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Rate-responsive pacing in patients with heart failure: long-term results of a randomized study

Herbert Nägele[1]*, Wilfried Rödiger[2], and Maria Angeles Castel[3]

[1]*Medical Department, Hamburger Str. 41, St Adolfstift, Reinbek D-21465, Germany;* [2]*University Heart Center, Wördemanns Weg 25-27, 22527 Hamburg, Germany; and* [3]*Hospital Clinic, Thorax Institute, Villarroel 170, 08036 Barcelona, Spain*

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Aims Chronotropic incompetence (CI) in patients with congestive heart failure (CHF) develops frequently under β-blocker and amiodarone therapy. It can be corrected by pacing. We performed a randomized study to test whether pacing is beneficial in CHF patients with CI.
Methods and results Congestive heart failure patients under combined beta-blocker and amiodarone therapy ($n = 77$) were randomly assigned to inhibited pacing (INH; basal rate 40 bpm/hysteresis 30 bpm; $n = 38$) or to DDDR pacing with optimized atrioventricular delay (OPT; stimulation rate 65–120 bpm, $n = 39$). Groups showed similar baseline values in NYHA class, heart rate, and ejection fraction (EF) and were followed up to 10 years. The resting and mean 24 h heart rate after 1 year decreased by $-2.6/-5$ bpm in INH, but increased by $+3.6/+6.0$ bpm in the OPT group ($P < 0.001$). The QRS interval after 1 year increased by 12 ± 23 ms in the INH group, but $+32 \pm 36$ ms in the OPT group ($P < 0.01$). Patients with INH developed a greater left ventricular EF (LVEF) when compared with OPT patients ($+10.6 \pm 8$ vs. $+2 \pm 10$%, respectively; $P = 0.04$). Changes in LVEF were negatively correlated with heart rate, but not with QRS width changes. Prognosis and the event rate were better in the INH group.
Conclusion In the long-term follow-up, single-site ventricular pacing in patients with CHF and low LVEF is associated with significant clinical events and a poor prognosis.

Introduction

Bradycardia and chronotropic incompetence (CI) in congestive heart failure (CHF) has been identified as a factor limiting exercise capacity and has been proposed as a therapeutic target.[1,2] The precise mechanisms for CI have not been defined—for example, in CHF β-blocker therapy, elevated sympathetic nervous outflow and reduced β-receptor density may alter heart rate regulation during exercise.[3–5] Therefore, we initiated a long-term study to test whether rate-responsive pacing with haemodynamically optimized atrioventricular delay (AVD) was beneficial in heart failure patients in addition to an optimized heart failure therapy including a maximized dose of β-blockers and amiodarone. We hypothesized that medically induced CI and bradyarrhythmia[6,7] corrected by optimized rate-responsive pacing (OPT) would translate into a clinical benefit. Pacing effects at the initiation of the study were not only expected from heart rate increase, but also from the correction of pre-systolic mitral regurgitation by shortening of the AVD.[8,9] Therefore, an AVD optimization algorithm was implemented in this study. At the time of inclusion in the study (1996–98), biventricular pacing was experimental, needing thoracotomy for placing left ventricular leads. Therefore, only conventional right heart apical pacing was used. In a preliminary publication in the form of a scientific letter, we reported a higher event rate in patients under OPT stimulation compared with inhibited pacing mode (INH).[10] We now present in detail the final analysis and conclusions of this study after a long-term follow-up.

Methods

Patient selection

We recruited 111 consecutive ambulatory patients in sinus rhythm for pacemaker implantation, out of 225 screened candidates for heart transplantation (HTx) from 1996 to 1998. Patients with symptomatic bradycardia, atrial fibrillation, expected HTx in the next 3 months, or refusal ($n = 164$) were excluded at study entry (*Figure 1*). Owing to our experience with a combined β-blocker

* Corresponding author. Tel: +49 40 7280 5158; fax: +49 40 7280 2729.
E-mail address: herbert.naegele@krankenhaus-reinbek.de

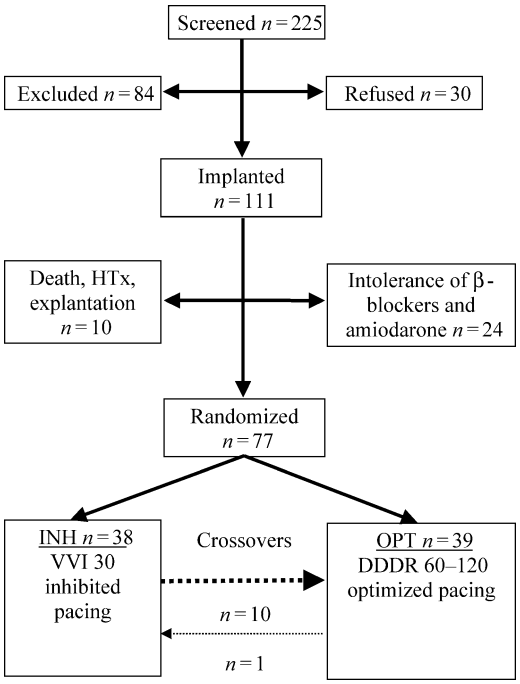

Figure 1 Consort diagram of the entire study population.

and amiodarone therapy, we expected CI in these patients at a high percentage.[7]

Ethics

The protocol including prophylactic pacemaker implants was approved by the Hamburg Ethics Committee, and patients gave written informed consent.

Evaluation and management

Medical therapy was intensified individually in all patients in a similar way, according to the results of repeated right heart catheterization studies. According to filling pressures [target right atrial (RA) pressure <4 mmHg and target pulmonary capillary wedge pressure (PCP) <15 mmHg], diuretic and vasodilator therapy was adjusted, mainly by adding xipamide (mean daily dose 16 ± 7 mg). In all patients, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were up-titrated to the highest tolerable dose (target systolic blood pressure ≤ 100 mmHg). Digitalis glycosides were given for every patient as digitoxin (mean daily dose 0.065 ± 0.01 mg). Digitoxin was given routinely for a 'complete heart failure therapy'. Digitoxin plasma levels were measured after 12 months; evaluations were within the therapeutic range (19 ± 9 ng/mL). Patients who received phenprocoumon to prevent embolic events (79%) were without any bleeding complications (target international normalized ratio 2–3). β-blockers (64% carvedilol, 20% metoprolol, and 16% bisoprolol) were given first in low doses and later uptitrated as much as possible, according to the guidelines. Additionally, patients received additional amiodarone therapy (200 mg/day for 3 months and 1000 mg/week later on) prophylactically for the suppression of either ventricular or supraventricular arrhythmia and to slow overall heart rate. At that time, prophylactic amiodarone therapy seems to be justified according to the results of the GESICA study.[11] Chronotropic incompetence was defined as failure to achieve 85% of the maximum exercise heart rate predicted for age and sex (220−age in men and 200−age in women) at maximum bicycle exercise. The maximum heart rate achieved at the time of randomization was 108 ± 14 min, so every patient fulfils this definition at time of randomization. In our theory at that time, we have reached a steady state to study the influences of pacing solely.

Pacemaker implantation and programming

Pacemaker implantation with RA and right ventricular (RV) leads was scheduled during the first 4 weeks of observation and was performed with standard techniques via cephalic or subclavian veins. Pulse generators CHORUS RM 7034 (ELA Medical, Paris, France) with ventilation sensors were used. Mortality due to the pacemaker implantation was zero. Two re-operations for ventricular and atrial lead dislodgements were necessary. The pacemakers were programmed in the VVI 40 hysteresis 30 backup mode (defined as INH), unless reprogramming to a higher rate was indicated due to persistent bradycardia <40/min and VVI-stimulation (crossovers, discussed subsequently). Three months after implantation (wash-out period), the patients were randomly assigned to further VVI 40 hysteresis 30 backup mode ($n = 38$) or to dual chamber rate responsive pacing mode (defined as OPT) with optimized AV delay (OPT group, $n = 39$, AUTO calibration ON). Patients were blind with regard to their pacing mode. The optimal AVD was adjusted during a right heart catheterization study using the AVD that resulted in lowest filling pressures and highest cardiac index. Atrioventricular delay at basic rate was programmed without sense compensation or rate adaptation in the OPT group as follows: 47 ms, 4 patients; 78 ms, 2 patients; 94 ms, 6 patients; 125 ms, 5 patients; 156 ms, 16 patients; 203 ms, 10 patients; and 234 ms, 7 patients. Twelve patients (23%) in the OPT group had their best haemodynamics achieved by spontaneous conduction, and therefore pacemakers were programmed to a long AVD resulting in atrial stimulation (with or without ventricular fusion beats). The rate spectrum was set from 65 (lower rate) to 120 bpm (upper rate, both for spontaneous atrial rate and sensor-induced rate). Patients' mean heart rates were calculated from the initial Holter recording up to randomization and later on from the event counter of the pacemakers (mean 24 h heart rate = total heart cycles/days $\times$ 1440).

Clinical events

Clinical events were defined as a combined hard endpoint including death from heart failure, sudden death, HTx, or the need for upgrade to biventricular pacing or to an ICD. Change in the pacing system to biventricular stimulation (from year 2001 onwards) fell also in the category of events because all of those were performed after hospitalization due to cardiac decompensation. Event rates were analysed according to the intention-to-treat analysis. The mean follow-up time was 4.95 ± 3 vs. 3.91 ± 2.5 years in the INH vs. OPT group.

Follow-up investigations

Follow-up investigations included right heart catheterization (filling pressures, stroke work, and cardiac index), physical examination, routine lab, resting ECG, and echocardiography [fractional shortening, left ventricular ejection fraction (EF), end-diastolic left ventricular diameter, and valve function]. The E-wave deceleration time (EDT) was defined and measured as the time from peak E-wave to the intersection of the E-wave slope at the baseline. Ejection fractions at randomization and at month 12 were determined by radionuclide ventriculography (RNV) with re-injected technetium-labelled erythrocytes (normal range $>55\%$). The variability of this method in our laboratory was $\pm 4\%$. According to this variability and to the literature,[12] we could state that the observed differences between the two measurements (entry and 1 year $+10.6\%$ in the INH group) are true changes and not the result of technologic variability. Left ventricular ejection fraction measured by RNV is independent of heart rate, because only systolic and diastolic activity counts were necessary for the calculation. Examiners of the RNV were blinded to the actual pacing mode. Blinding was not possible

during haemodynamic studies because pacing spikes were visible by the clinically indicated ECG monitoring. The course of the mean 24 h heart rate was calculated from the pacemaker memory data in both groups. Only complete data sets (INH: $n = 32$ and OPT: $n = 39$) were used for data analyses.

Statistical analysis

According to the sample size, the study was powered enough to detect at least moderate differences between groups, as measured by a *t*-test (Software package G*Power 3). Differences in the results of clinical and haemodynamic data were checked for significance by means of Student's *t*-tests for matched (entry and after 1 year) and non-matched (baseline between groups) pairs. Analyses were made according to the intention-to-treat principle. Non-parametric data were checked for significance by the Wilcoxon test. All data are expressed as mean $\pm$ standard deviation. Survival rate was calculated by the Kaplan–Meier analysis and the log-rank test (Winstat, Kalmia Inc., Cambridge, MA, USA and SPSS for Windows).

Results

Drop outs before randomization

Ten patients with already implanted pacemakers had a system explant, died, or were heart transplanted before randomization. Two systems were explanted due to infection after 1 and 5 weeks—one patient required tricuspid valve replacement due to staphylococci endocarditis, and in the second patient, no organism could be cultivated. Both recovered fully. Heart transplantation could have been related to the pacemaker implantation in one single case. This patient, with dilated cardiomyopathy, became catecholamine-dependent in the operation theatre, but successful high-urgency HTx could be performed 1 week later. Twenty-four patients did not tolerate either β-blocker and/or amiodarone and were therefore excluded from further analysis as pre-specified after the initial 'wash-out' period. From these 24 patients who were excluded from the analysis after the wash-out-period, there were 8 patients with side effects, which can be attributed directly to amiodarone toxicity [hyperthyroidism ($n = 4$), cutaneous problems ($n = 3$), and gastrointestinal intolerance ($n = 1$)]. Therefore, 77 patients could be randomized (*Figure 1*).

Crossovers after randomization

Crossovers were defined as a persistent change in the pacemaker mode (e.g. change from VVI-inhibited mode to rate response or vice versa). Ten of the 38 INH patients (27%) had to be reprogrammed to the OPT mode (crossover). Reasons were persistent bradycardia $<$40/min and VVI stimulation associated with dizziness, syncope, or presyncope. The actuarial rate of crossover was 20% (7 patients) after 1 year and 28% (10 patients) after 4 years. In every case, we were able to correlate the occurrence of symptoms with the time given by marker channel results. There were five patients with sinus bradycardia, three with sinus arrest, and two with AV block.

After randomization, there were several patients ($n = 28$) in whom amiodarone therapy was stopped after a mean time of 2.56 $\pm$ 1.2 years. The reasons were hyperthyroidism in 4 patients, skin problems in 5, blurred vision in 5, and without obvious reason in 14. No case of lung fibrosis was observed in our cohort.

Table 1 shows the characteristics of the study patients at the time of randomization. There were no major differences in underlying diseases and clinical or haemodynamic data between the INH and OPT groups at either time points. *Table 2* shows the changes in electrophysiological and haemodynamic data after 12 months. After randomization, the rate of VVI backup pacing in the INH group was as low as 0.4%. In contrast, 79% of all cardiac cycles of the patients in the OPT group were stimulated. Patients with OPT had significantly higher resting and 24 h mean heart rates as derived from the pacemaker counter. Optimized pacing yielded a significant shortening of the PR (P-Stimulus) interval and a significant lengthening of the evoked potential. With regard to other data, INH patients, in contrast to OPT patients, had a statistically significant increase in EF, whereas other changes after month 12 did not differ significantly between groups. *Table 3* shows the results of a list of the major cardiac events encountered by both groups according to the intention-to-treat principle. Significantly more events were found in the OPT vs. INH group. *Figure 2* illustrates the %change of the LVEF from randomization to month 12. It could be shown that the INH patients had a higher increase in LVEF after 12 months when compared with their paced counterparts ($P = 0.04$). When patients with fusion beats ($n = 12$), defined as atrial stimulation with spontaneous conduction and no change in the QRS width, were compared with their counterparts with inhibited pacing ($n = 28$) or ventricular capture ($n = 31$), it was found that, in this group, the EF increased only by 1% vs. 10 and 4%, respectively, from randomization to month 12. When changes in the heart rate were correlated with individual changes in LVEF, a negative correlation was found such that the higher the heart rate, the lower the increase in EF ($P < 0.0001$ and $r = -0.47$). No such correlation was found between the change in the QRS width and the increase in EF ($P =$ ns, $r = -0.18$). *Figure 3* shows changes in the EDT (in millisecond) before, 3, and 12 months after randomization in the VVI-inhibited mode (INH) or DDDR-optimized pacing mode (OPT). Patients in the inhibited mode had significantly higher values when compared with stimulated patients ($P = 0.04$ for months 3 and 12). *Figure 4* shows the occurrence of major clinical events (see *Table 3*, analysed according to intention-to-treat analysis). There were significantly more episodes such as death, HTx, or hospitalization in the OPT group compared with the INH group ($P = 0.03$, $\chi^2 = 4.5$). There were 21 cardiac events in the INH group vs. 32 in the OPT group. Total survival was higher in patients with the inhibited mode; however, this difference was not statistically significant (65 vs. 52% after 5 years and $P =$ ns; data not shown).

Discussion

In contrast to our hypothesis, rate-responsive pacing with optimized AVD yielded no benefit, but rather deleterious effects in heart failure and CI patients. Paced patients were not better in NYHA staging (*Table 2*), had no improved, and even diminished, heart transplant-free survival, and experienced significantly more clinical events (*Table 3* and *Figure 4*). Especially there were more heart transplantations and upgrade procedures to CRT systems in the OPT group, obviously due to worsening heart failure induced by OPT pacing. Patients without pacing showed a higher EF after

Table 1 Patients' characteristics at the time of randomization

	INH	OPT	*P*-value
n	38	39	
Age (years)	56.7 ± 7	55.7 ± 7	NS
Male (%)	85	83	NS
Dilated cardiomyopathy (%)	49	58	NS
Ischaemic cardiomyopathy (%)	51	34	NS
Valvular cardiomyopathy (%)	0	8	NS
NYHA stage	2.0 ± 0.6	2.04 ± 0.8	NS
PQ (R)—interval (ms)	205 ± 30	217 ± 55	NS
QRS duration (ms)	132 ± 32	143 ± 38	Ns
Prior atrial fibrillation episode (%)	13	17	NS
LBB (%)	36	44	NS
LAH (%)	14	6	NS
BIF block (%)	4	6	NS
RBBB (%)	—	4	—
LVEF—RNV (%)	33 ± 14	29.6 ± 14	NS
Resting heart rate (bpm)	61 ± 10	62 ± 11	NS
Pulmonary wedge pressure (mmHg)	8.7 ± 8	9.5 ± 8	NS
Mean pulmonary artery pressure (mmHg)	18 ± 9	19 ± 10	NS
Mean arterial pressure (mmHg)	77 ± 10	73 ± 12	NS
Mean right atrial pressure (mmHg)	2.5 ± 3	2.3 ± 4	NS
Cardiac index ($L/min/m^{-2}$)	2.5 ± 0.5	2.4 ± 0.5	NS
LV stroke work index (pm)	38 ± 14	35 ± 14	NS
LV end-diastolic diameter (cm)	6.4 ± 0.6	6.6 ± 0.6	NS
Fractional shortening (%)	23 ± 6	21 ± 6	NS
Mitral regurgitation (%)	0.8 ± 0.7	0.8 ± 0.8	NS
ACE inhibitors (%)	100	100	NS
β-Blockers (%)	100	100	NS
Amiodarone (%)	100	100	NS
Diuretics (%)	100	100	NS
Spironolactone (%)	84	80	NS

LBBB, left bundle brunch block; LAH, left anterior hemiblock; BIF, bifascicular; RBBB, right bundle brunch block; LVEF, left ventricular ejection fraction; RNV, radionuclide ventriculography; ACE, angiotensin-converting enzyme.

12 months (*Table 2*; *Figure 2*, $P = 0.04$). No benefit of pacing on mitral regurgitation after month 12 could be shown (*Table 2*).

Two major mechanisms may be responsible for these results: the increased heart rate and direct negative effects of RV pacing in the OPT group.

Effects on heart rate

Optimization of medical heart failure therapy induced low heart rates at rest and over 24 h, resulting in CI in every patient at the time of randomization as revealed by exercise testing at the time of randomization (see Methods). The basic rate of 65 bpm and rate-responsive pacing (upper rate limit 120 bpm) reversed the heart rate lowering in OPT patients. The mean heart rate over 24 h of OPT patients was ∼10 beats/min above the INH patients ($P < 0.001$, *Table 2*). Moreover, there was a significant negative correlation of the per cent change of heart rate during the first year of randomization and the per cent change of LVEF (see Results). In other words, heart rate lowering seemed to be associated with an increase in LVEF.

These results add information to the significance of heart rate in cardiovascular disease and heart failure, in particular.[13] A higher heart rate has been identified as a significant and independent cardiovascular risk factor in men.[14,15] Heart failure can be precipitated by rapid stimulation[16] and is correlated with the severity of the disease, most probably as a reflection of neurohumoral activation. A benefit of heart rate lowering in CHF can be expected from these data and from the results of the β-blocker trials. However, whether this decrease in heart rate was directly related to the positive outcome of β-blockade is unclear. Other mechanisms, such as β-blocker-mediated upregulation of β-receptors, improvement of β-receptor function, and protection from toxic catecholamine or calcium overload have been suggested.[17] Similar to the mechanisms by which a lower heart rate itself may translate in a better outcome, several hypotheses have been developed: a bradycardic heart rate may reduce myocardial stiffness,[18] myocardial energetics may be directly improved,[19] or high-energy phosphates may be more rapidly restored.[20] In regard to own data, we speculate that bradycardia improves diastolic function (*Figure 3*). Our patients in the INH group had a significantly longer EDT, a parameter of diastolic function with some prognostic implications.[21] The clinical benefit may be induced by improved passive filling during longer cardiac cycles. Accordingly other reports[22] could not show any benefit from rate-responsive pacing on quality of life and exercise capacity. In this regard, data from medical heart rate lowering trials fit also very well in the concept of 'the lower the heart rate, the better'.[23–25]

Table 2 Electrophysiological and haemodynamic changes of study patients after 12 months according to the intention-to-treat principle

	INH	OPT	*P*-value
n	33	35	
Stimulated cardiac cycles (%)	+3.4 ± 3	+79 ± 33	<0.001
Mean QRS width (ms)	+12 ± 23	+34 ± 36	<0.01
Mean PR interval (ms)	+6.4 ± 45	−49 ± 67	<0.01
ACEI (mg captopril equivalent)	+8.4 ± 23	5.8 ± 19	n.s.
Furosemide (mg furosemide equivalent)	−4.8 ± 19	−2.8 ± 26	n.s.
Resting heart rate (bpm)	−4.2 ± 12	+4.5 ± 14	<0.02
Mean 24 h heart rate (bpm)	−5 ± 8	+6 ± 8	<0.001
NYHA (class)	−0.1 ± 0.6	−0.2 ± 0.8	n.s.
Sodium (mmol/L)	−0.2 ± 3.0	+0.6 ± 3.8	n.s.
Body weight (kg)	+1.3 ± 6.0	+1.4 ± 5.0	n.s.
LVEF—RNV (%)	+10.6 ± 8	+2 ± 10	0.04
Fractional shortening (%)	+2.7 ± 6	+1.6 ± 7	n.s.
Left ventricular end-diastolic diameter (mm)	−2.3 ± 0.7	−1.6 ± 0.7	n.s.
Mitral regurgitation (grade)	+0.02 ± 0.7	+0.1 ± 0.7	n.s.
Tricuspid regurgitation (grade)	+0.1 ± 0.6	+0.05 ± 0.6	n.s
Pulmonary wedge pressure (mmHg)	+0.5 ± 6	−0.9 ± 7	n.s
Mean pulmonary artery pressure (mmHg)	+0.3 ± 6	−0.7 ± 8	n.s
Mean arterial presssure at rest (mmHg)	+0.4 ± 6	−2.5 ± 5	n.s.
Mean right atrial pressure (mmHg)	+0.2 ± 4	+0.3 ± 3	n.s
Cardiac index (L/min/m^{-2})	−0.1 ± 0.4	−0.1 ± 0.4	n.s
LV stroke work index (pm)	−0.4 ± 12	−3.3 ± 12	n.s

ACE, angiotensin-converting enzyme inhibitor; LVEF, left ventricular ejection fraction; RNV, radionuclide ventriculography.

Table 3 Cardiac events during the observation period INH vs. OPT

	INH	OPT
Heart transplantation	2	5
CHF death	2	3
Sudden death	10	10
Upgrade to biventricular pacing due to refractory heart failure	4	11
Upgrade to a defibrillator due to malignant VT	0	3
Total number of major cardiac events	18/32 (56%)	32/38 (84%)

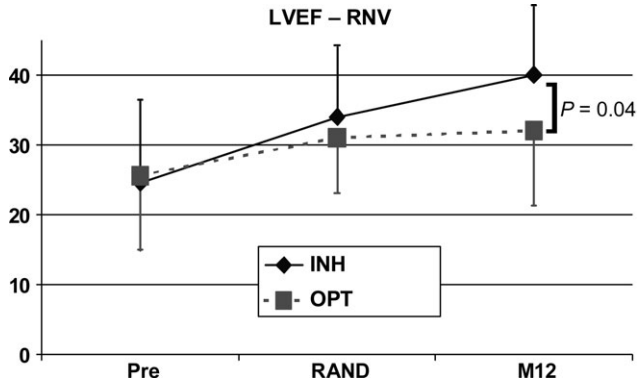

Figure 2 Left ventricular ejection fraction (LVEF): inhibited group (INH; $n = 38$) vs. optimized pacing group (OPT; $n = 39$).

Effects on right ventricular excitation

The other possibility for the more favourable outcome of the non-paced patients may be negative effects of pacing the right ventricle. This could induce ventricular dyssynchrony mimicking left bundle brunch block. Increased length of the QRS interval leads to reduced LV systolic function and filling time. Stimulation of the RV apex leads to such changes and reduced inotropy.[26–28] Animal experiments in RV-stimulated rabbits showed myocardial fibrosis and myocardial fibre disarrangements.[29] Long-term RV-stimulated patients showed myocardial perfusion defects and apical hypokinesis and depressed LV systolic and diastolic function.[30,31] Besides increased heart rate and shorter PR time intervals, our OPT patients showed a broader QRS width (Table 2). Our results fit well with the negative effects of RV stimulation found in the small series of Gold *et al.*[32] and in the DAVID study.[33,34] Accordingly, beneficial effects

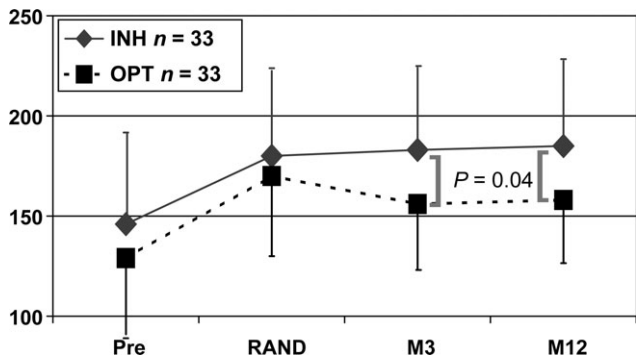

Figure 3 Changes in the E-wave deceleration time (EDT in millisecond) before and 12 months after randomization in the VVI-inhibited mode (INH) or DDDR-optimized pacing mode (OPT).

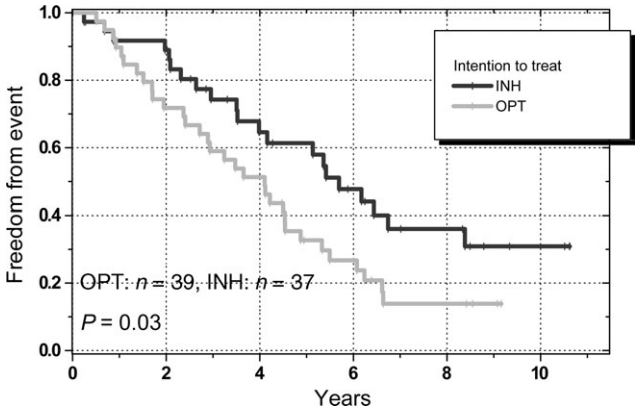

Figure 4 Cardiac event-free survival stratified to pacing mode (OPT vs. INH) according to the intention-to-treat analysis ($P = 0.03$).

of biventricular pacing have been demonstrated in several randomized studies. However, the mean QRS duration of our patients was below 150 ms and, therefore, many of those are not typical CRT candidates even today. The optimal pacing rate (basal rate and use of rate response) even with CRT has to be determined with additional studies, but it may be lower than formerly thought if extrapolated from the data presented here.

Conclusion

In the long-term follow-up, single-site ventricular pacing in patients with CHF and low LVEF is associated with significant clinical events and a poor prognosis. In this regard, our study supports the findings from the DAVID trial. Therefore, single-site ventricular pacing should be avoided in such patients if at all possible and if unavoidable, probably replaced by CRT or other pacing modes/sites showing out to be better in the future (e.g. His-bundle pacing). Early change to CRT should be considered, in our means, because of the high frequency of cardiac events encountered in the OPT group. It cannot be decided whether RV pacing or high heart rates were responsible for the worse outcome of the OPT group. Most probably, a mixture of these two factors contributed to our observations.

Limitations

Our study results are limited due to the high rate of cross-overs. In about one-quarter of the CHF patients, the heart rate was lowered 'too much', and therefore, these patients developed conventional pacemaker indications over time. This may allow for further uptitration of negative chronotropic drugs (β-blockers, digitalis, and amiodarone) to their maximal dosage, preventing symptomatic bradycardias. Furthermore, we cannot exclude that our method for AV delay optimization (acute haemodynamic testing) was inadequate in determining the best long-term value. However, AV delay adjustment according to PCP may be appropriate because this parameter reflects haemodynamic consequences of mitral regurgitation more precisely than echocardiography. A reliable method for AV delay optimization is yet to be validated. It also cannot be excluded that the minute ventilation sensor of the pacemakers was not adequate to reflect the demands of heart failure patients. Further investigations should be carried out in regard to AV delay optimization and biosensing for rate-response adaptation in heart failure patients. In this regard, our findings could help develop working hypotheses for new trials.

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