from apical view.
6. Global longitudinal strain (GLS): GLS will be measured as a parameter of left ventricular function.

The measurement will be conducted using 2D STE. The measurement will be conducted from a video clip recorded and stored as a still frame. This study will use 16-segments measurement in determining the ventricular strain. Calculation of each segment will be presented in the form of a bull eye to calculate the global longitudinal strain.

2.6. Biomarker

Biomarkers will be measured before pacemaker implantation, one month, and three months after pacemaker implantation. The measurement of IL-6, sTNFR-2, MMP-9, ZO-1, and N-Cad from plasma samples using the ELISA technique will be duplicated; miR-155 will be measured from serum samples using the reverse-transcriptase polymerase chain reaction (RT-PCR) technique.

2.7. Outcomes

2.7.1. Primary Outcome Measures

The primary outcome is a decrease in serum miR-155 level and increased plasma IL-6, sTNFR-2, MMP-

9, N-Cad, and ZO-1 levels in patients with TAVB who experienced LV dysfunction due to right ventricular septal pacemaker implantation as assessed by GLS at one and three months.

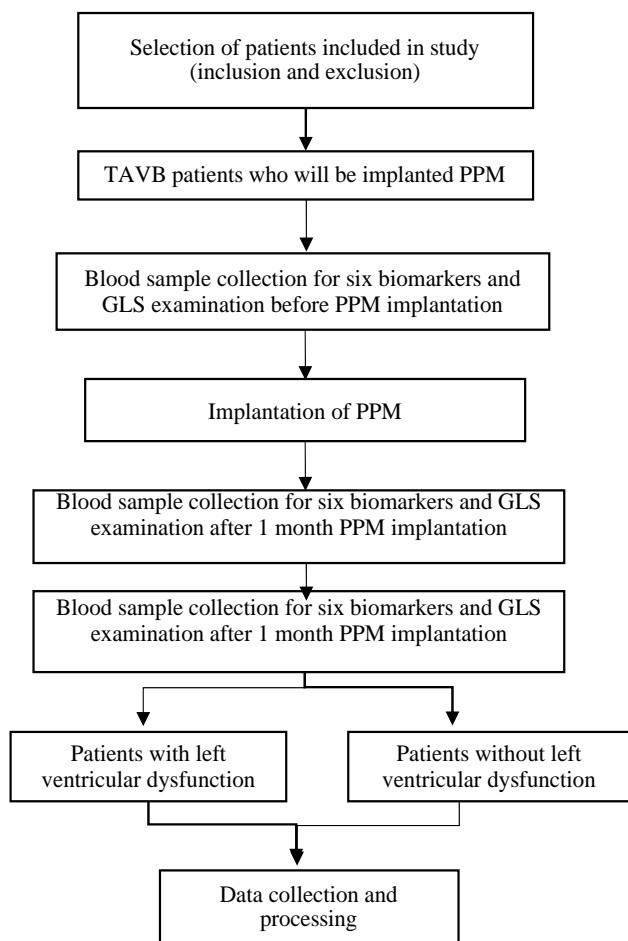


Fig. 1 Schematic of research methodology

Notes: TAVB – total atrioventricular block; PPM – permanent pacemaker; GLS – global longitudinal strain

2.7.2. Secondary Outcome Measures

The secondary outcome is to find the difference in serum levels of miR-155 and plasma levels of IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 between patients with TAVB who experienced LV dysfunction and do not experience LV dysfunction due to right ventricular septal pacemaker implantation as assessed by GLS at one and three month.

2.8. Statistical Methods

Numerical data will be presented as mean and standard deviation (SD) if normally distributed or median and interquartile range (IQR) if not normally distributed. Categorical data will be presented as relative frequencies (n, %). The categorical and numerical data relation will be analyzed using the ANOVA test if the data is normally distributed or the Friedman test if the data is not normally distributed. The mean differences between the two groups (left ventricular dysfunction and normal ventricular function) will be analyzed using an unpaired T-test if

the data is normally distributed or a Mann-Whitney test if the data is not normally distributed. A p-value less than 0.05 will be determined as statistically significant. Linear regression will determine the independent variable with the most dominant effect on the dependent variable.

2.9. Ethical Consideration

Medical Research Ethics Committee, Faculty of Medicine, University of Indonesia has approved this study protocol.

3. Main Findings

LV dysfunction is associated with biological markers such as miR-155, sTNFR-2, IL-6, MMP-9, N-Cad, and ZO-1. The MiR-155 function is linked to the AT-1R as a target. The MiR-155 has a negative correlation with the AT-1R. Increased expression of miR-155 inhibits AT-1R activity and prevents angiotensin II-induced cardiac hypertrophy [30]. In the presence of VKI dysfunction, inflammation occurs, and pro-inflammatory macrophages known as M1 induce extracellular matrix degradation by increasing the production of inflammatory mediators such as IL-6 and MMP-9 [31]. TNF- α may alter MMP-9 and IL-6 levels as LV dysfunction progresses. TNF- α activity can be defined by sTNFR-2 levels, which have a longer half-life and are more stable in the blood [32]. IL-6 has a role in regulating MMP-9 [33]. MMP-9, on the other hand, can process non-extracellular matrix substrates such as IL-6 [34]. In cardiac remodeling, monocytes/macrophages play a crucial part in the inflammatory process and scar formation [35]. When there is increased activation of monocytes/macrophages, there is an inter-regulatory mechanism between miR-155, TNF- α , IL-6, and MMP-9, which ultimately affects LV dysfunction [33-36].

Then histologically, ZO-1 is located at tight junctions in a more superficial layer than N-Cad, located at adherens junctions [37]. Increased plasma levels of ZO-1 and N-Cad, on the other hand, indicate persistent tissue injury [28]. Therefore, increased levels of sTNFR-2, IL-6, MMP-9, N-Cad, and ZO-1 and decreased levels of miR-155 were associated with LV dysfunction.

4. Discussion

Pacemaker implantation is a definitive treatment for patients with TAVB. However, patients could be at risk for developing PICM [19]. PICM may develop due to mechanical dyssynchrony in the cardiac conduction system. PICM is mainly seen in patients with a single chamber pacemaker on the right ventricle. However, a dual-chamber pacemaker could also play a dyssynchrony role [20]. In RV pacing, lead placement on both apical and septal is related to dyssynchrony, although the incidence of dyssynchrony is lower in the

septal location [21]. Mechanical dyssynchrony would impair LV structure and function due to alteration in tissue perfusion and metabolism [9]. Due to chronic neurohormonal exposure, inflammation, and strain on the cardiac wall, structure and function impairment also occur.

AT-1R represents neurohormonal exposure. Activation of AT-1R is related to pathological responses in the heart [22]. AT-1R is bound to the cell membrane. A specific microRNA-155 (miR-155) can be measured to detect AT-1R presence in blood. MiR-155 has a binding site with AT-1R mRNA to provide specific information about AT-1R in the cell membrane [10, 23]. sTNFR-2 and IL-6 are two components related to inflammatory response, and increased plasma levels of both sTNFR-2 and IL-6 have been associated with the progression of LV dysfunction. The dysfunction occurs due to a change in the contractility of cardiomyocytes and could cause fibrosis [13, 24, and 25]. MMP-9, a family of proteolytic enzymes, is also related to inflammation. Chronic exposure to MMP-9 would cause cardiac remodeling due to the destruction of elastin and collagen components [26]. Other essential components that hold the integrity of cardiac structure are N-Cad and ZO-1. N-Cad plays a vital role at adherence junction, while ZO-1 at the tight junction. Disruption of these proteins causes damage and instability of the heart structure [14, 27]. Measuring these two proteins is essential to see the extent to which cell damage has occurred [28, 29].

This study focuses on the alteration of biomarker levels at 1 and 3 months post-implantation. By looking at these changes, we can see that the pathological processes are related to the alteration of biomarker levels. M-Pace in LVD study is a multi-center, non-randomized, clinical study explaining the mechanism underlying cellular change in patients with TAVB who underwent pacemaker implantation.

4.1. Comparison with Other Studies

The high incidence of PICM makes it essential to study and understand in more depth. However, until now, the pathophysiological aspects of PICM at the cellular level are still not widely known [38]. By knowing the pathophysiological aspects of PICM, the determination of management and timing of therapy can be more precise. Kaufman et al. stated that PICM occurs due to impaired remodeling of cardiac muscle cells [39]. Other studies have reported that the process of cardiac remodeling does not only occur in cell components but also in the surrounding intercellular tissue [40]. Changes in the structure and function of cells and cardiac interstitial tissue are caused by chronic exposure to neurohormones, stretch in the heart wall, and inflammatory signals that will result in LV dysfunction [41]. These changes will eventually lead to decreased LV function. This etiognostic study aims to

see the mechanism of changes in the cellular level in TAVB patients undergoing septal PPM implantation.

4.2. Implication and Explanation of Findings

Knowledge of the mechanisms at the most basic level can form the basis for possible etiology, diagnosis, therapy, and even prognostication in patients with PICM. This study implies the role of decreased plasma miR-155 values and increased plasma values of IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 in LV dysfunction due to right ventricular septal PPM placement after one and three months in TAVB patients. This study also implies that GLS has an important role in assessing left ventricular dysfunction. LV dysfunction initially only showed a change in the structure before finally decreasing the ejection fraction. The GLS examination can provide an early picture of functional decline. Decreased cardiac function as measured by GLS and changes in cardiac structure seen from plasma biomarkers miR-155, sTNFR-2, IL-6, MMP-9, ZO-1, and N-Cad can provide an overview of the mechanism of PICM development.

5. Conclusion and Recommendations

This study identified a decrease in miR-155 levels and an increase in IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 levels in TAVB patients with LV dysfunction due to right ventricular septal PPM implantation as assessed by GLS at 1 and 3 months. Furthermore, this study aims to find out the differences in plasma values of miR-155, IL-6, sTNFR-2, MMP-9, N-Cad, and ZO-1 in BAVT patients with LV dysfunction and patients who did not have LV dysfunction due to right ventricular septal PPM implantation assessed by GLS at 1 and 3 month.

This study suggests a basis for the use of plasma miR155, IL-6, MMP-9, sTNFR-2, N-cad, and ZO-1 assessment of LV dysfunction due to right ventricular septal PPM insertion in clinical practice.

Progress has been made to understand the cellular mechanism of PICM.

6. Limitations and Further Study

The mechanism of pacemaker-induced LVD study is multi-center; therefore, enrolling patients in several centers improves the generalizability of study outcomes. In addition, research on the cellular mechanism of LV dysfunction induced by PPM implantation has never been published. Therefore, the PILVD study is an etiognostic study that aims to determine the etiology. So, this study did not establish therapeutic management or clinical implementation. For that reason, more research needs to be conducted. However, the limitation in this study is the possibility of loss to follow-up of patients after PPM implantation for assessment of biomarker samples and GLS at one and three months following PPM implantation.

Future studies about the clinical implication or potential therapies targeting the cellular level mechanism to effect reverse remodeling may improve clinical outcomes in TAVB patients.

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