**Risk factors for developing Pacing Induced LV dysfunction:**

**Experience from a large volume tertiary centre**

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Word count: 2787 (excluding references)

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**Abstract:**

**Introduction:**

The risk factors for developing pacing induced Left Ventricular dysfunction (LVD) in patients with high burden of right ventricular pacing (RVP) is poorly understood. Therefore, in the present study, we aimed to assess the determinants of pacing induced LVD.

**Methods:**

Our data were retrospectively collected from 146 patients with RVP > 40% who underwent generator change (GC) or cardiac resynchronisation therapy (CRT) upgrade between 2016-2019 who had left ventricular ejection fraction (EF) ≥50% at initial implant.

**Results:**

75 patients had CRT upgrade due to pacing induced LVD (EF<50%) and 71 patients with preserved LV function (EF ≥50%) had a GC. Primary indication for pacing in both groups was complete heart block. Male predominance (p=0.008), history of prior myocardial infarction (MI) (p=0.001), presence of atrial fibrillation (AF) (p=0.009), and chronic kidney disease (CKD) (p=0.005) were more prevalent in the CRT upgrade group. Presence of AF (OR=2.3, 95% CI 1.13-4.7; p=0.022), CKD (OR=2.19, 95% CI 1.09-4.43; p=0.027) and male gender (OR =2.63, 95% CI 1.26-5.48; p=0.01) were independent predictors for RVP induced LVD. The timeframe of development of pacing induced LVD was highly variable. A negative correlation was observed between age at implant and time to diagnosis of LVD since implant (r=-0.49; p≤0.001).

**Conclusions:**

Our results suggested that presence of AF, CKD and male gender are predictors for development of pacing induced LVD in patients with high RVP burden. LVD can occur at any time after pacemaker implant and increasing age is associated with earlier development of LVD.

**Keywords:** Pacemaker, Left Ventricular dysfunction, Heart Failure

**Introduction:**

Permanent pacemaker (PPM) implantation with right ventricular pacing (RVP) is the definitive treatment for symptomatic bradyarrhythmia with the most common indication being high degree atrioventricular block [1]. RVP has been shown to cause deleterious effects on the left ventricular function due to pacing induced electrical and mechanical left ventricular (LV) dyssynchrony (2,3).

Nevertheless, pacing induced LV dysfunction (LVD) is only observed in a subset of patients exposed to RVP and the incidence of this varies, ranging from 9% –26% depending on the follow up period and definition (4). Several factors have been identified as causative including pre-existing LV systolic function, RVP percentage, wide paced QRS (pQRS) duration, older age, chronic kidney disease (CKD), atrial fibrillation (AF) and history of ischaemic heart disease (4-14). The phenotype is variable with regard to the degree of pacing with some patients able to tolerate 100% ventricular pacing with no change in LV systolic function whereas others with pacing percentages as low as 20% can deteriorate. Furthermore, the rate of decline of LV function is variable with some patients developing LVD and heart failure within a year of the implant but in others this may take several years.

In the present study we aimed to 1) identify characteristics among patients with high burden of RVP who developed LV systolic dysfunction and 2) delineate the timeframe of development of LVD after implant and identify whether any factors affected the rate of development of LVD.

**Methods**

**Study population**

Data from 468 consecutive patients were retrospectively collected from electronic medical records and hospital device clinic database, who underwent generator box change (GC) or Cardiac resynchronisation (CRT) upgrade between July 2016 and July 2019 at Barts Heart Centre.

Our inclusion criteria were: i) LV ejection fraction EF ≥ 50% prior to initial implant and with ii) RVP burden of >40% undergoing pacemaker generator change (GC) or cardiac resynchronisation therapy (CRT) upgrade (from dual or single chamber PPM) due to LV systolic dysfunction due to chronic RVP.

Patients with incomplete data regarding PPM implant procedure and those without pre-implant echocardiographic details were excluded. Furthermore, we excluded patients who did not have LV assessment prior to GC due to frailty or dementia; any underlying chronic cardiac conditions that may contribute to deterioration of LV function irrespective of pacing such as complex adult congenital heart disease, evidence of ischaemia/infarction requiring revascularisation, severe valve disease and infiltrative or inherited cardiomyopathies. Study design and population are detailed in Fig 1.

Out of the 468 patients, 116 patients were excluded due to incomplete implant data or not fulfilling the study group criteria. In the remaining 252 patients, 106 patients were excluded due to alternate causes that may contribute directly to the LVD or not having LV assessment prior GC due to frailty. Only 146 patients were eligible to be included in the analysis and fulfilling the inclusion criteria (Figure 1). This was further categorised in to those who underwent CRT upgrade due to LV systolic dysfunction with EF < 50% and into those who

underwent only generator change due to EF ≥ 50%. The study protocol was approved by the clinical effectiveness unit of our institution (registration number 12126).

**Clinical data and measurements**

These include patient demographic data; pre-PPM medical history and echocardiographic findings; PPM procedure details; and PPM follow up diagnostics and echocardiographic/electrocardiographic findings. As a standard of care St Bartholomew's Hospital Cardiac Electrophysiology department follows a specific protocol prior to referring patients with RVP >40% for generator change. These patients will have a clinical assessment including echocardiography assessment irrespective of New York Heart Association (NYHA) class symptoms to assess the need for CRT upgrade at the time of generator change. If LV ejection fraction was lower than 40%, CRT upgrade if appropriate is discussed and offered. The clinical pathway is therefore a rigorous method of determining which patients develop pacing induced LVD. CKD stage 3 and below were classified as Chronic kidney disease according to the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines. Data on pQRSd was only complete in the CRT upgrade group and therefore the measurements were included only for subgroup analysis.

**Statistics**

The results are presented as absolute value with %, mean ± standard deviation (SD) or median and interquartile range (IQR). Normally distributed continuous variables were presented as mean (+/-SD) and non-normal distribution as median (IQR). Normally and non-normally distributed continuous variables were compared using student's t test and Mann-Whitney U test respectively whereas categorical variables were compared using $\chi^2$ test. Both univariate and multivariate logistic regression models were used to assess for possible confounders for

pacing induced cardiomyopathy for both groups (CRT vs GC) and for subgroup analysis within CRT group. A 2-sided α ($p < 0.05$) of less than 0.05 was considered statistically significant. Pearson correlation was used to assess the effect of QRS duration and age at implant in CRT group with pacing induced LVD. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software, version 27.0 software (IBM SPSS Statistics).

## Results

### Baseline characteristics

146 patients were included in the study with 75 patients having CRT upgrade and 71 patients having only GC (n=71). Baseline characteristics between these two groups are reported in Table 1. There were no significant different between the groups when considering the age and age at implant. Primary indication for pacing for both cohorts were similar with primary indication being complete heart block (72% in each group). There was no significant difference in the median RVP percentage for CRT upgrade versus (vs) GC group: 99% vs 100% (p=0.08). RV lead positions (apical vs non apical) were similar and were not statistically different between both groups.

### Comparison between GC and CRT groups

Compared to the GC group, the CRT group had a higher proportion of males (75 % vs 54%; p =0.008), a greater number of patients with a history of myocardial infarction (MI) (41% vs 17% p =0.001), atrial fibrillation (AF) (65% vs 43%; p =0.009) and chronic kidney disease (CKD) (61% vs 38%; p=0.005). Amongst patients with history of MI, both MI prior (27% vs 13%; p=0.03) and post (14% vs 4%; p=0.02) implant were more prevalent in the CRT group.

In multivariate analysis male gender (OR =2.63, 95% CI 1.26-5.48; p =0.01), presence of AF (OR=2.3, 95% CI 1.13-4.7; p =0.022) and CKD (OR=2.19, 95% CI 1.09-4.43; p =0.027) were independently associated with pacing induced LVD (summarised in Table 2).

Development of Pacing induced LVD

84% of the CRT upgrade group had LV ejection fraction ≤ 40%. Median LVEF was 35% IQR (29-40). Mean pQRSd in CRT upgrade group was 153±17 ms. CRT upgrade occurred after a median of 9 years IQR (3-11) after implant and the earliest upgrade was 2 months after pacemaker implant. The time course of development of pacing induced LVD within the CRT upgrade cohort varied considerably from less than one year to more than 10 years after implant (Figure 2). Eight out of seventy five patients (11%) had a CRT upgrade due to LV systolic dysfunction within 1 year of implant and 28 patients (37%) had CRT upgrade within 4 years of implant. Given the cluster of cases within the first 4 years after implant, risk profile in this group of patients were compared to those that developed LVD four years after PPM implantation. The patients who developed LVD within 4 years of implant were older (73yrs vs 65yrs; p =0.003), and had less valvular heart disease (11% vs 36%; p = 0.016) (Table 3). In multivariate analysis age (OR = 1.07, 95% CI 1.02-1.12; p =0.006), and presence of valve disease (OR=0.35, 95% CI 0.15-0.8; p =0.013) were independently associated with patients who developed LVD earlier after pacemaker (less than 4 years) compared to those that developed this after 4 years. Given the effect of increasing age in development of pacing induced LVD, the effect of age at implant was examined further. There was an inverse correlation between age at implant and the time to development of LVD (r=-.0.49; p ≤0.001) (Figure 3.)

## Discussion

PPM implantation is a critical therapy for patients with advanced heart block. Chronic RVP however has been shown to have detrimental effects on LV function eventually leading to symptomatic heart failure (5,15). The incidence of pacing induced LVD in previous studies has been estimated at 9-26% based on different definitions and follow-up period (4-14). Given the clinical impact of this with symptomatic heart failure, it is crucial to identify the clinical factors that are associated with its development.

In this study, we found a higher prevalence of pacing induced LVD amongst males, patients with history of MI, CKD, and AF. Furthermore, male gender, CKD and AF were independent predictors of LVD. Within the group of patients who went on to develop pacing induced LVD, this occurred at various time points after the implant with a cluster of cases early on after implant. Age was found to have a modest but significant effect within this group with earlier development of the phenotype.

The largest study to date which reported on the incidence of HF after pacemaker insertion in a large nationwide Danish registry demonstrated similar findings to our study with male gender, CKD and MI being established as risk factors for development of HF post pacemaker insertion (8). In a large cohort of patients who had a pacemaker implanted, AF was also a strong predictor of HF post pacemaker implantation (14). Smaller studies have found that age, paced QRS duration, pre-existing LVD, and RVP percentages were associated with development of HF (6,7, 9,10,12,13). The two largest studies to date have also shown that after PPM implant, there is a substantial early risk of HF (8,14). Our study corroborated these findings with 11% of cases developing HF within one year of implant.

It is still unclear the role of male gender as a predictor of pacing induced LVD however, this finding has also been confirmed by other studies (4,8). CKD, history of MI and AF are clear candidate risk factors however, given that they are likely to cause changes within myocardium and/or loading conditions, and thereby increase the susceptibility to heart failure after the added insult of RVP (16,17).

There is a variable timeframe of pacing induced LVD with some patients deteriorating rapidly with overt heart failure with the first year whereas others having a gradual decline in ejection fraction. The reason for these differences are unclear but suggest heterogeneity in susceptibility to pacing induced LVD. In our cohort, increasing age was an independent predictor of early LVD. With increasing age there is generally less reserve against any physiological stressors and therefore in the setting of RVP, elderly patients may be less likely to tolerate this compared to younger counterparts. There is already evidence to suggest risk of pacing induced heart failure does increase in older age groups (9,12,13). The reason why valvular heart disease may have been associated with apparent protection against early development of LVD in the CRT group may be due to the confounding nature of loading conditions (such as mitral valve regurgitation) with ejection fraction.

Our study was different to others evaluating pacing induced heart failure, in that it examined all patients who had generator changes and CRT upgrades in a set time period and then ascertained whether they had EF≥50% pre-implant and at least 40% RVP. Both groups had median 99% ventricular pacing and were similar with regard to pacing characteristics – lead position and indication for pacing. The similarities between these groups enabled the investigation of factors which would be associated with the development of heart failure without having to adjust for amount of ventricular pacing or LV function or site of pacing etc.

The clinical pathway of screening patients with an echocardiogram prior to generator change enabled comprehensive detection of pacing induced LVD. This together with data regarding the initial implant allowed a timeline of development of LVD to be built detailing patients who developed heart failure early on after pacing but also those that gradually deteriorated.

For patients with LVEF 35-50% who are anticipated to have high burden of RVP, international guidelines provide class II recommendations for either Cardiac Resynchronisation Therapy or His Bundle pacing as an alternative to RVP to decrease risk of pacing induced Heart failure (18,19). However in patients with LVEF>50% who need RVP consistently, there is no established guidance as how to avoid Heart Failure. The results from our study suggest that in patients with either CKD, history of MI or AF may potentially benefit from alternative pacing modalities such as CRT or conduction system pacing. These techniques are however associated with more complications than conventional RVP with other disadvantages (19). CRT requires three leads and though conduction system pacing only requires two, long term data is lacking. Confirmation of our results will require prospective studies with longer follow up.

Limitations

The main limitations of this study include its retrospective design and being a single-centre site, albeit from a high volume centre. Electrocardiographic data was incomplete for GC group however given the similar lead positions and RVP percentage with the CRT group, it is unlikely that the paced QRS duration would have had a significant effect on the study results. The lack of pre-implant data limited the patients included in the study and may have caused bias however this occurred in only 9 cases. In the case of AF and CKD it is unclear whether these factors occurred prior to or after pacemaker implant and therefore may be a consequence rather cause of the ensuing LVD / Heart Failure. Nevertheless both CKD and

AF are both likely to be pathogenic with potentiation of Heart failure being instigated in a vicious cycle (16,17).

## Conclusion

We have found that atrial fibrillation, chronic kidney disease and male gender are independent predictors for development of pacing induced left ventricular dysfunction in those patients who have a high RVP burden and LV ejection fraction ≥ 50%. Increasing age at implant is associated with rapid deterioration in those patients that develop LVD. Larger prospective studies with longer follow up are needed to confirm these findings.

**Funding:** None

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**Table 1:** Baseline characteristics

| Variables | CRT upgrade n= 75(%) | Generator change n=71 (%) | p value |
|---|---|---|---|
| Age (yrs) | 77 (±12) | 79 (±15) | 0.35 |
| Age at implant (yrs) | 68 (±14) | 67 (±18) | 0.7 |
| Gender | | | 0.008 |
| Female | 19 (25) | 33 (46) | |
| Male | 56 (75) | 38 (54) | |
| **Comorbidities** | | | |
| Diabetes | 25 (33) | 19 (27) | 0.4 |
| Hypertension | 40 (53) | 41 (58) | 0.6 |
| Ischaemic heart disease | 31 (41) | 12 (17) | 0.001 |
| MI prior PPM implant | 20 (27) | 9 (13) | 0.03 |
| MI after PPM implant | 11 (14) | 3 (4) | 0.02 |
| Atrial Fibrillation (AF) | 49 (65) | 31 (43) | 0.009 |
| Paroxysmal/persistent AF | 14 (19) | 11(16) | 0.6 |
| Permanent AF | 35 (46) | 19 (27) | 0.01 |
| Valvular heart disease | 20 (27) | 14 (20) | 0.4 |
| Functioning prosthetic valve | 9 (12) | 9 (13) | |
| Moderate prosthetic valvular disease | 9 (12) | 3 (4) | |
| Moderate native valvular disease | 2 (3) | 2 (3) | |
| Chemotherapy exposure | 2 (3) | 0 (0) | 0.16 |
| Chronic kidney disease with eGFR <60 | 46 (61) | 27 (38) | 0.005 |
| CKD 3a | 19 (25) | 16 (23) | |
| CKD 3b | 21 (28) | 6 (8.5) | |
| CKD 4 | 6 (8) | 5 (7) | |
| RV pacing % (median; IQR) | 99 (90-100) | 100 (99-100) | 0.08 |
| Years since implant | 8 (±6) | 11 (±4.5) | 0.01 |
| Paced QRS duration (pQRSd) | 153 (±17) | 136 (±10) | <0.0001 |
| RV lead position | | | 0.104 |
| Apical | 48 (64) | 36 (51) | |
| Non apical | 27 (36) | 35 (49) | |
| LV systolic function (EF %) at the time of GC (median;IQR) | 35 (29-40) | 58 (56-60) | <0.001 |
| >55 | 0 (0) | 65 (92) | -- |
| 51-55 | 0 (0) | 6 (8) | |
| 46-50 | 1(1) | 0 (0) | -- |
| 41-45 | 11 (15) | 0 (0) | -- |
| 36-40 | 18 (24) | 0 (0) | -- |
| ≤ 35 | 45 (60) | 0 (0) | -- |
| **Indication** | | | 0.23 |
| Sicksinus syndrome/tachy brady syndrome | 4 (6) | 8 (11) | -- |
| Mobitz type II (second degree AV block) | 7 (9) | 3 (4) | -- |
| Complete heart block | 54 (72) | 51 (72) | -- |
| Slowly conducted AF | 7 (9) | 4 (6) | -- |
| Congenital complete heart block | 0 (0) | 3 (4) | -- |
| For AV node ablation | 3 (4) | 2 (3) | -- |

Data are presented as n (%) or mean ± standard deviation unless specified as median (IQR). P values indicate difference between CRT upgrade and Generator change groups. P<0.05 was considered statistically significant. CRT, cardiac resynchronisation therapy; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; GC, generator change; EF, ejection fraction; AV, atrioventricular. Chronic kidney disease was classified in stages by eGFR according to the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines.

**Table 2:** Independent predictors of Pacing induced Left Ventricular Dysfunction

| | **Univariable analysis** | | | **Multivariate analysis** | | |
|---|---|---|---|---|---|---|
| **Predictors** | **OR** | **CI** | **P value** | **OR** | **CI** | **P value** |
| Age (yrs) | 1.01 | 0.98-1.04 | 0.35 | | | |
| Age at implant (yrs) | 1 | 0.98-1.02 | 0.72 | | | |
| Gender (male) | 0.4 | 0.19-0.79 | 0.008 | 2.63 | 1.26-5.48 | 0.01 |
| Diabetes | 0.7 | 0.36-1.49 | 0.4 | | | |
| Hypertension | 1.2 | 0.62-2.3 | 0.59 | | | |
| Myocardial infraction prior implant | 2.68 | 1.13-6.34 | 0.025 | 0.124 | 0.19-1.22 | 0.12 |
| Presence of atrial fibrillation | 0.4 | 0.2-0.8 | 0.01 | 2.3 | 1.13-4.7 | 0.022 |
| Valvular heart disease | 0.7 | 0.31-1.47 | 0.32 | | | |
| Chronic kidney disease (eGFR <60) | 2.59 | 1.33-5.04 | 0.005 | 2.19 | 1.09-4.43 | 0.027 |
| RV lead position (apical) | 0.6 | 0.32-1.16 | 0.13 | | | |

CI, confidence interval; OR, odds ratio; eGFR, estimated glomerular filtration rate. P<0.05 was considered statistically significant.

**Table 3:** Comparison of characteristics in CRT Upgrade in those that developed LV dysfunction before and after 4 years

| Variables | Less than = 4 years n(%) | More than 4 years n(%) | p value |
|---|---|---|---|
| Age at implant (yrs) [mean± SD] | 73 (±9) | 65 (±15) | 0.003 |
| Gender (male) | 23(82) | 33(70) | 0.25 |
| Diabetes | 8(29) | 17(36) | 0.5 |
| Hypertension | 17(60) | 23(49) | 0.32 |
| Myocardial infraction prior implant | 5(18) | 16(34) | 0.13 |
| Presence of atrial fibrillation | 17(61) | 32(68) | 0.5 |
| Chronic kidney disease (eGFR <60) | 18(64) | 28(60) | 0.68 |
| RV lead position (apical) | 18(64) | 30(64) | 0.96 |
| Valvular Heart disease | 3(11) | 17(36) | 0.016 |
| Paced QRS duration (ms) [mean± SD] | 154 (±16) | 153 (±18) | 0.48 |

**Figure Legend**

**Figure 1**: Study design

**Figure 2**: Timeline plot illustrating the time to detection of LV dysfunction since PPM implant.

**Figure 3**: Correlation between Age at initial pacemaker implant and time to develop LV dysfunction since implant

**Figure 1:** Study design

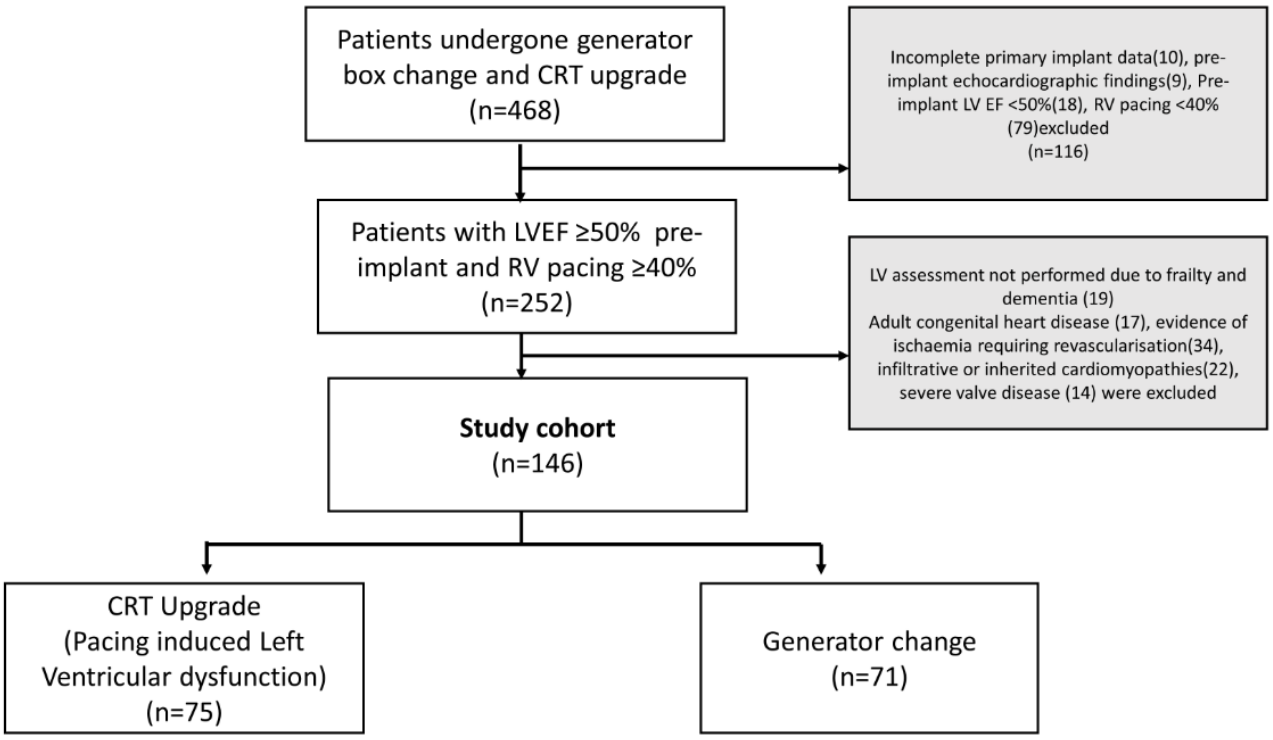

**Figure 2:** Timeline plot illustrating the time to detection of LV dysfunction since PPM implant.

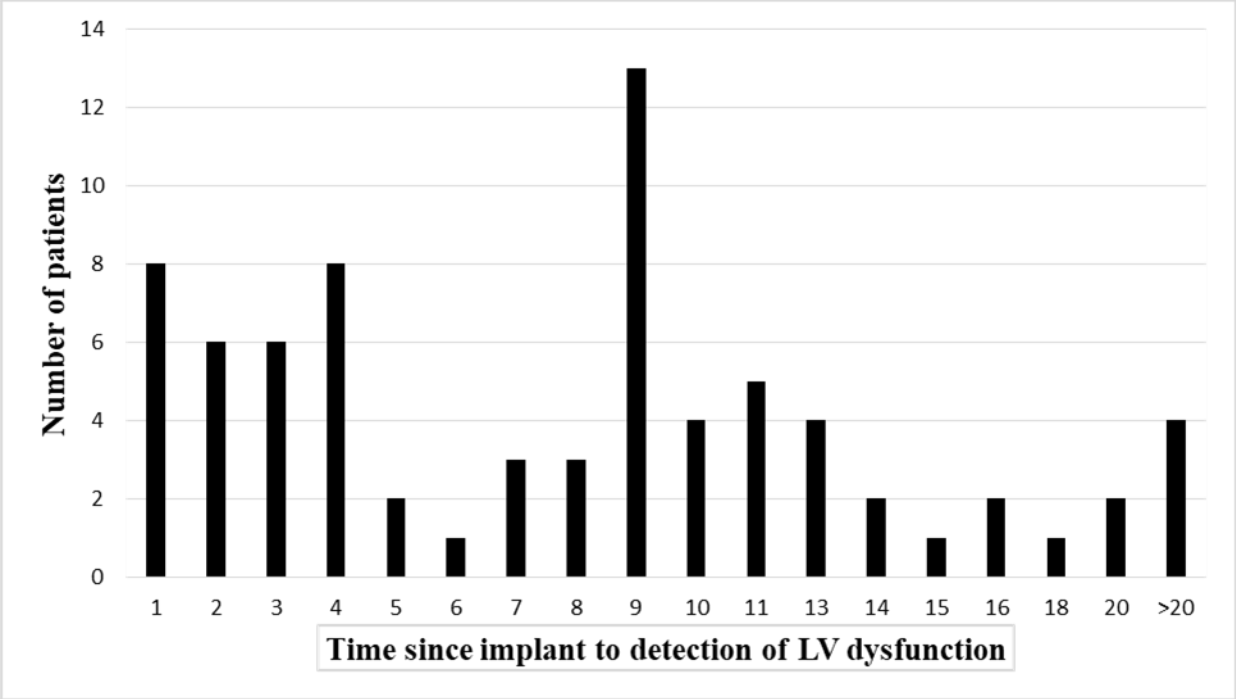


**Figure 3:** Correlation between Age at initial pacemaker implant and time to develop LV dysfunction since implant