

Late deterioration of left ventricular function after right ventricular pacemaker implantation

Barbara Bellmann^{1,2}, Bogdan G. Muntean¹, Tina Lin⁵, Christopher Gemein^{2,4}, Kathrin Schmitz², Patrick Schauerte^{2,3}

¹Department of Cardiology, Charité Berlin Campus Benjamin Franklin; Berlin-Germany

²Department of Cardiology, University Hospital Aachen RWTH; Aachen-Germany

³Kardiologie an der Rudower Chaussee; Berlin-Germany

⁴Department of Cardiology, University Hospital Gießen; Gießen-Germany

⁵Heartcare Victoria-Australia

ABSTRACT

Objectives: Right ventricular (RV) pacing induces a left bundle branch block pattern on ECG and may promote heart failure. Patients with dual chamber pacemakers (DCPs) who present with progressive reduction in left ventricular ejection fraction (LVEF) secondary to RV pacing are candidates for cardiac resynchronization therapy (CRT). This study analyzes whether upgrading DCP to CRT with the additional implantation of a left ventricular (LV) lead improves LV function in patients with reduced LVEF following DCP implantation.

Methods: Twenty-two patients (13 males) implanted with DCPs and a high RV pacing percentage (>90%) were evaluated in term of new-onset heart failure symptoms. The patients were enrolled in this retrospective single-center study after obvious causes for a reduced LVEF were excluded with echocardiography and coronary angiography. In all patients, DCPs were then upgraded to biventricular devices. LVEF was analyzed with a two-sided t-test. QRS duration and brain natriuretic peptide (BNP) levels were analyzed with the unpaired t-test.

Results: LVEF declined after DCP implantation from $54\pm 10\%$ to $31\pm 7\%$, and the mean QRS duration was 161 ± 20 ms during RV pacing. NT-pro BNP levels were elevated (3365 ± 11436 pmol/L). After upgrading to a biventricular device, a biventricular pacing percentage of $98.1\pm 2\%$ was achieved. QRS duration decreased to 108 ± 16 ms and 106 ± 20 ms after 1 and 6 months, respectively. There was a significant increase in LVEF to $38\pm 8\%$ and $41\pm 11\%$ and a decrease in NT-pro BNP levels to 3088 ± 2326 pmol/L and 1860 ± 1838 pmol/L at 1 and 6 months, respectively.

Conclusion: Upgrading to CRT may be beneficial in patients with DCPs and heart failure induced by a high RV pacing percentage. (*Anatol J Cardiol* 2016; 16: 678-83)

Keywords: CRT, pacemaker-mediated cardiomyopathy, pacemaker, heart failure, LV lead

Introduction

Cardiac pacing is an effective treatment option for patients with sick sinus syndrome (SSS) and atrioventricular conduction disorders. During the implantation of permanent pacemaker devices, the endocardial right ventricular (RV) pacing lead is often positioned at the RV apex. Previous studies have demonstrated that RV pacing (RVP) in patients with dual chamber pacemakers (DCPs) can produce long-term deleterious effects in the left ventricle (LV) not only in a previously compromised LV but also in patients with normal LV function (1, 2). RVP leads to abnormal myocardial activation and mimics a left bundle branch block with delayed activation of the LV free wall. During RVP, the electrical wave front propagates more slowly through the myocardium than the physiological recruitment of the His-

Purkinje system, which occurs during sinus rhythm. This leads to electrical and mechanical dyssynchrony, with a potential induction of heart failure (HF) and a decrease in cardiac output (3, 4). On a cellular level, RVP evokes mitochondrial variations and degenerative fibrosis (5). In addition, pacemaker-induced cardiomyopathy can lead to regional perfusion abnormalities and inadequate oxygen demand (6, 7). Patients with DCPs presenting with reduced LV ejection fraction (LVEF) are often considered as candidates for biventricular pacemaker or defibrillator implantation.

This study retrospectively investigates whether upgrading DCP to cardiac resynchronization therapy (CRT) with the addition of an LV lead improves LV function in patients in whom a reduction of LVEF was noticed late after DCP implantation without other identifiable causes of underlying heart disease.

Address for correspondence: Barbara Bellmann MD, Department of Medicine-Cardiology, Charité Berlin Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin-Germany
E-mail: barbara.bellmann@charite.de

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Methods

German patients from the University Hospital of Aachen, Germany, treated between 1997 and 2012 with DCPs because of symptomatic bradycardia (SSS, high-grade atrioventricular block) for an average period of 5 years were included in this retrospective single-center study. They presented with clinical symptoms and signs of HF, a high ventricular pacing percentage (>90%), and a decrease in LVEF (Table 1). Patients with a recently diagnosed reduced LVEF and clear reasons for this impaired LVEF, such as the progression of coronary heart disease or a new relevant valvular heart disease, were excluded from the study. All patients included in the analysis had RV leads positioned in the RV apex. DCPs were programmed to DDD pacing mode with a lower rate of 60 beats per min (bpm) and with a physiological atrioventricular delay. All patients underwent a thorough cardiovascular examination, as well as a transthoracic echocardiography (TTE) and coronary angiography, to rule out the progression of or new onset of a heart disease leading to HF. Coronary artery disease was ruled out in 10 patients. Twelve of 22 patients had a history of coronary artery disease (Table 1) and angiographically showed no progress. A relevant valvular heart disease as a cause of HF was excluded by echocardiography in all patients. In all patients, the reprogramming of the pacemaker device in an attempt to reduce the RVP percentage was not possible due to an intrinsic ventricular rhythm lower than 30 bpm. All patients were optimized on guideline-based HF medication comprising angiotensin-converting enzyme inhibitors (ACE-inhibitor), beta-blockers, diuretics, and mineralocorticoid receptor antagonists. All 22 patients had well-controlled arterial hypertension with normotensive blood pressure (<135/85 mm Hg) during the hospital stay. This was also confirmed in the daily conducted routine blood pressure measurements. DCPs were then upgraded to biventricular devices with the implantation of an LV lead. In addition, 15 of the 22 patients were upgraded to a CRT-defibrillator device. The CRT pacemaker devices were programmed with standard monitor zones for the detection of ventricular arrhythmias (>170 bpm).

Follow-up

All patients were followed-up at 1, 6, and 12 months after the CRT implant. At each follow-up, clinical examination, TTE, 12-lead ECG, and device interrogation were performed. In addition, NT-pro brain natriuretic peptide (BNP) levels were assessed to evaluate the severity of HF.

Statistical analysis

Continuous variables were expressed as mean±standard deviation. LVEF was analyzed with a two-sided t-test after testing with the Shapiro–Wilk method for normal distribution. A p-value of <0.05 was considered to be statistically significant. QRS duration and BNP levels were analyzed with the unpaired t-test due to abnormal distribution.

Table 1. Baseline characteristics

Number of patients	22
Sex, male/female	13/9
Age, years (average, SD)	71±11
LVEF, % (average, SD)	37±7
Ventricular pacing percentage, % (average, SD)	90±14
Sick Sinus Syndrome	1/22
Brady-tachy Syndrome	11/22
3 rd degree atrioventricular block	10/22
Atrial fibrillation	13/22
Coronary heart disease	12/22
Arterial hypertension	22/22
Valvular heart disease	5/22
Diabetes mellitus	5/22
Renal impairment	8/22
Beta-blocker	22/22
ACE-inhibitor	22/22
Diuretics	22/22
Mineralocorticoid receptor antagonist	22/22
Statin	22/22
Age, LVEF, and ventricular pacing percentage were expressed as mean±standard deviation. SD- standard deviation	

Results

During a 1-year period in 2014, 2250 patients with implanted pacemakers underwent routine device interrogations in the University Hospital of Aachen, Germany. Twenty-two patients (13 males, age=71 years) with DCPs and high RVP percentages (>90%) were evaluated because of clinical symptoms and signs of HF. The average period from DCP implantation to HF onset was 5 years (shortest, 2 years; longest, 17 years). LVEF significantly declined from the initial 54±10% to 37±7% (p=0.001), and the mean QRS duration was 161±20 ms during RVP. Clinical signs included dyspnea (NYHA class III) and peripheral edema. As an expression of HF, BNP levels were elevated (3365±11436 pmol/L). Twelve patients had coronary artery disease (Table 1). All patients underwent coronary angiography to exclude an ischemic cause of the newly emerged HF. Concomitant diseases included arterial hypertension (22/22), diabetes mellitus (5/22), and renal function impairment (8/22) with a glomerular filtration rate between 30 and 50 mL/min. Five patients suffered from 1st degree mitral regurgitation.

After other causes of HF were excluded, pacemaker-induced cardiomyopathy was assumed to be the cause for the reduced LVEF in these 22 patients. Therefore, all DCPs were upgraded to biventricular devices with the implantation of an LV lead. Only bipolar electrodes were used. These were positioned in the posterolateral vein in 16 patients and in the anterolateral vein in 6.

Table 2. BNP, QRS duration, and left ventricular ejection fraction of all CRT patients at baseline, advent of heart failure, and 1-, 6-, and 12-month follow-up

	Initial pacemaker implantation n=22	Baseline before Bivent upgrade n=22	Follow-up 1 month n=21	Follow-up 6 months n=12	Follow-up 12 months n=20
BNP, pmol/L (average, SD)	–	3365±11436	3088±2326	1860±1838	2177±2397
QRS, ms (average, SD)	80±15	161±20	108±16	106±20	100±11
LV ejection fraction, % (average, SD)	54±10	31±7	38±8	41±11	42±8
Biventricular pacing percentage, % (average, SD)	–	–	98±2	97±5	98±3

The variables were expressed as mean±standard deviation. SD - standard deviation

Follow-up

Twenty of the 22 patients completed the follow-up. The patient with the shortest period (2 years) between DCP implantation and HF onset was admitted to hospital with acute decompensated HF and died 2 weeks after LV lead implantation. One patient was lost to follow-up.

At the 1-month follow-up after CRT upgrade, LVEF significantly increased to mean 38±8% ($p=0.005$) compared with that before LV lead implantation (31±7%). There was a trend toward reduction in BNP levels from 3365±11436 pmol/L to 3088±2326 pmol/L ($p=0.28$). QRS duration decreased from 161±20 ms to 108±16 ms (Table 2, Fig. 1). A biventricular pacing percentage of 98±2% was achieved. One patient with CRT-D had atrial fibrillation at the 1-month follow-up. In this patient, the biventricular pacing percentage was reduced at 85%; however, this improved to 99% after successful cardioversion and the concomitant start of an antiarrhythmic therapy with amiodarone. There was an improvement in the symptoms of dyspnea to NYHA class II.

At the 6-month follow-up, LVEF increased further from 38±8% to 41±11% ($p=0.01$). Under biventricular pacing, QRS duration remained stable compared with that of the 1-month follow-up data (106±20 ms) (Table 2). BNP levels significantly decreased from 3088±2326 pmol/L to 1860±1838 pmol/L ($p=0.02$). In 1 patient from the CRT-D group, device interrogation detected ventricular tachycardia, which was appropriately identified and treated by the device with shock delivery. One patient was hospitalized because of a stroke in the middle cerebral artery territory after the autonomous withdrawal of anticoagulation. This anticoagulation was prescribed in atrial fibrillation with a CHA2DS2-VASc score of 3. For preventing thromboembolic stroke in patients with atrial fibrillation and a CHA2DS2-VASc score of >2, anticoagulation is mandatory. In this case, the patient himself had stopped the oral anticoagulation, which unfortunately was leading to a stroke. There was no thrombolytic therapy initiated in this patient. Oral anticoagulation with warfarin was continued. Fortunately, the patient was discharged from the hospital without any residual neurological sequelae.

At the 12-month follow-up, LVEF increased from 41±11% to 42±8% ($p<0.000$), and a biventricular pacing percentage of 98±3% was maintained. The average QRS duration was 100±11 ms. BNP levels significantly decreased from an initial 3365±11436 pmol/L to 2177±2397 pmol/L ($p=0.017$); however, there was a slight increase compared with the 6-month BNP levels (Fig. 1). Dyspnea improved

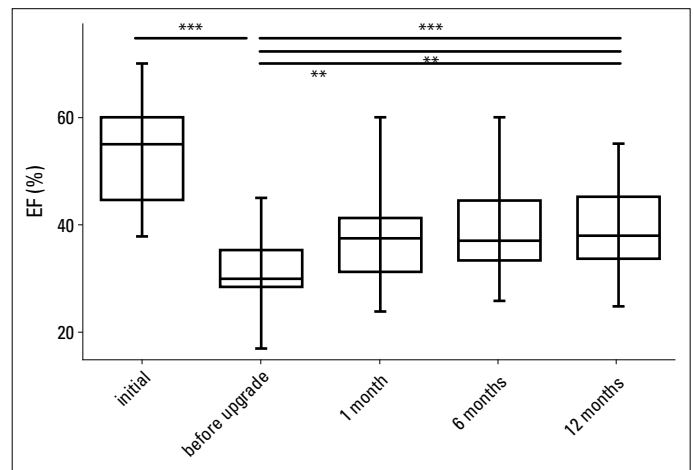


Figure 1. LVEF was analyzed with a two-sided t-test after testing with the Shapiro–Wilk method for normal distribution. A P -value of <0.05 was considered to be statistically significant

LVEF at initial dual chamber pacemaker implantation, heart failure advent and 1-, 6-, and 12-month follow-up. ***= P -value<0.005, **= P -value>0.005–0.01

to NYHA class II. Between the 6- and 12-month follow-up, no patient suffered from ventricular tachycardia or required ICD therapy. During the duration of the entire follow-up period, no patient received inappropriate ICD therapies. In all 20 patients who completed follow-up, no lead complications or device dysfunction occurred.

Subgroup analysis CRT-P

A subgroup analysis performed in 7 CRT-P patients demonstrated an improvement in LVEF, QRS duration, and BNP levels. LVEF before DCP implantation in this group was 59±11%, with a QRS duration of 80±12 ms. Before LV lead implantation, LVEF decreased to 35±6%, with a QRS duration of 158±15 ms. BNP levels were elevated at 2959±2957 pmol/L.

At the 1-month follow-up, LVEF increased from 35±6% to 39±7%, with a QRS duration of 96±16 ms. BNP levels were 3480±2805 pmol/L. At the 6-month follow-up, LVEF improved to 41±11%, with a QRS duration of 100±21ms. BNP levels decreased from 3480±2805 pmol/L to 2401±2805 pmol/L. At the 12-month follow-up, there were no further improvements in the parameters assessed. LVEF was 41±6%, QRS duration was 103±9 ms (Fig. 2a), and BNP levels were 3062±4816 pmol/L (Fig. 2b). Dyspnea improved from an initial NYHA class III-IV to NYHA class II at the 12-month follow-up.

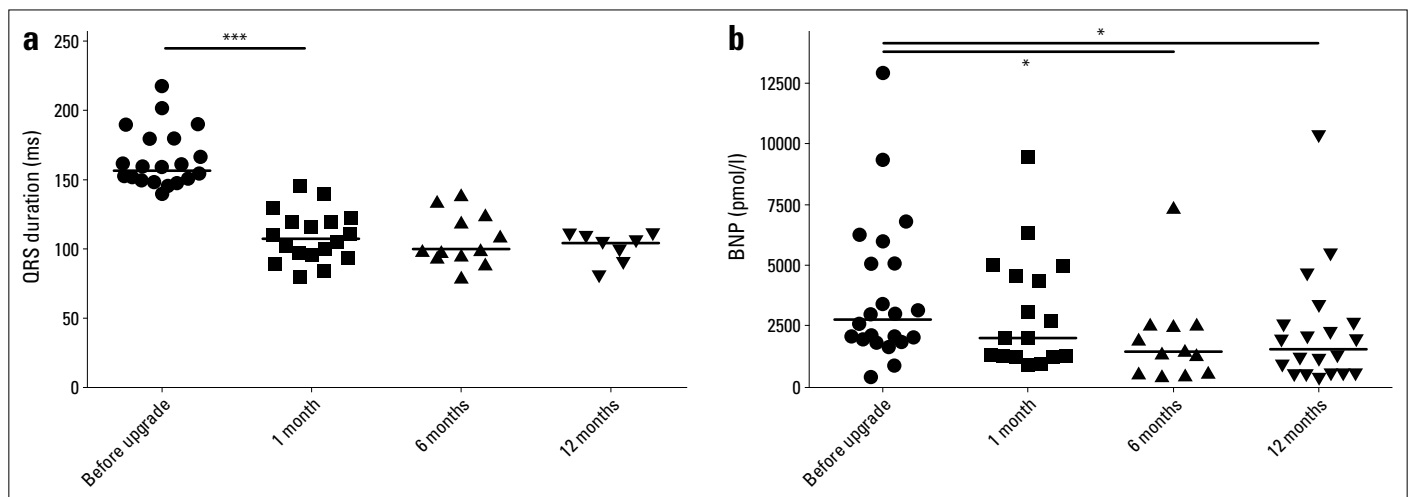


Figure 2. QRS duration and BNP levels were analyzed with the unpaired t-test due to abnormal distribution

(a) QRS duration at heart failure advent and 1-, 6-, and 12-month follow-up. ***= $P < 0.005$, **= $P > 0.005-0.01$, *= $P > 0.01-0.05$. (b) BNP levels at heart failure advent and 1-, 6-, and 12-month follow-up. ***= $P < 0.005$, **= $P > 0.005-0.01$, *= $P > 0.01-0.05$

Table 3. BNP, QRS duration, and left ventricular ejection fraction of CRT-P patients at baseline, advent of heart failure, and 1-, 6-, and 12-month follow-up

	Initial pacemaker implantation n=7	Baseline before CRT-P n=7	Follow-up 1 month n=5	Follow-up 6 month n=5	Follow-up 12 month n=4
BNP, pmol/L (average, SD)	–	2959±2957	3480±2805	2401±2805	3062±4816
QRS, ms (average, SD)	80±12	158±15	96±16	100±21	103±9
LV ejection fraction, % (average, SD)	59±11	35±6	39±7	41±11	41±6
Registration of ventricular tachycardia <170 bpm	–	–	0	0	0
Biventricular pacing percentage, % (average, SD)	–	–	99±2	99±1	99±1

The variables were expressed as mean±standard deviation. Bpm - beats per min; SD - standard deviation

During the 12-month follow-up, the biventricular pacing percentage was maintained at >98%. None of the 7 patients implanted with the CRT-P device developed ventricular tachycardia within the programmed monitor zone (>170 bpm) (Table 3). In this subgroup, no patients experienced sudden cardiac death. None of the CRT-P-patients were treated with antiarrhythmics other than beta-blockers.

Discussion

In patients with decreased LV ejection fraction secondary to dual pacemaker implantation, an additional implantation of an LV pacing lead can significantly reverse LV remodeling, leading to an improvement in LV function and reduction in HF. The negative effects of high-volume RVP have been previously well described (8). RVP is associated with an increased risk of HF, hospitalization, and death as described inter alia in the BLOCK-HF-study (9). However, data on the incidence of pacemaker-mediated cardiomyopathy are inconsistent, and the underlying mechanisms are not yet well understood. In our study, 2250 patients were evaluated during a period of 1 year in our pacemaker clinics, during when routine pacemaker checks were performed. Of these patients, 22 were identified to have probable pacemaker-

induced cardiomyopathy with clinical symptoms and signs of HF, after other possible causes of HF were ruled out. One must also take into account that the incidence of pacemaker-induced cardiomyopathy detected in our study may be conservative as the early deterioration of cardiac function often remains clinically unrecognized. Previous studies have reported an incidence of approximately 9–15% after 1 year of RVP (2, 10). In our study, the average time between the implantation of DCPs and advent of clinical HF was 5 years; however, we demonstrated that HF can present even after 17 years. This was not related to the burden of RVP as the RVP percentage in this particular group of patients was 100% due to 3rd degree atrioventricular block. The etiology for such a late deterioration of LVEF is unclear; however, TTE and coronary angiography were performed to rule out other causes for new-onset LVEF deterioration, and the patient was optimized on medical therapy. On the other hand, the patient with the shortest period from the implantation of DCPs to advent of clinical HF (2 years) was admitted to hospital with acute decompensation of HF. This was a 75-year-old woman who had DCP implanted for the management of intermittent 3rd degree atrioventricular block. An LV lead was implanted due to suspected pacing-induced cardiomyopathy secondary to this presentation. However, she died of acute, therapy-resistant HF with subsequent multiple organ

failure 2 weeks after LV lead implantation. This case suggests that pacemaker-induced cardiomyopathy can be an acute disease with fulminant progression. Perhaps an early CRT upgrade should be considered in patients with suspected pacemaker-induced cardiomyopathy to prevent such severe progression of HF, when the first signs of decreasing LVEF after DCP implantation are identified, and vigilant screening may be indicated.

The true incidence of LV remodeling due to RVP is not well known. The current data available in literature show that an RVP percentage of >40% may be a relevant factor (11). This is consistent with the data from our study, where the RVP percentage was >90% in all 22 patients. However, the reasons why some pacemaker-dependent patients with a high burden of RVP do not develop LV dysfunction remain unclear. We demonstrate that in patients with decreased LV ejection fraction secondary to DCP implantation and high RVP percentage, the additional implantation of an LV lead can significantly reverse left ventricular remodeling. We used the parameters of BNP level, QRS duration, and LVEF as measurements for the effectiveness of CRT. The results show a statistically significant improvement of all parameters. It was ensured that the patients did not any other drugs except for their HF medications. In addition, it appears that optimal HF medication therapy itself is insufficient to improve pacemaker-induced cardiomyopathy in these patients, and the additional implantation of an LV lead was the only effective treatment.

A decision of whether patients with suspected pacing-induced HF should be treated with CRT-P or CRT-D was also considered. The current guidelines (EHRA pacing guidelines) state that patients with a reduced LVEF (<35%) and high pacing percentage should be recommended for CRT-D therapy (12). However, in these patients, CRT-P therapy may be sufficient to increase LVEF over the relevant level of 35%. In our study, none of the 7 patients with an implanted CRT-P developed ventricular tachycardia within the programmed monitor zone (>170 bpm). In addition, in this group of CRT-P patients, LVEF increased to >35% (39±7%) at the 1-month follow-up (Table 3), to 41±11% at the 6-month follow-up, and to 41±6% at the 12-month follow-up. Therefore, after only 4 weeks of CRT, LVEF significantly increased in patients with suspected pacing-induced cardiomyopathy, and there was no longer an indication for a CRT-D device. This is an important consideration given the increased peri-procedural and long-term complication risks associated with CRT-D devices such as device malfunction, infection, and inappropriate ICD therapy secondary to other arrhythmias such as atrial fibrillation (13). In fact, 13 of the 22 patients in our study suffered from atrial fibrillation. Although none of the 15 patients treated with CRT-D experienced inappropriate ICD therapies most likely due to complete AV block, this complication is well known in all ICD patients, and approximately 9.5% of all ICD therapies are inappropriate (14). Furthermore, CRT-P devices have a substantially better longevity than CRT-D devices due to the lower energy consumption and different battery capacity (15). However, data from larger studies are missing, and this will need to be confirmed with further studies (16).

Response to CRT appears to be associated with a favorable prognosis. Lower long-term mortality and fewer hospitalizations are seen in patients who demonstrate an increase in LVEF of ≥30% after CRT (15). Patients with extensive intraventricular conduction disease (long QRS durations) and left bundle-branch block are more likely to be responders to CRT. A relatively short duration of HF symptoms before CRT implantation is associated with a better CRT response (17). In a recent sub-analysis of our data, all patients with a particularly good response to CRT were with a 3rd degree atrioventricular block as the initial indication for DCP implantation. Curtis et al. (9) already described a good response from patients with a 3rd degree atrioventricular block to CRT. Two patients had stable coronary heart disease, and 7 suffered from dilated cardiomyopathy. Also, the time point for the re-evaluation of patients after CRT implantation is important as reverse remodeling takes a variable amount of time. Assessment performed too early may underestimate the degree of reverse remodeling. However in our study, improvements after CRT upgrade could be detected after only 1 month, with progressively improved parameters seen after 6 months. Interestingly, our study showed no further significant LV reverse remodeling at 12 months compared with that at 6 months (18).

Study limitations

Even if these results are statistically significant, a shortcoming is the small number of patients and the retrospective nature of the study. Our data should be confirmed in a larger prospective, randomized trial.

Conclusion

In patients with decreased LV ejection fraction secondary to dual pacemaker implantation, an additional implantation of an LV pacing lead can significantly reverse LV remodeling, leading to improvement in LV function and reduction in HF. Thus, inappropriate CRT-D implantation may be avoided. We suppose the benefit of CRT in patients with dual chamber pacemakers with a high ventricular pacing percentage and pacing-induced HF. Our data should be confirmed in a larger randomized trial.

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