Europace (2012) **14**, 238–242
doi:10.1093/europace/eur258

Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years

Henryk Dreger*, Katja Maethner, Hansjürgen Bondke, Gert Baumann, and Christoph Melzer

Medizinische Klinik für Kardiologie und Angiologie, Campus Mitte, Charité—Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany

Received 31 January 2011; accepted after revision 6 July 2011; online publish-ahead-of-print 15 August 2011

Aims The prevalence of pacing-induced cardiomyopathy (PiCMP) has been reported to be 9% 1 year after implantation. As long-term data are sparse, the aim of our study was to evaluate the prevalence of PiCMP in a cohort of patients with at least 15 years of right ventricular (RV) pacing.

Methods and results Inclusion criteria were RV stimulation for at least 15 years due to atrioventricular block III° and absence of structural heart disease at the time of initial implantation. All patients were examined by echocardiography and spiroergometry. Pacing-induced cardiomyopathy was pre-defined as left ventricular (LV) ejection fraction (LVEF) ≤45%, dyskinesia during RV pacing and absence of other known causes of cardiomyopathy. Twenty-six patients from our outpatient department met the inclusion criteria. Pacing-induced cardiomyopathy was diagnosed in four patients (15.4%). Echocardiography showed significant LV remodelling in PiCMP patients [LVEF 41.0 ± 4.5%, LV end-diastolic diameter (LVEDD) 54.0 ± 2.7 mm] compared with patients with preserved LVEF (LVEF 61.2 ± 5.8%, $P = 0.002$, LVEDD 45.6 ± 4.0 mm, $P = 0.004$). There were no significant differences regarding age, gender, duration of RV pacing, heart rate, interventricular mechanical delay, QRS duration or prevalence of sinus rhythm, and arterial hypertension between both groups. The longest intraventricular delay was significantly shorter in patients with preserved LVEF (65.5 ± 43.0 ms) compared with PiCMP patients (112.5 ± 15.0 ms, $P = 0.043$). Exercise capacity and quality of life did not differ significantly between both groups.

Conclusion Considering the very long duration of RV stimulation in our study population (24.6 ± 6.6 years), the prevalence of PiCMP was remarkably low. Pacing-induced cardiomyopathy was associated with more pronounced intraventricular dyssynchrony.

Keywords Pacemaker • Pacing-induced cardiomyopathy • Cardiac dyssynchrony • Cardiac resynchronization therapy • Quality of life

Introduction

A variety of studies have shown a potentially deleterious effect of apical right ventricular (RV) pacing on left ventricular (LV) function.[1–6] Accordingly, current guidelines recommend avoiding RV stimulation in patients suffering from sick sinus syndrome.[7] In patients with high-grade atrioventricular (AV) block, however, RV pacing is inevitable with conventional dual-chamber pacemakers (PMs). Biventricular PMs—usually implanted for cardiac resynchronization therapy (CRT)—represent a potential alternative.[8] Yet, it is not clear which patients with high-grade AV block might benefit from CRT device implantation. Compared with conventional PMs, CRT devices are associated with increased perioperative risks and considerably higher costs.[9,10] Therefore—especially when considering that ~900 conventional PM are implanted per one million residents in Europe each year—prophylactic implantation of CRT devices in all PM patients is not feasible.[11]

While apical RV pacing is associated with adverse effects on cardiac function in general, a subset of patients shows a relevant decline in LV function resulting in pacing-induced cardiomyopathy (PiCMP).[1,12] The prevalence of PiCMP—as defined by an LV ejection fraction (LVEF) ≤45%—has been reported to be 9% 1 year

* Corresponding author. Tel: +49 30 450 613 496; fax: +49 30 450 513 941, Email: henryk.dreger@charite.de

after implantation.[1] However, data on the prevalence of PiCMP after long-term RV pacing are sparse. In part, this can be explained by the intricacy to determine the exact prevalence of PiCMP: first, not all PM patients require continuous RV pacing. Secondly, PM patients often suffer from comorbidities that also cause adverse LV remodelling [e.g. coronary artery disease (CAD)]. In addition, assessment of LV function by echocardiography is usually not part of follow-up visits after PM implantation.

The first aim of the present study was to assess the prevalence of PiCMP after long-term RV pacing, i.e. RV stimulation for at least 15 years. Furthermore, we sought to determine the impact of PiCMP on exercise capacity and quality of life. As little is known about the relationship between the extent of cardiac dyssynchrony induced by RV pacing and the development of PiCMP another focus of our study was the evaluation of cardiac dyssynchrony in our patients.

Methods

Study design

Patients for this observational, cross-sectional study were recruited from a pool of ~1300 PM patients that routinely visit our outpatient department. The inclusion criteria were as follows:

- Continuous RV stimulation for at least 15 years due to AV block III° (>99% RV pacing confirmed in PM interrogation).
- No structural heart disease at the time of implantation.
- DDD mode since the introduction of dual chamber PM.
- Ability to provide written consent to study participation.

Pacing-induced cardiomyopathy was pre-defined as a combination of LVEF ≤45%, dyskinesia during RV pacing and absence of other known causes of cardiomyopathy.[8] Accordingly, the exclusion criteria included all comorbidities that themselves might cause LV remodelling such as history of chemotherapy with cardiotoxic agents, CAD, hypertensive heart disease, chronic alcohol abuse, and valvular heart disease.

Among our patients that met the inclusion criteria, we identified four patients with a LVEF ≤45%. In two of these patients, an impaired LVEF had been diagnosed earlier and both patients had already been tested negative for CAD by coronary angiography or computed tomography angiography (CTA). In the other two cases, LV systolic dysfunction was diagnosed for the first time. In both patients, CAD could be excluded by coronary angiography and CTA, respectively.

All patients provided written consent. The study conforms to local university ethics guidelines and the principles outlined in the Declaration of Helsinki.

To estimate the all-cause mortality in patients with long-term RV pacing, we investigated the vital status and causes of death of a subset of our patient database, i.e. all patients that received a PM for third-grade AV block in the absence of structural heart disease in our centre between 1980 and 2001.

Examinations

All patients were examined by echocardiography using a Vivid 7 ultrasound system (GE Medical Systems, Horton, Norway). Left ventricular ejection fraction was assessed using Simpson's biplane approach.[13]

The right ventricular mechanical delay (RVMD) and left ventricular mechanical delay (LVMD)—i.e. the intervals between the beginning of the QRS complex and the opening of the semilunar valves—were determined by pw-Doppler.[14] Interventricular dyssynchrony was defined as an interventricular mechanical delay (IVMD) >40 ms.[15]

Intraventricular dyssynchrony was assessed as described previously.[16] Briefly, the interval between the opening of the aortic valve (AVO) and the peak systolic velocity (S′) was determined by tissue Doppler imaging in six basal LV segments. Tissue synchronization imaging served as an internal plausibility control and confirmed correct determination of S′ in patients with an impaired acoustic window. The segment with the shortest AVO-S′ interval was used as the reference segment as it most likely represents intact myocardium. To identify dyssynchronous segments, we calculated the time differences between the AVO-S′ intervals of the reference and the other segments. Regions were considered dyssynchronous when the calculated delay was above the upper limit of normal.[16] Furthermore, we calculated the longest intraventricular delay (i.e. the delay between the segments with the shortest and longest AVO-S′ intervals) as an approximate estimate of the extent of LV intraventricular dyssynchrony.

Exercise capacity was determined by treadmill spiroergometry. Peak oxygen consumption (VO_{2max}) and anaerobic threshold (AT) were compared with predicted values based on healthy controls.[17]

Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) which yields a score ranging from 0 to 105 (with higher values indicating worse quality of life due to heart failure).[18]

Statistics and figures

Data are expressed as mean ± standard deviation (SD). Statistical significance was calculated using *z*-tests and *t*-tests when appropriate (SigmaStat 3.0, SPSS Inc.). An error probability of $P < 0.05$ was considered statistically significant. The Kaplan–Meier survival plot was calculated using Predictive Analytics Software statistics 18 (SPSS Inc.).

In the box plot, the lower boundary indicates the 25th percentile, the upper boundary the 75th percentile and a line within the box the median. Whiskers above and below the box represent the 90th and 10th percentiles, respectively. Statistical outliers are marked by dots (SigmaPlot 9.0, SPSS Inc.).

Results

Prevalence of pacing-induced cardiomyopathy

Screening our database of ~1300 PM outpatients identified 26 patients who matched the inclusion criteria and were willing to participate in the study. Four of these patients (15.4%) met the pre-defined criteria of PiCMP. None of the patients with impaired LVEF had signs of ischaemic heart disease in coronary angiography or CTA.

There were no significant differences regarding gender, age, heart rate, QRS duration or prevalence of sinus rhythm, and arterial hypertension between both groups (*Table 1*). Pacing-induced cardiomyopathy patients had a significantly higher body mass index ($P = 0.046$). There was a non-significant trend for longer duration of RV pacing in PiCMP patients (30.8 ± 6.8 years) compared with patients with a preserved LVEF (23.5 ± 6.1 years, $P = 0.070$). Right ventricular leads were implanted apically in all patients.

Expectedly, PiCMP patients had a significantly lower LVEF (*Table 2*). As another sign for LV adverse remodelling, PiCMP

Table 1 Patient characteristics

	Preserved LVEF	PiCMP	P value
n	22	4	–
Male, *n* (%)	5 (22.7%)	1 (25.0%)	0.585
Age, years	56.7 ± 16.9	56.1 ± 8.2	0.972
Duration of continuous RV pacing, years	23.5 ± 6.1	30.8 ± 6.8	0.070
Body mass index, kg m^{-2}	25.0 ± 4.0	29.4 ± 3.2	0.046
Heart rate, *n* min^{-1}	72.1 ± 8.7	82.0 ± 23.7	0.619
Sinus rhythm, *n* (%)	22 (100%)	4 (100%)	–
QRS duration, ms	157.8 ± 13.1	162.5 ± 15.0	0.355
Arterial hypertension, *n* (%)	10 (45.5%)	2 (50.0%)	0.706

Values are mean ± SD when appropriate.

Table 2 Echocardiographic characteristics and dyssynchrony parameters of the study population

	Preserved LVEF	PiCMP	P value
LVEF, %	61.2 ± 5.8	41.0 ± 4.5	0.002
LVEDD, mm	45.6 ± 4.0	54.0 ± 2.7	0.004
IVS, mm	10.4 ± 1.6	10.8 ± 1.9	0.704
Left atrial diameter, mm	35.0 ± 4.4	37.3 ± 2.1	0.318
RVMD, ms	101.2 ± 22.9	106.0 ± 14.7	0.692
LVMD, ms	136.9 ± 19.0	141.3 ± 20.1	0.680
IVMD, ms	35.7 ± 18.0	35.3 ± 14.9	0.961
Interventricular dyssynchrony, *n* (%)	9 (40.9%)	2 (50.0%)	0.832
Intraventricular dyssynchrony, *n* (%)	14 (63.6%)	4 (100%)	0.389
Longest intraventricular delay, ms	65.5 ± 43.0	112.5 ± 15.0	0.043
Number of dyssynchronous LV segments, *n*	1.5 ± 1.3	3.0 ± 0.0	0.050

Values are mean ± SD.
IVMD, interventricular mechanical delay; IVS, interventricular septum; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMD, left ventricular mechanical delay; RVMD, right ventricular mechanical delay.

patients presented with significantly larger LV end-diastolic diameters (LVEDDs) compared with patients with a preserved LVEF ($P = 0.004$). Interestingly, PiCMP was neither associated with LV hypertrophy nor with left atrial dilation.

The average IVMD was almost identical in both groups ($P = 0.961$, *Table 2*). Accordingly, the prevalence of interventricular dyssynchrony did not differ significantly between PiCMP patients (50%) and patients with preserved LVEF (40.9%, $P = 0.832$). Interestingly though, assessment of intraventricular dyssynchrony revealed that the longest LV intraventricular delay was significantly shorter in patients with preserved LVEF (65.5 ± 43.0 ms) compared with PiCMP patients (112.5 ± 15.0 ms, $P = 0.043$, *Figure 1*). In addition, more LV segments showed delayed contraction in PiCMP patients ($P = 0.050$). Overall, signs of intraventricular dyssynchrony were apparent in all PiCMP patients and in 63.6% of the patients with preserved LVEF ($P = 0.389$).

Treadmill spiroergometry revealed preserved exercise capacity in all patients—with a non-significant trend for inferior performance of PiCMP patients (*Table 3*). Corresponding results were obtained regarding the quality of life: MLHFQ scores suggest a non-significant trend for heart failure-related reduction of quality of life in PiCMP patients (*Table 3*).

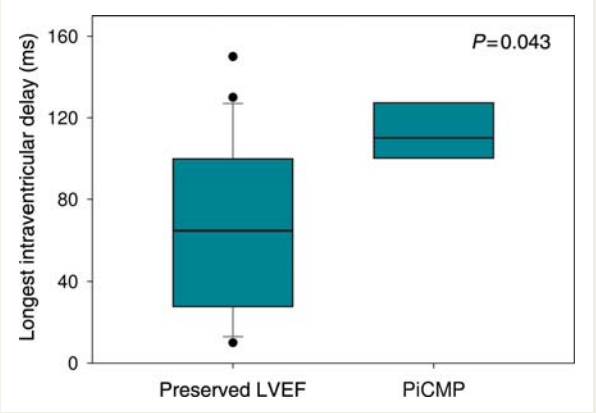

Figure 1 The longest intraventricular delay in patients with preserved left ventricular ejection fraction and with pacing-induced cardiomyopathy.

Table 3 Exercise capacity and quality-of-life assessment of the study population

	Preserved LVEF	PiCMP	P-value
VO_{2max}, mL min^{-1} kg^{-1}	24.7 ± 6.1	19.0 ± 1.4	0.085
VO_{2max}/predicted, %	111.9 ± 21.7	92.7 ± 10.0	0.102
AT, mL min^{-1} kg^{-1}	18.9 ± 3.3	16.6 ± 1.1	0.186
AT/predicted, %	119.7 ± 17.8	103.8 ± 20.9	0.126
MLHFQ score	11.3 ± 12.3	18.5 ± 25.9	0.670
Physical dimension score	6.3 ± 7.0	10.3 ± 12.7	0.499
Emotional dimension score	2.3 ± 3.2	4.0 ± 6.7	0.749

Values are mean ± SD.
AT, anaerobic threshold; VO_{2max}, peak oxygen consumption. The MLHFQ score ranges from 0 to 105. Higher values indicate impaired quality of life due to heart failure-related symptoms.

All-cause mortality in patients with long-term right ventricular pacing

To estimate the all-cause mortality in patients with long-term RV pacing, we screened our outpatient database and identified 94 patients that received a PM for third-grade AV block in the absence of structural heart disease in our centre between 1980 and 2001. The vital status could successfully be determined in 88 patients (*Figure 2*). Mean age at first implantation was 32.2 ± 17.2 years. Mean follow-up was 19.0 ± 5.8 years (median 19.5 years, range 4–31 years). Overall, six patients (6.8%) had died from the following causes: cancer (three patients), stroke (one patient), suicide (one patient), and sudden cardiac death (one patient). Unfortunately, the latter patient had not been examined by echocardiography before his death which occurred 8 years after PM implantation. Hence, it remains uncertain as to whether this death was related to PiCMP.

Discussion

In our study population, prevalence of RV PiCMP was 15.4%. Considering the very long duration of RV stimulation in our patients (on average, 24.6 ± 6.6 years), this is remarkably low and only slightly higher than the prevalence reported 1 year after PM implantation.[1] Hence, our finding suggests that—after the first year—the prevalence of PiCMP increases only slowly with the time of RV stimulation.

The fact that we rarely see PM patients with fatal heart failure in the absence of other known causes of cardiomyopathy somewhat questions that severe PiCMP affects a large number of patients. This observation is corroborated by another study which reported a PiCMP prevalence of 13% among patients with, on average, 9.7 ± 2.9 years RV stimulation.[12] Taken together, the latter study, the data from Yu *et al.*[1] as well as our own results suggest that PiCMP develops rather quickly and that the subset of affected patients increases only slightly after the first year—even after long-term RV stimulation. Importantly, our mortality analysis identified only one cardiac-related death among 88 PM patients after a mean follow-up of 19.0 ± 5.8 years. Whether this death was related to PiCMP remains unclear since no information on LV function are available for this patient. In any case, these results suggest a rather low mortality from PiCMP.

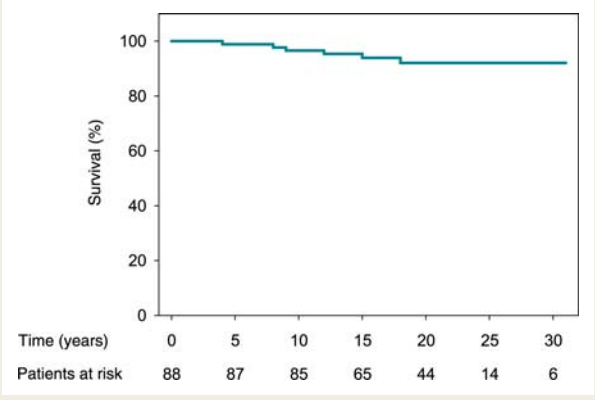

Figure 2 Kaplan–Meier survival analysis of all patients that received a pacemaker for third-grade AV block in the absence of structural heart disease in our centre between 1980 and 2001.

Two recent studies have shown that PiCMP can be prevented or—at least partially—reversed by biventricular pacing.[1,8] This suggests that cardiac dyssynchrony plays a major role in the development of PiCMP. This assumption is substantiated by our results which indicate a higher extent of intraventricular dyssynchrony in PiCMP patients: on average, the longest intraventricular delay was 42% shorter in patients with a preserved LVEF ($P = 0.043$, *Figure 1*) and PiCMP patients had twice as many dyssynchronous segments ($P = 0.050$, *Table 2*). It is noteworthy, though, that 63.6% of our patients with preserved LVEF had signs of intraventricular dyssynchrony—indicating that RV-induced cardiac dyssynchrony does not inevitably lead to PiCMP. In addition, there was no difference in the IVMD between both groups which suggests that interventricular dyssynchrony does not contribute to the pathogenic mechanisms responsible for PiCMP.

Interestingly, PiCMP was not associated with a statistically significant reduction in exercise capacity or quality of life (*Table 3*). However, patients with preserved LVEF had slightly superior results in both exercise performance results and MLHFQ scores. Therefore, our results might lack significance mainly due to the low number of patients.

Compared with conventional PMs, CRT device implantation is associated with a two-fold increase of perioperative complications.[9,19] In addition, CRT fails in one of three patients within 2.5 years—in 10% due to loss of LV capture.[20] Given its high costs, rate of complications and the low prevalence of PiCMP we do not think it is reasonable to propose prophylactic implantation of CRT devices in all patients with high-grade AV block in the absence of structural heart disease. Rather, we recommend echocardiographic examination of PM patients 1 year after implantation.

Exclusion of patients with comorbidities that themselves may result in adverse LV remodelling allows attribution of all pathological findings to RV stimulation. It has the disadvantage, however, that our study is not able to answer the clinically relevant question whether RV stimulation might be even 'more deleterious' in patients suffering from pre-existent structural heart disease—as suggested by previous reports.[3,5] Finding a solution to this problem is complex as definite dissection of the harmful effects of RV stimulation and of the concomitant cardiomyopathy is no easy task, especially since the need for PM implantation might itself indicate progressed structural cardiac damage.

Limitations

Our study is clearly limited by the low number of patients recruited in a single centre. Furthermore, patients were not examined by echocardiography before implantation. However, the first implantation among our patients was performed in 1969—at a time when echocardiography was not available. To the best of our judgement, all patients were free from signs of heart failure at the time of implantation. In addition, our cross-sectional study gives no information on the course of PiCMP. Lastly, as a consequence of the inclusion criteria our results were obtained from

extraordinarily young and healthy patients that represent only a small fraction of the average PM population. Accordingly, our data cannot be generalized for day-to-day PM patients.

Conclusion

In our cohort of patients with, on average, 24.6 ± 6.6 years RV stimulation, the prevalence of PiCMP was 15.4%. Since previous studies reported a prevalence of 9% 1 year after implantation, our results suggest a rather slow increase of affected patients after the first year. Furthermore, our data indicate that intraventricular—but not interventricular—dyssynchrony induced by RV pacing contributes to the pathogenesis of PiCMP.

Due to the low prevalence of PiCMP—even after long-term RV pacing—we conclude that implantation of CRT devices in all patients with high-grade AV block and freedom from structural heart disease is not warranted. Rather, we recommend routine assessment of LVEF by echocardiography 1 year after implantation followed by an upgrade to CRT in patients identified with PiCMP. Whether RV pacing is more harmful in patients with concomitant structural heart disease and whether pacing-induced deterioration can be prevented by biventricular pacing will have to be answered by trials with clinical endpoints such as BIOPACE and BLOCK-HF.[21,22]

Conflict of interest: none declared.

References

1. Yu CM, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A *et al.* Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009;**361**:2123–34.
2. Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. *Circulation* 2006;**113**:2082–8.
3. O'Keefe JH Jr, Abuissa H, Jones PG, Thompson RC, Bateman TM, McGhie AI *et al.* Effect of chronic right ventricular apical pacing on left ventricular function. *Am J Cardiol* 2005;**95**:771–3.
4. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL *et al.* Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**:2932–7.
5. Thackray SD, Witte KK, Nikitin NP, Clark AL, Kaye GC, Cleland JG. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. *Eur Heart J* 2003;**24**:1143–52.
6. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H *et al.* Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;**288**:3115–23.
7. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H *et al.* Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace* 2007;**9**:959–98.
8. Nazeri A, Massumi A, Rasekh A, Saeed M, Frank C, Razavi M. Cardiac resynchronization therapy in patients with right ventricular pacing-induced cardiomyopathy. *Pacing Clin Electrophysiol* 2010;**33**:37–40.
9. Leon AR, Abraham WT, Curtis AB, Daubert JP, Fisher WG, Gurley J *et al.* Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. *J Am Coll Cardiol* 2005;**46**:2348–56.
10. Boriani G, Biffi M, Martignani C, Valzania C, Diemberger I, Bertini M *et al.* Is cardiac resynchronization therapy cost-effective? *Europace* 2009;**11**(Suppl 5):v93–7.
11. van Veldhuisen DJ, Maass AH, Priori SG, Stolt P, Van Gelder IC, Dickstein K *et al.* Implementation of device therapy (cardiac resynchronization therapy and implantable cardioverter defibrillator) for patients with heart failure in Europe: changes from 2004 to 2008. *Eur J Heart Fail* 2009;**11**:1143–51.
12. Thambo JB, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S *et al.* Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation* 2004;**110**:3766–72.
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;**2**:358–67.
14. Dreger H, Borges AC, Baumann G, Melzer C. Successful reduction of intraventricular asynchrony is associated with superior response to cardiac resynchronization therapy. *Cardiovasc Ultrasound* 2010;**8**:35.
15. Cazeau S, Bordachar P, Jauvert G, Lazarus A, Alonso C, Vandrell MC *et al.* Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study. *Pacing Clin Electrophysiol* 2003;**26**:137–43.
16. Dreger H, Borges AC, Ismer B, Schattke S, Stegemann B, Baumann G *et al.* A modified echocardiographic protocol with intrinsic plausibility control to determine intraventricular asynchrony based on TDI and TSI. *Cardiovasc Ultrasound* 2009;**7**:46.
17. Pothoff G, Winter UJ, Waßermann K, Jäkel D, Steinbach M. Ergospirometrische Normalkollektivuntersuchungen für ein Unsteadystate-Stufentestprogramm. *Z Kardiol* 1994;**83**:116–23.
18. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. Part 2: content, reliability and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. *Heart Fail* 1987;**3**:198–209.
19. Pavia S, Wilkoff B. The management of surgical complications of pacemaker and implantable cardioverter-defibrillators. *Curr Opin Cardiol* 2001;**16**:66–71.
20. Knight BP, Desai A, Coman J, Faddis M, Yong P. Long-term retention of cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;**44**:72–7.
21. Funck RC, Blanc JJ, Mueller HH, Schade-Brittinger C, Bailleul C, Maisch B. Biventricular stimulation to prevent cardiac desynchronization: rationale, design, and endpoints of the 'Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace)' study. *Europace* 2006;**8**:629–35.
22. Curtis AB, Adamson PB, Chung E, Sutton MS, Tang F, Worley S. Biventricular versus right ventricular pacing in patients with AV block (BLOCK HF): clinical study design and rationale. *J Cardiovasc Electrophysiol* 2007;**18**:965–71.