

## Pacing Induced Cardiomyopathy: What is The Solution?

Maruli Butarbutar<sup>1</sup>, Sunu Budhi Raharjo<sup>2</sup>

### Abstract

**Background:** Right ventricular (RV) pacing is associated with adverse outcome including increased risks of cardiovascular morbidity and mortality. It causes abnormal ventricular activation which results in an inefficient myocardial contraction pattern due to ventricular dyssynchrony and may lead to LV dilatation, systolic dysfunction and clinical HF. Pacing induced cardiomyopathy (PICM) is caused by chronic and high burden RV pacing that may occur several months or years after permanent pacemaker implantation.

**Case Illustration:** A male, 56 years old, complained DOE (+), PND (+) and OP (+) since April 2017. He had history of PPM DDDR implantation due to high degree AV block (2016) and failed CRT-P implantation (2018). Physical examination revealed pansystolic murmur grade 2/6 at apex, no rales and no oedema at both legs. ECG showed intrinsic rhythm was type 2 second degree AV block and RBBB with prolonged QRS duration 150 ms. Echocardiography showed global hypokinetic and dilated LV (LV EDD 71 mm, LV ESD 63 mm) with progressively reduced EF 38% to 33% (Simpson), functional moderate MR and mild TR. CAG showed non-significant coronary artery stenosis with 20% stenosis at distal LAD. Patient was diagnosed as pacing induced cardiomyopathy (PICM). Patient was planned to undergo His-Bundle pacing (HBP) or CRT-P implantation. CRT-P implantation was preferred rather than HBP because the capture threshold His-bundle were too high (3V @ 1.0 ms). At general ward, ECG evaluation showed biventricular pacing rhythm and there was no signs and symptoms of HF. Patient was then discharged in a good condition.

**Summary:** PICM is caused by high burden and chronic RV pacing. Options to treat or to prevent it, may include conduction system pacing (e.g.: HBP) or CRT-P implantation. Beside device therapy, pharmacotherapy also has important role in treatment of HF<sub>r</sub>EF. Patient with HF<sub>r</sub>EF should receive guideline directed medical therapy.

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## Introduction

Permanent pacemakers (PPM) are a safe and effective treatment for symptomatic irreversible bradycardia. Under the proper indications, cardiac pacing might bring significant clinical benefits. However, many literatures stated that the action of the artificial pacing system, mainly right ventricular pacing, produces several negative effects to cardiac structure (e.g.: LV remodelling, dilatation) and function (e.g.: ventricular dyssynchrony) leading to decreased left ventricular (LV) ejection fraction (EF) and increased hospitalizations due to HF.<sup>1</sup> This condition is called pacing induced cardiomyopathy (PICM) which can be managed by either conduction system pacing (e.g.: HBP) or CRT-P implantation.<sup>2</sup>

Several factors could afflict specificity of the test leading to false-positive results. These conditions are in patients with some metabolic conditions (anemia, glucose load, hyperventilation, and hypokalemia), structural heart diseases (severe aortic stenosis, mitral valve prolapsed, severe aortic or mitral regurgitation, cardiomyopathies, and left ventricular hypertrophy), marked resting ST-segment depression, intraventricular conduction disturbances, pre-excitation syndromes, severe hypertension, severe hypoxia, sudden excessive exercise, supra-ventricular arrhythmias or digitalis therapy.<sup>1,2</sup>

## Case Illustration

A male, 56 years old, was referred to National Cardiovascular Center Harapan Kita (NCCHK) from dr. M. Djamil General Hospital with diagnosis of CHF

Fc II, history of PPM DDDR due to high degree AV block (2016) and failed CRT-P implantation (2018). In 2016, he suffered high degree AV block and was managed with PPM DDDR implantation. In April 2017, he complained DOE (+), PND (+) and OP (+). The echocardiography done at dr. M. Djamil General Hospital showed global hypokinetic and dilated LV (LVEDD 71 mm, LVESD 63 mm) with progressively reduced LVEF (38% in 2017 to 33% in 2018, Simpson), functional moderate MR and mild TR (**Table 1**). Coronary angiography done at dr. M. Djamil General Hospital showed non-significant coronary artery stenosis with 20% stenosis at distal LAD. He was treated with Furosemide 1x40 mg, Candesartan 2x8 mg, Carvedilol 2x6.25 mg, Spironolactone 1x25 mg and Clopidogrel 1x75 mg. In 2018, upgrade to CRT-P was planned, however the CRT-P implantation was failed. Therefore, he was referred to NCCHK for further management.

Physical examination revealed pansystolic murmur grade 2/6 at apex, no rales and no oedema at both legs. Other physical examination found no remarkable findings. ECG showed pacing rhythm atrial sensing ventricular pacing with RVOT pacing origin (Fig. 1). Patient was then diagnosed as pacing induced cardiomyopathy (PICM) and was planned to undergo HBP/CRT-P implantation.

At catheter laboratory, PPM interrogation showed pacing rhythm As Vp 84.6% therefore the patient was ventricular pacing dependent. After PPM was inhibited, ECG showed intrinsic rhythm of type 2 second degree AV block and RBBB with QRS duration 150 ms. His-Bundle pacing (HBP) was planned at first, however capture threshold His-bundle were too high (3V @1.0 ms) so that CRT-P with biventricular epicardial pacing

**Table 1.** Progression of signs & symptoms of heart failure, LV dilation and reduced LV EF in 2016-2020.

2016	2017	2018	2020
- Symptoms: Symptomatic bradycardia, no history of HF, Cardiovascular risk factors: HT, ex-smoker	- Symptoms: Symptomatic bradycardia, no history of HF, Cardiovascular risk factors: HT, ex-smoker	- Symptoms: DOE (+), PND (-) and OP (-)	- Symptoms: DOE (+), PND (+) and OP (+)
- ECG: High	- ECG: High	- TTE: LVEF 36% (Simpson), TAPSE 24 mm, LVEDD 63 mm, LVESD 52 mm	- TTE: LVEF 33% (Simpson), 24% (Teicholz), TAPSE 28 mm, LVEDD 71 mm, LVESD 63 mm
- Diagnosis: High degree AVB	- Diagnosis: High degree AVB	- CAG: Stenosis 20% at distal LAD	- Holter ECG: AsVp >80%
- Treatment: PPM DDDR	- Treatment: PPM DDDR	- Diagnosis: PPM induced CM Fc III	- Diagnosis: PPM induced CM Fc III
		- Treatment: CRT-P implantation → failed	- Plan: Refer to NCCHK for CRT-P upgrade

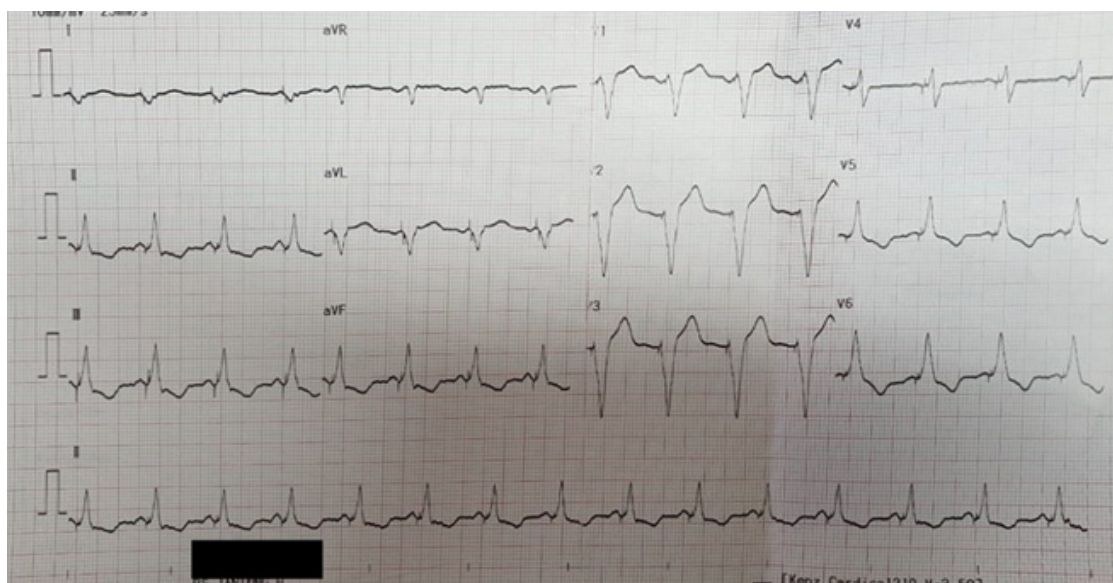
was preferred. The RA and RV leads were on their position. LV lead was inserted through right axillary vein due to stenosis of left subclavian vein (Fig. 2A). It was inserted into left lateral cardiac vein through coronary sinus and then tunneled subcutaneously to left deltoideo-pectoralis junction where the CRT-P generator implanted (Fig. 2B).

At general ward, ECG evaluation showed biventricular pacing rhythm, rate 86 bpm, QRS axis shifted to RAD, QS in lead I, QrS in lead V4-V6 with narrower QRS 120 ms (Fig. 3). There was no signs and

symptoms of heart failure. Echocardiography taken post procedure showed dilated heart (LVEDD 72 mm, LVESD 66 mm), reduced ejection fraction (LVEF 19%, Teicholz). Patient was hospitalized for 3 days and then discharged in a good condition.

## Discussion

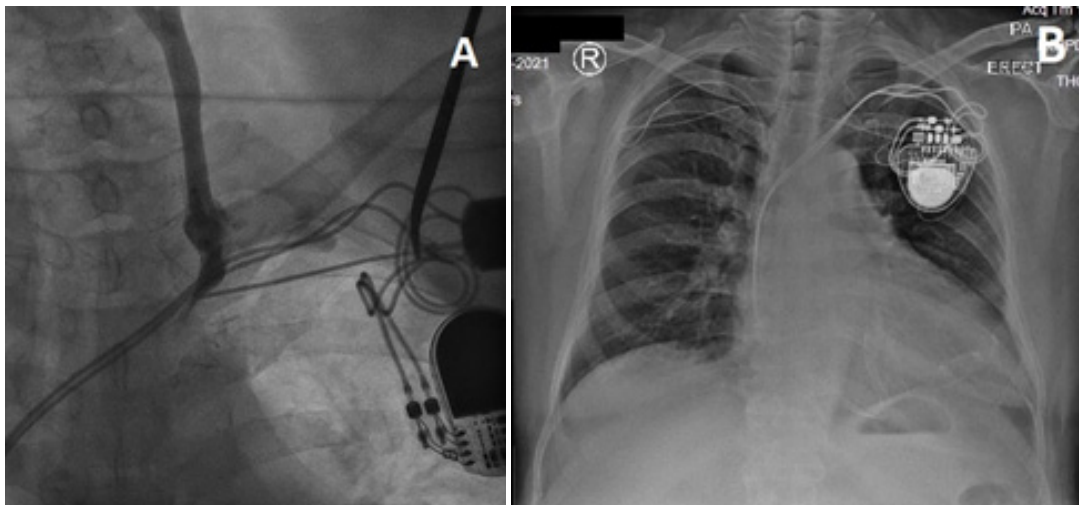
The definition of pacing induced cardiomyopathy (PICM) has varied widely across studies. Pacing induced



**Figure 1.** ECG taken at dr. M. Djamil General Hospital showed pacing rhythm atrial sensing ventricular pacing, 86 bpm, QRS dur 140 ms, LBBB morphology, inferior axis, precordial transition at V3-V4, no notching at limb leads suggesting RVOT septum pacing.

**Table 2.** Progression of signs & symptoms of heart failure, LV dilation and reduced LV EF in 2016-2020.

Pacing Indication	Normal EF (>50%)	Mildly impaired EF (35-49%)	Low EF (<35%)
Sinus node dysfunction (anticipated low RV pacing burden)	Atrial or dual chamber PPM	CSP CRT	CSP CRT
Prolonged PR interval with narrow QRS	CSP Dual chamber PPM	CSP CRT	CSP CRT
Heart block (anticipated high RV pacing burden)	CSP Dual chamber PPM	CRT CSP	CRT CSP
Left bundle branch block	Undefined	CSP CRT	CSP CRT
Non-LBBB wide QRS	Undefined	CSP CRT	CSP CRT



**Figure 2.** A. Stenosis of left subclavian vein is a complication of transvenous PPM lead placement before; B. CRT-P generator was implanted at left deltoideo-pectoralis junction. Atrial lead was located at right atrium. RV lead was located at RVOT. LV lead was located at epicardial LV RVOT septum pacing.

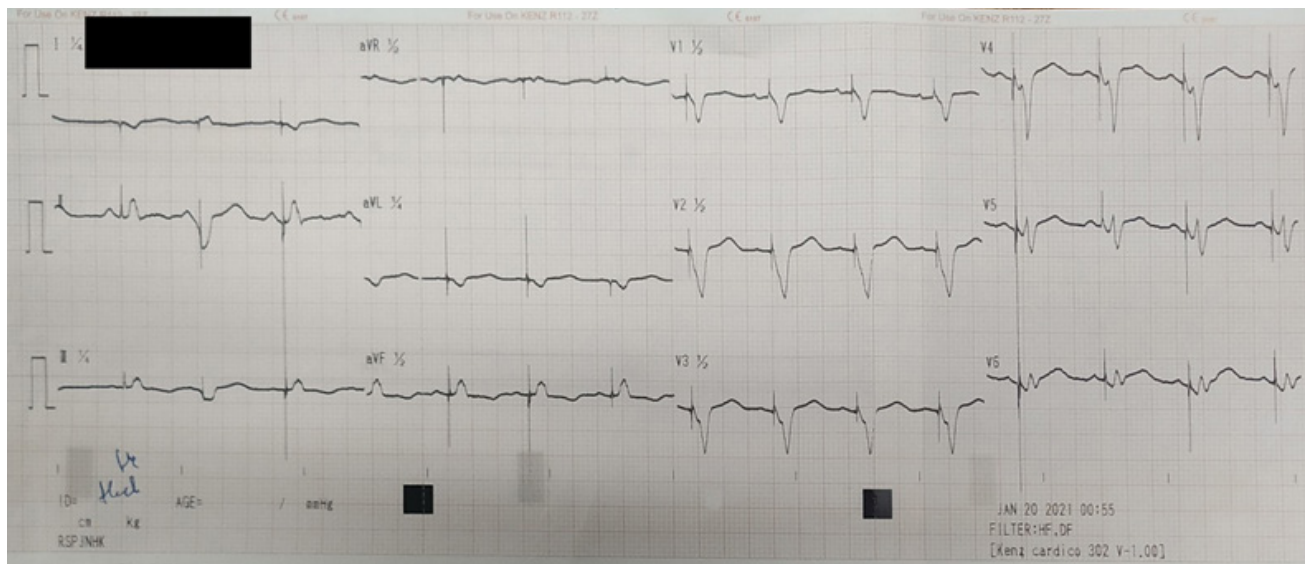
cardiomyopathy (PICM) is most commonly defined as a drop in left ventricle ejection fraction (LVEF) in the setting of chronic, high burden right ventricle (RV) pacing. Traditionally, PICM has been viewed as a form of heart failure with reduced ejection fraction (HFrEF) with ejection fraction  $\leq 40\%$ . There are several definitions of PICM: 1) LVEF  $\leq 40\%$ , if baseline LVEF was  $\geq 50\%$ , or absolute reduction in LVEF  $\geq 5\%$  if baseline was  $< 50\%$ ; 2) LVEF  $\leq 40\%$ , if baseline LVEF was  $\geq 50\%$ , or absolute reduction in LVEF  $\geq 10\%$  if baseline was  $< 50\%$ ; and 3) absolute reduction in LVEF  $\geq 10\%$ , regardless of baseline. The third definition is considered the most clinically relevant. It has been reported that 10-20% of patients with permanent pacemaker (PPM) develop PICM after 3–4 years of RV pacing. However, there is a study reporting the higher incidence of new HF diagnoses was most notable within the first 6 months after in the institution of RV pacing.<sup>2</sup> Kaye et al compared three different definitions during a follow up of  $3.4 \pm 1.4$  years, the prevalence of PICM was 9.3%, 5.9% and 39.0% based on definitions 1, 2 and 3, respectively.<sup>3</sup> In our patient, patient complained signs and symptoms of heart failure after about 1 year after PPM implantation. Echocardiography showed progressively reduced LVEF (38% in 2017 to 33% in 2018) with LV dilatation (LVEDD 71 mm, LV ESD 63 mm), with functional moderate MR. PPM interrogation showed ventricular pacing dependent with rhythm atrial sensing ventricular pacing (AsVp) 84.6%. The

possibility of coronary artery disease causing decreased LVEF can be excluded because coronary angiography showed a non-significant coronary stenosis (20% stenosis at distal LAD) and no history of acute coronary syndrome or typical chest pain.

Several baseline clinical variables, present before pacemaker implantation, have been associated with an increased risk of PICM (i.e.: older age, male gender, wider intrinsic QRS, history of atrial fibrillation and impaired LVEF). After pacemaker implantation, high RV pacing burden and wider paced QRS also become risk factors of PICM.<sup>2</sup> Khurshid et al found that PICM may be more common than previously reported, and risk for its occurrence may begin below the commonly accepted threshold of 40% pacing burden. Men with wider native QRS duration (particularly  $> 115$  ms) are also at increased risk.<sup>4</sup> Kiehl et al found that PICM is common in patients receiving PPM for complete heart block with preserved LVEF and is strongly associated with RV pacing burden  $> 20\%$ .<sup>5</sup> In our patient, his risk factors developing PICM were male gender, wider intrinsic QRS (150 ms), high burden RV pacing (84.6%) and wider paced QRS (140 ms).

The pathophysiology of PICM is not clearly explained. Effect of RV pacing on LV function may be multifactorial. Underlying myocardial disease and biological factors may affect the timing and probability of developing HF in patients with an RV pacing device. During RV pacing, an altered activation



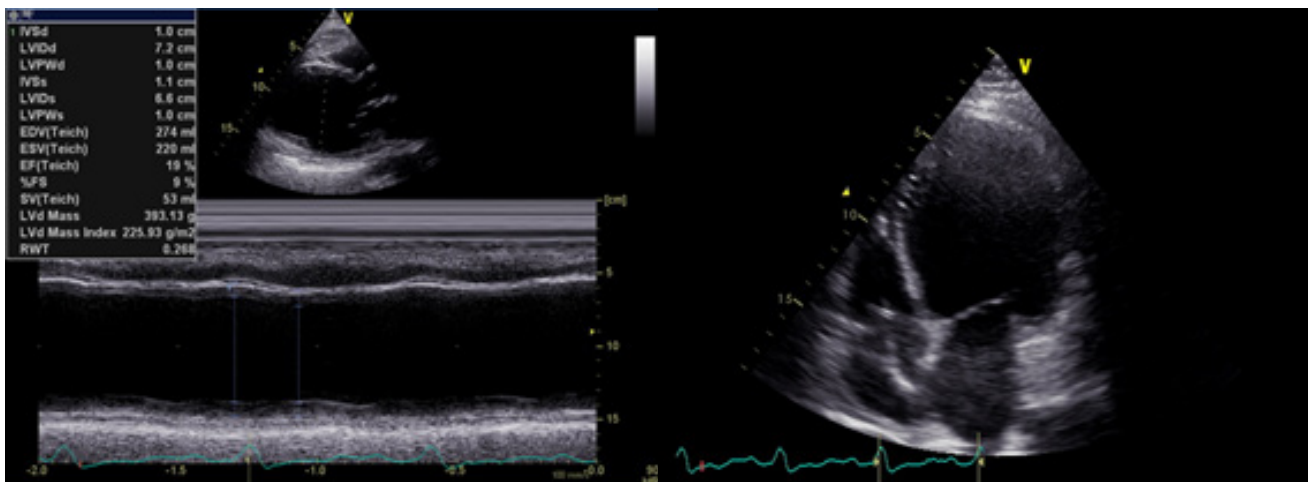


**Figure 3.** Post CRT-P implantation, ECG showed biventricular pacing rhythm, rate 86 bpm, QRS axis shifted to RAD, QS in lead I, QrS in lead V4-V6 with narrower QRS 120 ms.

pattern similar to left bundle branch block is observed with electrical activation beginning at the septum and considerably delayed activation of the LV free wall as the electrical impulse traverses from myocardial cell-to-cell rather than through the fast Purkinje system. This perturbed electrical myocardial activation leads to impaired mechanical contraction, with sites closest to the pacing site demonstrating rapid systolic shortening, resulting in pre-stretch of late activating sites and an overall redistribution of myocardial strain and work with overall less effective contraction. These result in abnormal myocardial metabolism and altered regional perfusion, increased fibrosis and myofibrillar disarray, functional mitral regurgitation, reduced cardiac output and increased filling pressures leading to inefficient contraction pattern with ventricular dyssynchrony and loss of myocardial work that may lead to LV dilation, systolic dysfunction, and clinical HF.<sup>6</sup> It should be noted that most of the data on the deleterious effects of RV pacing comes from RV apical pacing. Although some studies have suggested that pacing from RV septal or outflow tract positions may result in lesser degrees of dyssynchrony than pacing from the RV apex.<sup>2</sup> In our patient, the ECG showed LBBB morphology, inferior axis, precordial transition at V3-V4, no notching at limb leads suggesting RVOT septum pacing.

PICM is reversible if the extent of dyssynchrony can be ameliorated. A reduction in the “dose” of dyssynchrony

can reverse cardiomyopathy. This can be accomplished either through algorithms to reduce RV pacing or by alternative forms of pacing such as conduction system pacing (CSP or HBP) or CRT, both of which are associated with significantly less interventricular dyssynchrony (Table. 2). The most commonly used approach to treating PICM is upgrading PPM to CRT system.<sup>7</sup> Beside device therapy, pharmacotherapy is also a cornerstone in treating heart failure reduced ejection fraction (HFrEF). The major goals of treatment for patients with HFrEF are i) mortality reduction, ii) prevention of recurrent hospitalizations due to worsening HF, and iii) improvement in clinical status, functional capacity and quality of life. The ACE-I/ARNI, beta-blocker and MRA are recommended as cornerstone therapies. ARNI was recommended as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker and MRA, however, ARNI may be considered as first line therapy instead of ACE-I.<sup>(8)</sup> A meta-analysis compared ARNI vs. ACE-I/ARB in patient with HFrEF done by Wang et al conclude that ARNI improves functional capacity including increasing NYHA functional class and 6-MWT distance; ARNI also improves cardiac reverse remodelling (CRR) with striking changes in LV EF, diameter and volume. These improvement of CRR indices were observed at 3 months and became more significant with longer follow-up to 12 months.<sup>9</sup> Our patient was treated with Furosemide



**Figure 4.** Four chamber view showed LA-LV dilatation. PLAX view showed LVEDD 72 mm, LVESD 66 mm and EF 19% (Teichholz).

1x40 mg, Candesartan 2x8 mg, Carvedilol 2x6.25 mg, Spironolactone 1x25 mg. ARNI may be recommended in our patient.

In a recent retrospective review of 1279 consecutive CRT procedures, in which 78 patients were diagnosed as PICM and received CRT system upgrade, showed that CRT was highly effective in reversing PICM. About 86% of patients whose LVEF  $\leq 35\%$  at baseline showed improved LVEF to  $>35\%$  after CRT implantation. Importantly, the greatest improvement in LVEF occurred within the first 3 months of device upgrade.<sup>2,10</sup> There are several mechanisms explaining this improved LVEF after CRT upgrade. Yu et al proposed that biventricular pacing in CRT-P improve intraventricular synchrony, atrioventricular synchrony, and interventricular synchrony which lead to reverse LV remodelling and improvement of cardiac function.<sup>11</sup> ESC guidelines on cardiac pacing and cardiac resynchronization therapy stated that CRT upgrade from conventional PM or ICD is indicated in HF patients with LVEF  $<35\%$  and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment (Class IB).<sup>7</sup> Beside CRT-P, the other emerging strategy appears to be the most promising; namely, to pursue conduction system pacing (CSP), such as His bundle pacing (HBP). The feasibility and impact of HBP were reported in 85 patients with chronic RV pacing and longstanding AV block. HBP was successful in 79 (93%) patients. In a subset of 60 patients in whom the LV ejection fraction had decreased from 54%

$\pm 7.7\%$  to  $34\% \pm 9.6\%$  with RV pacing, the institution of HBP resulted in a significant increase in LV ejection fraction (to  $48.2\% \pm 9.8\%$ ,  $p < 0.001$ ). The limitations of this approach include challenges in device implantation, elevated pacing thresholds (leading to lead revisions and/or premature battery depletion), sensing problems and challenges with device programming.<sup>2,12</sup> In our patient, HBP was planned at first, however the capture threshold His-bundle were too high (3V @1.0 ms) therefore CRT-P with biventricular epicardial pacing was then preferred. The RA and RV leads were on their position. The venography showed stenosis of left subclavian vein related to previous transvenous PPM lead placement. LV lead was inserted through right axillary vein into left lateral cardiac vein through coronary sinus and then was tunnelled subcutaneously to left deltoideo-pectoralis junction where the CRT-P generator implanted.

Venous stenosis is a recognized complication following the implantation of an ICD or a pacemaker. Data on venous occlusion following device implantation are limited, and the risk factors for the development of this complication are not well defined. In more than one study, it was shown that various degrees of venous stenosis occur in 20% to 50% of patients following device implantation. Abu-El-Hajja et al found there was a significant association exists between venous stenosis and the number of implanted leads and also the sum of the lead diameters.<sup>13</sup>

During follow up at general ward, ECG showed biventricular pacing rhythm, rate 86 bpm, QRS axis

shifted to RAD, QS in lead I, QrS in lead V4-V6 with narrower QRS 120 ms. Improvement of LVEF was not seen soon after CRT-P implantation (post procedural LVEF was 19%, Teicholz) (Figure 4), it may need further echocardiography follow up in several months or a year later in order to look for the reverse LV remodelling.

## Summary

We reported a case of pacing induced cardiomyopathy (PICM) managed by CRT-P implantation in 56 years old male patient. High burden RV pacing may lead LV dilation, systolic dysfunction, and clinical HF. In many cases, the deleterious effects of RV pacing may occur much more quickly, within weeks to months of RV pacing. Options to treat PICM or to prevent it may include CRT and CSP (e.g.: HBP). Beside device therapy, pharmacotherapy also has important role in treatment of HFrEF. Patient with HFrEF should receive guideline directed medical therapy.

## Publication Approval

All authors read and approved the final manuscript.

## Conflict of Interest

None.

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## Ethical Clearance

Not Applicable.

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