Europace (2007) **9**, 380–384
doi:10.1093/europace/eum040

Analysis of terminal arrhythmias stored in the memory of pacemakers from patients dying suddenly

H. Nägele[1]*, S. Hashagen[1], M. Azizi[2], S. Behrens[1], and M.A. Castel[3]

[1] *St Adolfstift, Medical Clinic, Reinbek, Germany, Hamburger Str. 41, D-21465 Hamburg;* [2] *Albertinenkrankenhaus, Hamburg, Germany; and* [3] *Hospital Clinic, Barcelona, Spain*

Received 28 October 2006; accepted after revision 22 February 2007; online publish-ahead-of-print 13 April 2007

KEYWORDS
Sudden death;
Pacemaker memory;
Arrhythmia

Aims Stored electrograms or marker channels are available in most of modern cardiac pacemaker models. We sought to analyse these information to uncover terminal events of pacemaker patients dying suddenly.

Method and results We made post-mortem pacemaker (PM) interrogations in 19 patients dying suddenly out of hospital between the years 1997 and 2005 (mean age 59 ± 13 years, 90% males). The systems had activated arrhythmia monitoring algorithms. Indications of pacing were sick sinus syndrome in seven, AV-block in five, and heart failure due to asynchrony in seven cases. The interrogated pacemakers were CHORUS 7034 ($n = 12$), CONTAK TR ($n = 2$), and INSYNC III ($n = 5$). For interpretation stored marker channels and electrograms were analysed. The mean observation time after PM implantation prior death was 2.11 ± 1.44 years, the mean left ventricular ejection fraction from the last available echo examination in the year prior death was 27.5 ± 8%, mean age was 63 ± 12 years. In 17/19 cases (89%), a tachycardia (most likely ventricular tachycardia) was found correlating to the time of death. The mean cycle length of the terminal arrhythmia was 307 ± 144 (250–344) ms, corresponding to a heart rate of 195 ± 95 (174–240) bpm. We found no evidence of specific pacemaker-related problems such as electronic failure, battery depletion, or undersensing.

Conclusions Post-mortem analysis of arrhythmia monitoring of pacemaker patients revealed tachycardias (most likely ventricular tachycardia) to be related to sudden death. These findings give some insight in mechanisms of terminal events in this group.

Introduction

Sudden death (SD) is responsible for 10–30% of death in conventional pacemaker patients.[1,2] Sudden death is dependent on the underlying disease, can occur during different pacing modes and could be triggered in some cases by pacing induced proarrhythmia.[3] Reduced ventricular function increased its risk[4–6] and logically in the most critically ill patients with implanted cardiac resynchronization devices (without defibrillation backup) SD rate increased up to 40–50% in regard to causes of death.[7] A detailed knowledge of the exact mode of death would have major clinical implications. Tachyarrhythmic death may be preventable by defibrillation, whereas nearly no therapy was possible in electromechanical dissociation (EMD). Despite many studies focus on SD[8] only a few investigated terminal episodes of SD in detail by means of Holter ECG recordings.[9–11]

New storage algorithms of implanted pacemakers offer a unique possibility to uncover the events exactly at time of death and in the preceding period.[12–14] They have been helpful in the management of patients with atrial fibrillation[15] and implanted defibrillators,[16] but up to now only one case report was published on their diagnostic impact in SD.[17]

We report on the results of the analysis of pacemaker memory in 19 patients, which had been obtained from post-mortem after sudden unexpected outpatient death.

Methods

This is an observational retrospective study. In every case relatives were asked to give consent to post-mortem pacemaker interrogation. We examined 19 pacemaker patients who died suddenly outside hospital between the years 1997 and 2005 (mean age 59 ± 13 years, 90% males). In hospital, SD patients were excluded from this report to yield a more homogeneous population. Hospitalized patients are mostly very sick and could have various reasons for death such as pulmonary embolism, heart failure,

* Corresponding author. Tel: +49 40 7280 5158; fax: +49 40 7280 2729.
E-mail address: herbert_naegele@yahoo.de

sepsis, and hyperkalemia resulting in secondary arrhythmias.[11] The 19 analysed cases stem from our cohort of 645 patients having a new pacemaker implantation at our centre during these 9 years. One hundred and fifty-five of the systems used had storage algorithm with the capability to characterize arrhythmia in more detail. Out of these 155 patients, 58 died during the observation period, 34 of them died suddenly. Therefore, SD accounts for 58% of death in the group of patients with monitoring capabilities. We were notified just in time in the case of 19 of the 34 SD patients so that we can interrogate their devices before burial. Indications of pacing in these cases were sick sinus syndrome in seven, AV-block in five, and heart failure due to asynchrony in seven cases. Before death, patients were followed every 3–6 months in our outpatient clinic and were characterized prior death in regard to their heart failure stage, ejection fraction, and medical therapy. For characterization, the last available information prior death was used. All patients received ACE inhibitors and 86% ß-blockers and were in a stable condition (mostly NYHA I and II). Amiodarone was given in eight cases for the prevention of supraventricular arrhythmias. Internal cardioverter defibrillator (ICD) indication was not considered at the time of pacemaker implantation, patients had neither ventricular arrhythmia on holter or syncope. All patients received their pacemakers before publication of the SCD-HeFT-Study.[18] In all cases, our service was informed from relatives or the police that the patient died suddenly and unexpectedly. Then a member of our team visited the home, the mortuary, or the department of legal justice to make the interrogation. The interrogated pacemakers were CHORUS 7034 (ELA medical, Paris, France, $n = 12$), CONTAK TR (Guidant Corp., Indianapolis, IN, $n = 2$), and INSYNC III (-Medtronic Inc., Minneapolis, MN, $n = 5$). For interpretation, stored marker channels (patient number 1–12) and if available additional electrograms (patient number 13–19) were analysed. The lower detection rate for ventricular tachycardia (VT) was routinely set to 160/min. All marker channels and stored electrograms were printed out and analysed. Ventricular tachycardia was suspected when a sudden rise in the ventricular rate without a corresponding high atrial rate was present or in the case of a missed initial event a continuous high ventricular rate (usually > 160/min as this was the programmed lower detection limit) also without corresponding atrial activity. No signs of memory overflow were found. Post-mortem analysis in the department of legal medicine was done in five patients (number 1, 4, 14, 18, and 19). Results did not show evidence of cause of death besides arrhythmia.

Results

The mean observation time prior death was 2.11 ± 1.44 years, the mean left ventricular ejection fraction (LVEF) was $27.5 \pm 8\%$, and mean age was 63 ± 12 years. In 17/19 cases (89%), a tachycardia (most likely ventricular tachycardia) could be found correlated to the time of death. In two patients no arrhythmia was stored in the memory. The mean cycle length of the terminal arrhythmia was 307 ± 144 (250–344) ms, corresponding to a heart rate of 195 ± 95 (174–240) bpm. We found no evidence of specific pacemaker-related problems such as electronic failure, battery depletion, or undersensing. In *Table 1* characteristics of all patients were listed including the terminal VT cycle length, the preceding RR-interval (if available), and the time of the lethal arrhythmia. In regard to time and situation of death, it could be said that 12/19 events occurred during night-time (11/12 while sleeping and one during sexual activity) and seven during daytime. From the seven cases which occurred during daytime, four could be attributed to physical activity (car washing, running for the bus, carrying heavy shopping bags, and climbing stairs). For three cases during day no information on activity was available.

The 49-year-old patient described in *Figures 1* and *2* had primary dilated cardiomyopathy. Left ventricular ejection fraction at first evaluation was 20% angiographically. Due to bradyarrhythmia, he received a DDD pacemaker which was later programmed to DDI mode with a low basal rate due to normal rate response and conversion to sinus rhythm. From a clinical point of view, he was very stable without any dyspnoea (NYHA I) and the LVEF increased to

Table 1 Characteristics of SD Patients having post-mortem pacemaker marker channels and electrogram analysis

Number	Age (years)	Sex	CAD	NYHA PreSD	LVEF implantion (%)	Observation time (years)	PM mode	Intervall PreSD (ms)	Intervall SD (ms)	Time of SD (hour)
1	38	Male	No	1	8	2.95	VVI	810	313	7:59
2	40	Male	No	1	20	0.74	VVI	Not determined	281	1:15
3	43	Male	Yes	1	26	0.47	VVI	699	283	0:04
4	49	Male	No	1	20	1.85	VVI	1180	320	4:43
5	55	Male	Yes	1	34	2.00	VVI	Not determined	344	8:05
6	56	Male	No	1	25	5.92	VVI	Not determined	344	13:00
7	58	Male	Yes	2	25	6.09	DDD	645	362	22:23
8	60	Male	No	1	20	3.27	DDD	835	313	17:13
9	60	Male	Yes	1	35	1.29	DDD	909	280	13:00
10	61	Male	Yes	2	20	5.57	DDD	735	no data	4:00
11	64	Male	Yes	1	10	9.30	DDD	734	344	6:11
12	65	Male	Yes	2	25	4.02	DDD	781	no data	7:00
13	70	Female	No	2	22	4.19	DDD	602	285	16:34
14	64	Male	Yes	2	21	4.89	BIV	821	260	18:30
15	35	Male	No	2	37	0.21	BIV	Not determined	335	11:36
16	66	Male	No	2	21	0.67	BIV	Not determined	300	17:00
17	74	Male	Yes	3	27	2.08	BIV	Not determined	300	6:12
18	80	Male	Yes	2	25	0.30	BIV	Not determined	320	5:30
19	77	Female	No	3	35	0.43	BIV	Not determined	250	7:00

CAD, coronary artery disease; Observation time, observation time after PM implantation; PM mode, pacemaker stimulation mode; BIV, biventricular; intervall pre SD, RR-intervals preceding terminal arrhythmia (ms); intervall SD, terminal RR-intervall (ms).

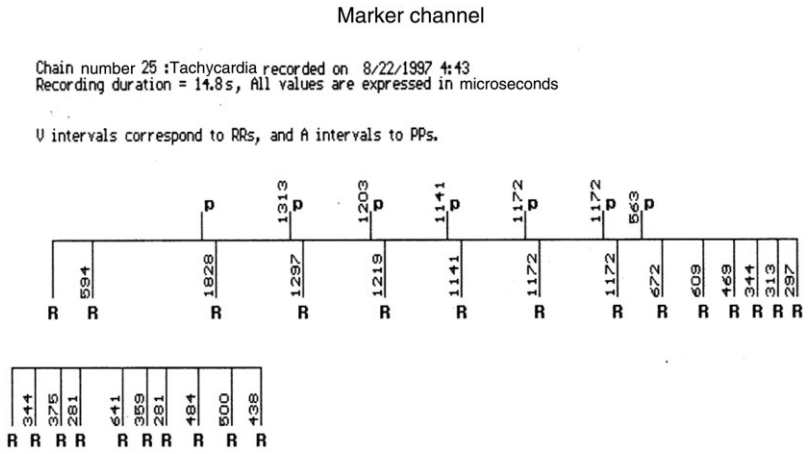

Figure 1 The terminal event of patient number 4. The irregular tachycardia was defined by markers channel analysis of an ELA medical Chorus RM pacemaker and developed in the morning hours out of a bradycardic heart rate (46/min) is initiated after a supraventricular premature beat. P, spontaneous P-wave; R, spontaneous R-wave.

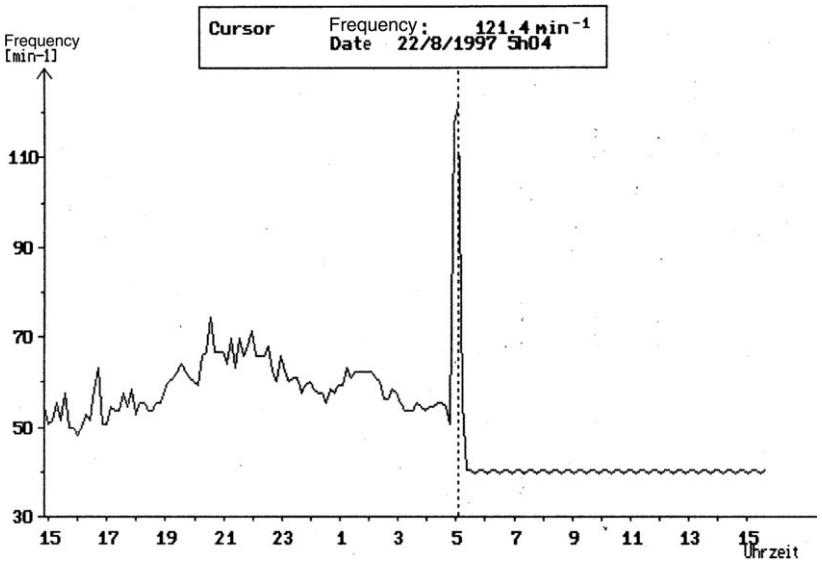

Figure 2 Twenty-four hour heart rate profile of the same patient described in figures, one prior to SD, as determined by conventional pacemaker holter. The rise in heart rate in the morning hours correlates with sustained ventricular tachycardia.

44% in echo under beta-blocker therapy. Therefore, prophylactic defibrillator implantation was judged not to be indicated. The terminal event are shown in *Figure 1*. At 04:43 a.m. during sleep, an irregular fast rhythm (most likely ventricular tachycardia) developed from a bradycardic baseline heart rate (46 bpm). While irregular VT is the most likely explanation, rapid supraventricular tachycardia or atrial fibrillation with either undersensing in the atrium thereafter or atrial events in the blanking period which are not marked may also be possible. *Figure 2* shows the mean heart rate calculated from the monitoring program. A low heart rate during night developed in a sharp increase (ventricular tachycardia) and after death relapsed to pacemaker stimulation at the lower rate of 40 bpm. The patient was found dead in the morning. Post-mortem analysis was performed and excluded cerebral or myocardial infarction or pulmonary emboli as cause of death. *Figure 3* showed a second patient who died suddenly while climbing stairs with heavy shopping bags. He improved to NYHA class 2 under cardiac resynchronization therapy (CRT). Post-mortem analysis in this case also was performed and also showed no evidence of a non-arrhythmic death. *Figure 4* showed a third patient who died suddenly while washing his car. He also felt very well before this event. From a presumed slow VT fast VT developed and the patient went into cardiac arrest and finally died before emergency personnel arrived.

Discussion

Post-mortem analysis of pacemaker memory in our cohort of stable outpatients revealed tachycardia (most likely ventricular tachycardia) to be related to SD in the vast majority of analysed data (90%). All these patients had a reduced ventricular function but were in a low NYHA class. The events we found are potential preventable and treatable, especially since all of the patients are in a stable condition and SD comes completely unexpectedly.[5] These results are in

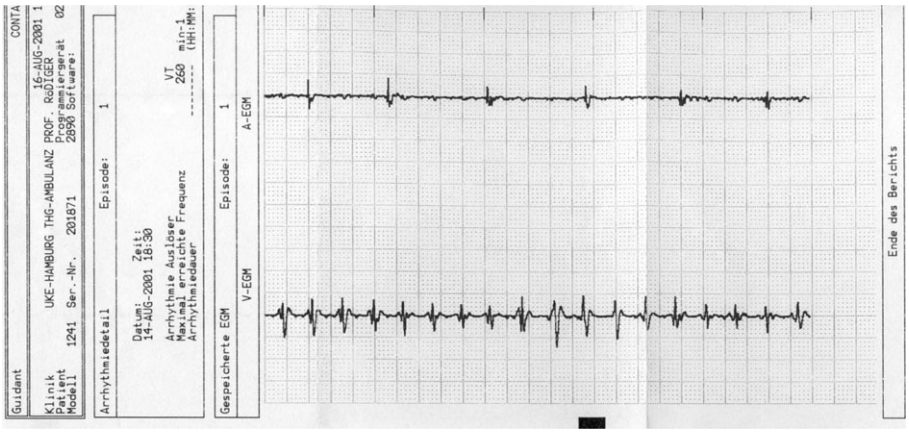

Figure 3 The terminal event of patient number 14. Sustained ventricular tachycardia was defined as a high rate in the ventricular channel and a normal rate in the atrial channel of the stored information of a Guidant CONTAK TR biventricular pacemaker. This patient died suddenly during climbing a staircase with heavy shopping bags.

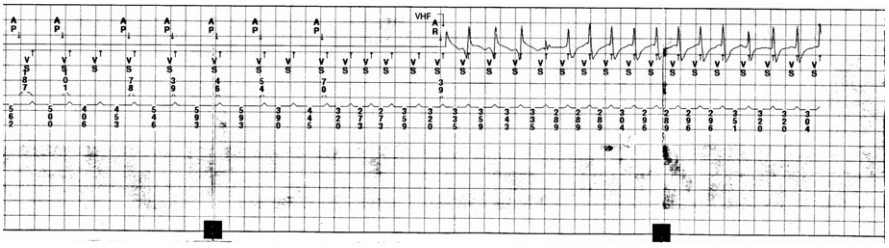

Figure 4 The terminal event of patient number 16. Sustained ventricular tachycardia started after a period of ventricular sensing (possibly slow VT) as analysed from an interrogation of the patients Medtronic INSYNC III biventricular pacemaker. This patient died suddenly during car washing.

contrast to Luu *et al*. who report that EMD may be responsible for a substantial number of SD in heart failure patients.[11] However, their cohort consists of inpatients who are acutely decompensated and are haemodynamically unstable. Bradycardic death may have been prevented by effective stimulation in our group (but would be ineffective in EMD). Furthermore, bradycardias as a final heart failure stage may have been come to notice only after an unwitnessed period of VT, possibly slow VT. Slow VT, which is a well known and serious problem in patients with dilated hearts (*Figure 4*)[19], at a rate lower than the programmed detection rate may be the cause of SD in patients number 10 and 12 without stored arrhythmia. Otherwise, these deaths may be caused by fine ventricular fibrillation (VF) below the sensing threshold or EMD, suggesting a relatively low incidence of fine VF or EMD. Older reports summarizing terminal events of patients wearing holter recorders at time of death support our findings of predominant tachycardic SD.[9,10]

Furthermore, data of our study add to the chronobiology of SD.[20] Most events occurred during sleep at night. The only one patient who died in the night-time who was not asleep was sexually active. It could be speculated that triggers from the autonomic nervous system and/or pulmonary problems (sleep apnoea)[21] may play a role. During daytime, exercise activity may trigger ischaemia or may lead to SD as suggested by the fact that many patients who died during the day performed at least some activity. A more detailed analysis of trigger events may give more information on possible preventive measures.[22] In regard of risk stratification data of continuous pacemaker monitoring may yield more diagnostic information than conventional holter.[6] This may be more improved by online transmission of data through the Internet providing a warning system of SD,[23] a system just becoming available worldwide.

The most important message to be derived from our data is that in patients with a bradycardia pacing indication and heart failure primary defibrillator implantation should be considered, as antiarrhythmic drugs had shown disappointing results.[18,24,25] Taken into account, the miniaturization of batteries and leads one could provocatively state that if a device has to be implanted at all, why not a defibrillator as a first-line measure? In our personal opinion, this is a logical consequence of recent data that prophylactic defibrillator implantation results in a reduced mortality in high-risk patients.[18,26] However, only a minority of patients had been supplied with these devices, whether due to economic reasons or of unknown status of ventricular function. Knowledge of the last seems to be crucial because patients of our cohort are almost asymptomatic or only mildly symptomatic prior SD. Or in other words, the thread of SD is present in symptomatic- and asymptomatic- heart failure. Prevention of these fatal events in asymptomatic heart failure patients may prolong life even more than in higher NYHA classes, where patients often die from pump failure. Therefore, we recommend routine echo examination before every pacemaker implantation even in the asymptomatic patient.

In regard to CRT, the findings in the CARE-HF extension study suggested that CRT itself reduces SD,[27] however, a recent metaanalysis did not support this finding.[7] In our limited experience, a substantial number of these fatal events could occur even after a long time of effective biventricular stimulation (*Table 1*), demanding defibrillation capabilities especially in this group. In this regard, it is of interest that arrhythmia may be caused by resynchronization therapy itself by an increase of QT dispersion.[28]

Limitations

Our report is a small observational study and may be limited by a selection bias. Because of this and the fact that the in hospital deaths were excluded the data is purposely biased towards arrhythmic deaths. Therefore, conclusions about widening of the ICD indications and speculations about the mechanism of death in general should be taken with caution. Furthermore, we could not investigate all pacemaker patients, but only those with arrhythmia monitoring systems. Marker channels can be misleading in the exact diagnosis of the arrhythmia whether it was ventricular or supraventricular origin when no electrograms were available (*Figure 1*)[14]. However, a typical pattern of the marker channels (such as sudden onset, stability, and no association with atrial rate) at least strongly suggests that they reflect true ventricular arrhythmia. Furthermore, it is not 100% certain that the arrhythmias are the direct cause of death. This is a circumstantial inference. However, post-mortem analysis was done in five patients, showing no evidence of non-arrhythmic death.

References

1. Müller C, Cernin J, Glogar D, Laczkovics A, Mayr H, Scheibelhofer W *et al*. Survival rate and causes of death in patients with pacemakers: dependence on symptoms leading to pacemaker implantation. *Eur Heart J* 1988;**9**:1003–9.
2. Zehender M, Büchner C, Meinertz T, Just H. Prevalence, circumstances, mechanisms, and risk stratification of sudden cardiac death in unipolar single-chamber ventricular pacing. *Circulation* 1992;**85**:596–605.
3. Himmrich E, Prizibille O, Zellerhoff C, Liebrich A, Rosocha S, Andreas K *et al*. Proarrhythmic effect of pacemaker stimulation in patients with implanted cardioverter-defibrillators. *Circulation* 2003;**108**:192–7.
4. Mattioli AV, Rossi R, Annicchiarico E, Mattioli G. Causes of death in patients with unipolar single chamber ventricular pacing: prevalence and circumstances in dependence on arrhythmias leading to pacemaker implantation. *Pacing Clin Electrophysiol* 1995;**18**:11–7.
5. Nägele H, Rödiger W. Sudden death and tailored medical therapy in candidates for heart transplantation. *J Heart Lung Transplant* 1999;**18**:869–76.
6. Ritter P. The 24-hour holter is not the gold standard technique to assess the efficacy of anti-arrhythmic therapies in the brady-tachy syndrome. *Eur J Clin Pacing Electrophysiol* 1996;**6**:208.
7. Rivero-Ayerza M, Theuns DAMJ, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2006;**27**:2682–8.
8. Podrid PJ, Myerburg RJ. Epidemiology and stratification of risk for sudden cardiac death. *Clin Cardiol* 2005;**28**(11 Suppl. 1):I3–11.
9. Roelandt J, Klootwijk P, Lubsen J, Janse MJ. Sudden death during long-term ambulatory monitoring. *Eur Heart J* 1984;**5**:7–20.
10. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. *Am Heart J* 1989;**117**:151–9.
11. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;**80**:1675–80.
12. Huikuri H. Effect of stored electrograms on management in the paced patient. *Am J Cardiol* 2000;**86**:101K-3K.
13. Nowak B. Pacemaker stored electrograms: teaching us what is really going on in our patients. *Pacing Clin Electrophysiol* 2002;**25**:838–49.
14. Nowak B, McMeekin J, Knops M, Wille B, Schröder E, Conception M *et al*. Validation of dual-chamber pacemaker diagnostic data using dual-channel stored electrograms. *Pacing Clin Electrophysiol* 2005;**28**:620–9.
15. Pollak WM, Simmons JD, Interian A, Atapattu SA, Castellanos A, Myerburg RJ *et al*. Clinical utility of intraatrial pacemaker stored electrograms to diagnose atrial fibrillation and flutter. *Pacing Clin Electrophysiol* 2001;**24**:424–9.
16. Whang W, Mittleman MA, Rich DQ, Wang PJ, Ruskin JN, Tofler GH *et al*. Heart failure and the risk of shocks in patients with implantable cardioverter defibrillators: results from the Triggers of Ventricular Arrhythmias (TOVA) study. *Circulation* 2004;**109**:1386–91.
17. Stevenson IH, Mond HG. A Coroner's request for closure: the value of the stored electrogram. *Pacing Clin Electrophysiol* 2006;**29**:670–3.
18. Bardy GM, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R *et al*. for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure. *N Engl J Med* 2005;**352**:225–37.
19. Bänsch D, Steffgen F, Gronefeld G, Wolpert C, Bocker D, Mletzko RU *et al*. The 1+1 trial: a prospective trial of a dual- versus a single-chamber implantable defibrillator in patients with slow ventricular tachycardias. *Circulation* 2004;**110**:1022–9.
20. Aronow WS, Ahn C. Circadian variation of primary cardiac arrest or sudden cardiac death in patients aged 62 to 100 years. *Am J Cardiol* 1993;**71**:1455–6.
21. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet* 1991;**338**:1480–4.
22. Kay GN, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *J Am Coll Cardiol*.1983;**2**:806–17.
23. Perings C, Klein G, Toft E, Moro C, Klug D, Bocker D *et al*. The RIONI study rationale and design: validation of the first stored electrograms transmitted via home monitoring in patients with implantable defibrillators. *Europace* 2006;**8**:288–92.
24. McAlister FA, Teo KK. Antiarrhythmic therapies for the prevention of sudden cardiac death. *Drugs* 1997;**54**:235–52.
25. Ruskin JN. The cardiac arrhythmia suppression trial (CAST). *N Engl J Med* 1989;**321**:386–89.
26. Moss AJ, Hall J, Cannom DS, Daubert JP, Higgins SL, Klein H *et al*. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;**335**:1933–40.
27. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al*. on behalf of The CARE-HF Study Investigators. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the Cardiac Resynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1440–6.
28. Chalil S, Yousef ZR, Muyhaldeen SA, Smith RE, Jordan P, Gibbs CR *et al*. Pacing-induced increase in QT dispersion predicts sudden cardiac death following cardiac resynchronization therapy. *J Am Coll Cardiol* 2006;**47**:2486–92.