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Progression of heart failure in right univentricular pacing compared to biventricular pacing

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Abstract

Background: Cardiac resynchronization therapy (CRT) improves hemodynamics and symptoms of heart failure by reducing ventricular dyssynchronity. Conversely, recent studies have demonstrated that right univentricular pacing in patients with an ejection fraction below 40% aggravates heart failure. In this retrospective study, we compared progression of disease in patients with mild to moderate heart failure that were treated with a right univentricular pacing device and patients with congestive heart failure that were treated with a biventricular system.
Methods: 107 patients were included. 59 received a right ventricular pacing device and 48 a biventricular system. Patients were assessed after 1 and 6 months by NYHA class, echocardiographic parameters (EF, LVEDD) and hospitalization for heart failure.
Results: Hospitalization for heart failure after implantation of the devices was more frequent in patients that received a conventional pacemaker with a single lead in the right ventricle than in patients that were treated with a CRT system (12% vs. 6%, $p<0.05$), although heart failure was more advanced in the CRT group at baseline. Ejection fraction in the right ventricular pacing group further decreased from 43%±4 at baseline to 38%±4 after 6 months ($p<0.05$). Left ventricular enddiastolic diameter (LVEDD) was 51±7 mm and 58±6 mm ($p<0.05$) at 6 months. In the CRT group, EF was 23%±4 at baseline and 31%±7 after 6 months ($p<0.05$.). LVEDD improved from 56±4 mm before implantation to 52±7 mm and 6 months ($p<0.05$).
Conclusion: Progression of heart failure symptoms in the right univentricular pacing group was more pronounced compared to the CRT group, despite the fact that patients assigned to the CRT group had more severe symptoms of heart failure at baseline. Biventricular pacing relieved symptoms of heart failure, whereas right univentricular pacing with subsequent conduction delay of the left ventricle further deteriorated pre-existing heart failure. Therefore, patients with an indication for pacemaker therapy because of bradycardia and co-existing mild to moderate heart failure might benefit from early implantation of a CRT system.

Keywords: Heart failure; CRT; Pacemaker; Hospitalization

1. Introduction

Intraventricular conduction delay in heart failure patients is very common. 30% of patients with non-ischemic cardiomyopathy display left bundle brunch block [1,2]. In patients with ischemic cardiomyopathy, 50% have a QRS complex >120 ms [3]. Intraventricular conduction delay in heart failure is correlated to decreased survival [4]. The loss of ventricular synchrony aggravates the symptoms of heart failure caused by decreased myocyte contractility. Recent studies [5–7] have demonstrated the beneficial effect of biventricular pacing or cardiac resynchronization therapy (CRT) on functional status and mortality [8,9]. Criteria for implantation of a CRT system are heart failure despite optimal drug therapy, intraventricular conduction delay of the left ventricle with a QRS duration >150 ms (>120 ms in some studies [6,7]) and an ejection fraction (EF) below

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Table 1
Baseline characteristics

	RV-PM group, $n=59$	CRT group, $n=48$
Age (years)	69±9	72±8
Gender	30 m/29 f	32 m/16 w
EF (%)	43.3±3.3	23±3.7
LVEDD (mm)	51.1±5.1	56±4.9
QRS duration (ms)	92.7±24	162±27
NYHA class	2.1	3.1
Diagnosis		
CAD	53	43
DCM	4	4
HHT	2	1
Medication		
β-Blocker	39	42
ACE-inhibitor	48	37
AT1-blocker	7	5
Diuretics	55	42
Digitalis	34	39
Spironolactone	19	13

Baseline characteristics. RV-PM=right univentricular pacing, CRT=cardiac resynchronisation therapy, EF=ejection fraction, LVEDD=left ventricular enddiastolic diameter; CAD=coronary artery disease, DCM=dilative cardiomyopathy, HHT=hypertensive heart disease. Diagnosis is given in absolute patient numbers.

35%. As demonstrated recently [9], additional ICD function of the device seems reasonable.

Conversely, recent trails (MADIT II [3], DAVID [10]) have demonstrated that right univentricular pacing aggravates pre-existing heart failure. This might be caused by induction of ventricular dyssynchronity under pacing conditions. Heart failure patients with chronic atrial fibrillation that require pacemaker therapy because of bradycardia also have improved exercise tolerance under biventricular stimulation [11].

Given the results from this trials, patients with the necessity for pacemaker therapy and only mild heart failure (i.e. ejection fraction <45%) and normal intrinsic QRS duration might profit from biventricular stimulation compared to single right ventricular stimulation.

However, to date there are no data on CRT in patients with mild heart failure (EF 35–45%), conventional pacemaker indication and normal ORS duration. Implantation of a pacemaker with a single lead for the right ventricle in these patients would cause left bundle brunch block under pacing conditions resulting in ventricular dyssynchronity. It is not clear whether early implantation of a CRT system to prevent intraventricular conduction delay under pacing conditions in these patients is beneficial.

The intention of this study was to investigate whether patients with indication for a normal pacemaker system and accompanying mild heart failure might profit from early implantation of a biventricular pacing system although they have no intrinsic conduction delay. The natural history of heart failure shows progression of disease [12–14].

Therefore, in this retrospective study, we compared progression of disease and clinical outcome of two groups of heart failure patients: (a) heart failure patients that have received a CRT system according to the current recommendations (EF below 35% and an intrinsic QRS duration >130 ms) and (b) heart failure patients with an ejection fraction between 35% and 45% and normal intrinsic QRS duration (<100 ms) that have received a right univentricular pacemaker resulting in a paced QRS duration over 180 ms. Indication for pacemaker implantation was sick-sinus syndrome or higher degree AV-block.

2. Methods

2.1. Patient selection

In the screening period, 278 patients that received a pacemaker and 57 CRT patients were screened for matching the inclusion criteria. From the screened patients, we included and investigated 59 subsequent patients that received a conventional pacemaker with a right univentricular lead and 48 CRT subsequent patients that received a CRT system. All patients were in sinus rhythm.

Reasons for implantation of a pacemaker were sick-sinus syndrome or higher degree AV-block. Inclusion criterion for the retrospective analysis for the right univentricular pacemaker group was a paced QRS duration >180 ms during right ventricular (RV) pacing. Intrinsic QRS duration had to be <100 ms. Ejection fraction had to be between 35% and 45% (as determined by echocardiography) and patients were NYHA class II at least. Patients received optimized drug treatment for heart failure, i.e. diuretics, digitalis and ACE-inhibitors or AT-receptor blockers. However, particularly in this group, some patients were not treated with β-blockers before implantation of a pacemaker because of bradycardia. In this case, β-blocking agents (metoprolol or bisoprolol) were started after pacemaker implantation. For detailed drug therapy, see Table 1.

The reason for implantation of a CRT system was treatment of heart failure. Patients in the CRT group fulfilled the criteria according to current guidelines [15,16], i.e. ORS duration >130 ms, left bundle brunch block, EF<35%, NYHA III–IV and optimized drug therapy for heart failure. The majority of these patients were on β-blocking agents before implantation (Table 1). All patients in our population received a combined CRT/ICD system.

2.2. Device description

CRT devices were capable of providing both CRT and ICD therapy (Contak Renewal II, Guidant Corporation). The left ventricular lead (EasyTrak 3 coronary venous pace/sense lead, Guidant Corporation) was placed via the coronary sinus preferably in a lateral vein. Atrial lead was Flextend 2 (Guidant Corporation) and ventricular pace/sense-ICD lead was Endotak Reliance RV (Guidant Corporation).

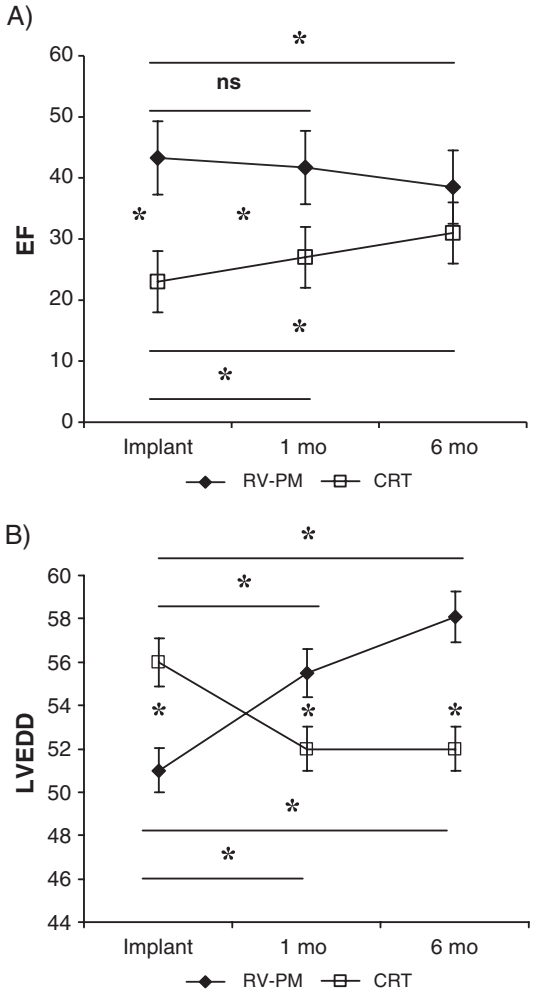

Fig. 1. Echocardiographic data. (A) Ejection fraction (EF) of RV-pacemaker and CRT patients at implantation and after 1 and 6 months of follow-up and (B) left ventricular enddiastolic pressure (LVEDD) of the same patients.

Conventional pacemakers were Saphir 3 VDD or Clarity DDD (Vitatron), Elect VDD or Elect D DDD (Sorin) and Integrity DDD (St. Jude). Pacemaker leads were Pirouet (active fixation), Crystalline (passive fixation) or Brilliant VDD (Vitatron).

2.3. Study design

This retrospective study is an intra-patient long-term follow-up for patients that received either a right univentricular pacemaker or a CRT system. Baseline testing was paced QRS duration, echocardiographic examination, NYHA class and assessment for hospitalization for heart failure. This was followed by a longitudinal follow-up after 1 and 6 months. At these points, QRS duration, echocardiographic examination, NYHA class and hospitalization for heart failure were assessed. Thus, baseline and 1- and 6-month follow-up parameters were compared within the patient groups and between the patient groups. Patients in the pacemaker group had to have a ventricular pacing rate of at least 50% over time to be included. This inclusion criterion was assessed a posteriori. Percentage of pacing was confirmed from data from the device.

2.4. Evaluated parameters

The best pacing site for the LV lead was tested by assessment of ventricular dyssynchronity with transesophageal echocardiography (TEE) and by continuous measurement of the arterial blood pressure during the implantation procedure.

For the follow-up, patients were evaluated with NYHA class, 12-lead surface electrocardiogram (ECG) and Doppler echocardiography. The QRS duration was measured during biventricular pacing or right univentricular pacing with a basic rate of 65 beats/min. The LV ejection fraction and the LV enddiastolic diameter were assessed echocardiographically under right univentricular pacing in the pacemaker group and under biventricular pacing in the CRT group, respectively. The LV dimensions were measured by two-dimension guided M-mode method and ejection fraction was assessed according to the method of Simpson. All tests were performed at baseline and after 1 and 6 months. Hospitalizations and pacemaker complications were monitored at each follow-up.

2.5. Statistical analysis

Two different comparisons were made: (A) a within-group analysis between baseline and follow-up data for the pacemaker and the CRT groups and (B) a between-group analysis for the baseline and the follow-up data of the pacemaker and the CRT group. The baseline characteristics and follow-up data of the two groups (right univentricular versus CRT) were compared using Mann–Whitney test. The within-group differences (baseline vs. follow-up) were compared using the Wilcoxon test. Echocardiographic measurements are summarized as medians along with the 95% confidence interval for the median. Threshold of significance was set 0.05. Values are presented as mean ± S.E.M.

3. Results

3.1. Pacemaker/ICD performance

Implantation of the devices and leads in the RV-pacemaker (PM) group was uneventful. RV leads were placed in the RV apex. No revision had to be performed. In the CRT group, two patients had to be revised because of dislocation of the RV lead. In five patients, the LV lead could not be placed in the coronary sinus/lateral vein. Epicardial leads were used instead (Medtronic CapSure Epi Steroid Eluting). No other complications related to the LV lead were found.

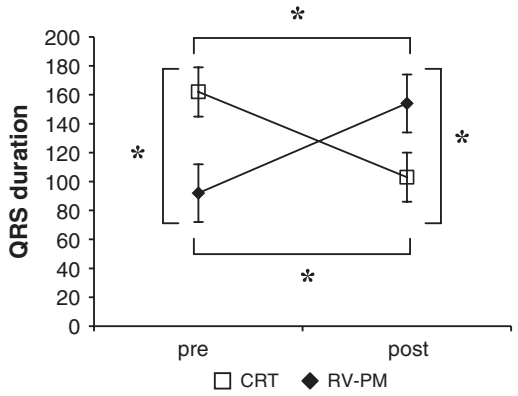

Fig. 2. QRS duration in the right univentricular pacing group (RV-PM) and in the cardiac resynchronisation therapy (CRT) group. Values are before (pre) and after (post) implantation of devices.

3.2. Clinical characteristics

The clinical characteristics at baseline are presented in Table 1. The indication [15] for implantation of a CRT system was treatment of heart failure. Reasons for implantation of a pacemaker were sick-sinus syndrome, or second or third degree AV-block. Patients were in sinus rhythm at implantation and throughout the follow-up checks. All patients received atrial and ventricular leads to assure AV-sequential pacing. Mean age was 69±9 in the right univentricular pacing group (PM) group and 72±8 in the CRT group. Of the 59 pacemaker patients, 30 were male and 29 female. Of the 48 CRT patients, 32 were male and 16 were female. Mean ejection fraction was 43.3±3.3% in the pacemaker patients and 23±3.7% in the CRT patients. Mean left ventricular enddiastolic diameters were 51.1±5.1 (PM) mm and 56±4.9 mm (CRT), respectively. Intrinsic QRS duration was 91±24 ms at average (PM) and 162±27 ms (CRT). Average NYHA class was 2.1 in the PM group and 3.1 in the CRT group. 39 patients in the pacemaker group received β-blocker before implantation. All patients in this group were set on β-blocker after implantation of the device. The majority of patients in the CRT group were on β-blockers before implantation. Most of the 107 patients received diuretics, digitalis and ACE-inhibitors or AT-receptor blockers. For detailed drug therapy, see Table 1. The baseline characteristics presented here demonstrate that patients receiving a CRT device had more severe heart failure compared to the right univentricular pacing group. Patients with underlying coronary artery disease were fully revascularized. No ischemic episodes were documented.

3.3. Echocardiographic data

The LV echocardiographic data are given in Fig. 1. In the pacemaker group, ejection fraction (EF) decreased significantly during the follow-up period. Mean EF was 43%±4 at baseline, 41%±5 (p=n.s.) after 1 month and 38%±4 after 6 months ($p<0.05$). Mean left ventricular enddiastolic diameter (LVEDD) was 51±7 mm and deteriorated as well over time with 55±5 mm ($p<0.05$) after 1 month and 58±6 mm ($p<0.05$) at 6 months.

In the CRT group, EF increased over time with 23%±4 at baseline, 27%±5 after 1 month and 31%±7 after 6 months ($p<0.05$). LVEDD improved from an average of 56±4 mm before implantation to 52±7 mm at 1 and 6 months ($p<0.05$).

Pre-existing mitral regurgitation became worse in the pacemaker group after starting right ventricular pacing. Average vena contracta diameter was 3.8±0.8 mm before and 6.2±0.6 mm after implantation ($p<0.05$). Patients without mitral regurgitation did not develop regurgitation after pacing therapy started. In the CRT group, average vena contracta diameter was 6.8±0.8 mm before and 5.2±0.3 mm after implantation ($p<0.05$).

3.4. QRS duration and percentage of pacing

In the RV pacing group, the mean percentage of ventricular pacing was 78±13% (range 50% to 100%). The ventricular pacing rate in the CRT group was 100% because of short programmed V delays.

In the right univentricular pacing group, the QRS duration increased from 92±24 ms at average (not paced) to 154±27 ms in the paced QRS complexes ($p<0.01$). In the CRT group, QRS duration decreased from 162±27 ms to 103±17 ms in paced QRS complexes ($p<0.01$) (Fig. 2). Values were taken in the direct post-implantation period. However, in the CRT group, there were six “non-responders” with no improvement in QRS duration, despite correct anatomical position and function (pacing threshold, sensing). Intrinsic QRS duration did not change significantly at the follow-up points in both groups. In the CRT group, intrinsic QRS duration was 159±23 ms at 1 month and 157±17 ms at 6 months. In the PM group, intrinsic QRS duration increased from 98±20 ms at 1 month to 104±19 ms at 6 months.

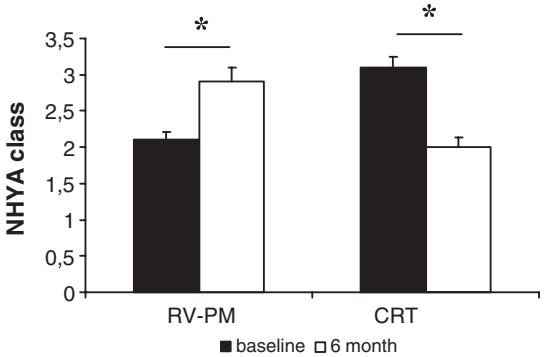

Fig. 3. Functional NHYA class. Patients with mild heart failure symptoms that were treated with a right univentricular pacing lead showed significant worsening of their NYHA class. Patients with heart failure NHYA class III experienced a significant improvement of their condition after implantation of a CRT device.

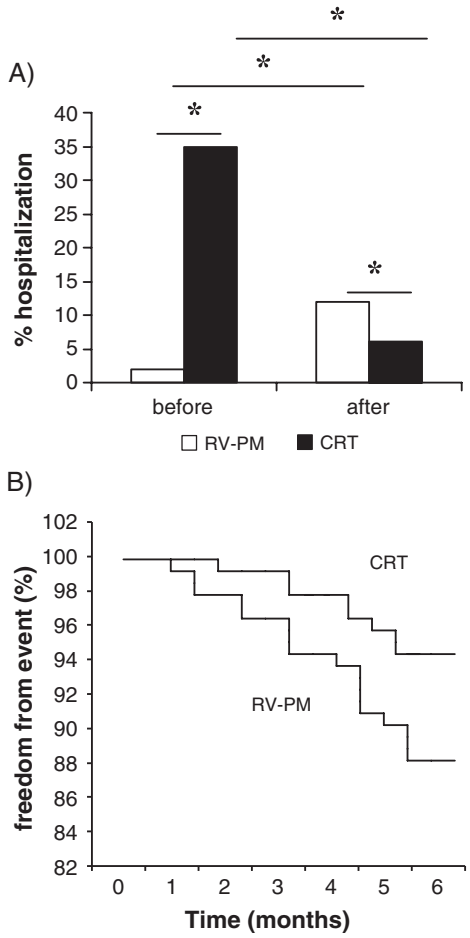

Fig. 4. (A) Number of hospitalisations for heart failure 6 months before and after implantation of devices. (B) Kaplan–Meier curve for heart failure hospitalization. RV-PM = right univentricular pacing, CRT = cardiac resynchronisation therapy.

3.5. Hospitalizations for heart failure and NYHA class

The NYHA class worsened from 2.1 ± 0.3 in the PM group to 2.9 ± 0.3 ($p < 0.05$) and improved from 3.1 ± 0.4 to 2 ± 0.3 in the CRT group ($p < 0.05$) as demonstrated in Fig. 3.

Before implantation of a pacemaker with a right univentricular lead, hospitalization for heart failure was 2% (1 patient) in the pacemaker group. In the CRT group, 17 patients (35%) ($p < 0.05$) had to be admitted to a hospital because of heart failure within 6 months before implantation. In the 6 months after implantation of the devices, in the pacemaker group, seven patients (12%) had to be hospitalized; in the CRT group, there were only three patients (6%) ($p < 0.05$) admitted to the hospital because of heart failure (Fig. 4).

4. Discussion

The medical interest in heart failure (HF) has been greatly stimulated by the epidemic proportions it has taken in the last 30 years. In recent data from the Framingham study, the lifetime risk for developing HF has been estimated to be 1 in 5 both in men and in women. Prognosis of heart failure is bad. Median survival after onset of symptoms is about 3 years at best [17]. Pharmacological approaches could decrease mortality by 46% as shown in clinical trials in the last 10 years [18]. Despite these major advances in medical therapy, heart failure is still the leading cause of death in the western world. Pump failure and fatal rhythm disturbances are responsible each for 50% of deaths in those patients [18].

Recent studies [3,19] have proven the benefits of ICD therapy on mortality. Additional studies on the more specialized form of cardiac resynchronization therapy demonstrated improvements in heart failure symptoms, hospitalization [5–7,20] and mortality [8,9].

In cardiac resynchronization therapy, patients with a conduction delay in the left ventricle receive an additional left ventricular pacing lead via the coronary sinus or, alternatively, an epicardial lead. This improves ventricular dyssynchrony and left ventricular function and may subsequently relief symptoms of heart failure. There is evidence that even heart failure patients with narrow QRS complexes profit from biventricular stimulation if there is ventricular dyssynchrony [21].

To date, only small studies [22] investigated outcome or progression of disease in patients with heart failure that received either conventional right univentricular pacing, compared to patients that received a CRT system. Hansen et al. investigated acute hemodynamic effects [23]. The study by Leon et al. [11] investigated the effects of upgrading of right univentricular pacing to biventricular pacing and Leclercq et al. [22] demonstrated the impact of biventricular pacing compared to right univentricular pacing in a cross-over design in patients with pre-existing left bundle branch block. In the latter two studies, patients were in chronic atrial fibrillation. Despite several shortcomings of these studies, biventricular pacing seemed to be superior to conventional right univentricular pacing in patients with heart failure. The objective of this study was to compare further progress of heart failure after implantation of pacemakers or CRT systems with the hypothesis that early implantation of a CRT system in regular pacemaker patients might be beneficial.

In this study, patients were selected to have stable NYHA II–IV heart failure despite optimized medical treatment. The majority of patients in both groups were on stable drug therapy before and after implantation of the devices. Therefore, alterations in drug therapy may not account for changes in clinical outcome. Patients in the pacemaker group had to have a ventricular pacing rate of at least 50% over time to be included. CRT patients were paced for 100% in the ventricles. Pacing mode was VDD or DDD in both groups to assure AV sequential pacing. Here, two distinct patient populations were compared: Patients with mild heart failure, normal intrinsic QRS duration and indication for a normal (right univentricular) pacemaker and patients with

standard indications for a CRT system, i.e. advanced heart failure and QRS duration >130 ms.

In the CRT group, biventricular pacing reduced QRS duration significantly. The successful hemodynamic effects of biventricular pacing were regularly tested during implantation of the LV lead. However, in a small subset of patients, there was no effect of left ventricular pacing on QRS duration. This is in line with other studies that observed up to 30% of electrophysiological non-responders to CRT therapy [24]. The putative mechanisms have been discussed elsewhere [25,26].

During follow-up, echocardiographic measurements were performed under stimulation in both groups. In the RV pacemaker group, the LV ejection fraction (EF) decreased significantly after 1 and 6 months. Conversely, in the CRT group, EF increased significantly. These findings are in accordance with other studies on CRT and provide evidence for reverse remodeling of the myocardium [27,28].

A hallmark of this study is the functional improvement caused by CRT compared to right univentricular pacing. NYHA class was significantly improved in the CRT group, whereas RV pacing worsened NYHA class. The relief in heart failure symptoms in the CRT group was comparable in this study to the results reported in other trials [5–9].

Hospitalization of heart failure patients causes the highest costs for those patients in the whole treatment for heart failure [29]. Several studies of CRT have demonstrated beneficial effects of this therapy on hospitalization rates. Therefore, CRT may be cost-effective [30]. Hospitalization due to heart failure is also a surrogate parameter for the progression of the disease. In this study, we observed a significantly higher hospitalization rate of heart failure in patients treated with right ventricular pacing compared to CRT patients. As demonstrated by this and other studies, CRT can slow the progression of heart failure. In contrast, solely right ventricular pacing might further aggravate pre-existing heart failure by causing ventricular dyssynchrony in the pacing mode as demonstrated in the MADIT II and DAVID trails [3,10]. Recently, the “Mode Selection Trial Investigators” confirmed this finding [31]. Furthermore, it has been suggested that permanent ventricular pacing is a risk factor for the development of heart failure. Many trials [31–34] compared pacing modes in patients with an indication for pacing. In general, these studies demonstrate that intrinsic activation of the ventricles is superior to right ventricular pacing because a high percentage of right ventricular pacing increased the incidence of heart failure or deteriorated pre-existing heart failure.

Mortality was not an endpoint in this study as we compared pacemaker patients with patients that received a combined CRT/ICD device. Also hospitalization due to device associated problems was not taken into account here.

A result of this study is that CRT can improve symptoms of heart failure and even slow progression of the disease which is in line with other observations [5–9], despite the fact that the natural course of heart failure shows progression even under optimized medical treatment [12–14,35] and the median survival of patients with asymptomatic left venricular dysfunction was 7 years [13].

However, the major finding here is that right univentricular pacing in patients with heart failure further deteriorates their condition. This is remarkable as patients in the RV-PM group predominantly had only moderate heart failure (EF 35–45%, NYHA II). Nevertheless, hospitalization was more frequent and the deterioration in echocardiographic data was more intense as compared to the CRT group (EF<35%, NYHA III–IV) with already severe heart failure at baseline.

4.1. Limitations

From current data, there is no justification for implantation of a CRT device in patients with mild heart failure and normal QRS duration. Therefore, in this study, we compared two patient groups with differences in baseline characteristics. As a major result, we found that the PM group that had better baseline values with regard to heart failure experienced further worsening of symptoms, whereas the CRT group, despite more symptoms of heart failure at baseline, improved within 6 months.

Sample size in the groups was not large enough to detect significant differences in subgroups like different etiologies of heart failure. Also more objective parameters like 6 min walk test or peak oxygen consumption were not used in this study, as chronotropic incompetent patients in the RV pacemaker group have decreased exercise tolerance not only by heart failure but also by bradycardia, whereas the intention of CRT is not to relieve bradycardia-induced symptoms but rather to improve heart failure-related symptoms.

5. Conclusions

The main finding of this study was a significant increase in hospitalization of heart failure patients treated with a right univentricular pacemaker compared to CRT patients. Remarkably, heart failure was less advanced in the RV pacing group at baseline testing but outcome was worse than in the CRT group. Right ventricular pacing causes conduction delay of the left ventricle resulting in ventricular dyssynchrony. This condition was prevented in patients receiving a CRT system. Significant changes in echocardiographic parameters were observed also. With the limitations of this study in mind we conclude, that patients with only mild heart failure and the need for a conventional pacemaker might profit from early implantation of a CRT system. First controlled studies with longer follow-up periods and larger patient numbers started to establish beneficial effects of CRT in heart failure patients with an indication for pacemaker therapy but without pre-existing left bundle branch block [36].

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