Implantable defibrillator therapy: More than defibrillation…

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ISBN 90-8559-035-3

Layout & Print: Optima Grafische Communicatie, Rotterdam

Cover illustration: Stored electrogram, ICD model H155, Guidant Inc, St Paul, MN, USA

Implantable defibrillator therapy
More than defibrillation…

Therapie met de implanteerbare defibrillator
Meer dan alleen defibrillatie…

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 27 april 2005 om 11:45 uur

door

Dominicus Anna Margaretha Johannes Theuns
geboren te Maastricht

Promotiecommissie

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Introduction

Introduction

During the past 25 years, the implantable cardioverter-defibrillator (ICD) has evolved from treatment for survivors of cardiac arrest to the standard therapy for patients at high risk for ventricular tachyarrhythmias. High-risk patients include not only survivors of cardiac arrest but also patients with cardiac diseases who are at risk to develop ventricular tachyarrhythmias but still are without symptoms. The current generation of devices not only provides treatment for ventricular tachyarrhythmias, but is also capable to treat atrial arrhythmias, and by means of biventricular pacing congestive heart failure.

The history of ventricular defibrillation

Prevost and Batelli first introduced the concept of defibrillation in 1899.(1) They noted that the application of large voltages across an animal's heart could stop ventricular fibrillation. In 1933, the existing knowledge about defibrillation was refined when alternating current was applied for internal defibrillation in dogs.(2) Fourteen years later, the first human internal defibrillation by application of alternating current was reported.(3) By the 1950s, Kouwenhoven was able to defibrillate dogs externally.(4) In 1956, Zoll and coworkers performed the first successful external defibrillation in man.(5) Alternating current was changed to direct current (DC) as this current appeared more effective and produced fewer side effects.(6,7) The DC pulse waveform was further improved in the 1960s.(8,9) The application of external defibrillation increased the survival of out-of-hospital cardiac arrest.(10) By the late 1960s, external cardiac defibrillation was acknowledged as an effective tool of terminating ventricular fibrillation and restoring sinus rhythm.

The evolution of the implantable cardioverter-defibrillator

The idea of developing an automatic implantable defibrillater originated from Dr. Michel Mirowski. The concept he pioneered was "blind and immediate defibrillation treatment of cardiac arrest". The device had to quickly recognize and treat ventricular fibrillation, and had to be small enough to implant in patients. The first prototype was tested in dogs.(11) The first human implantation took place on February 4, 1980, at the John Hopkins Hospital.(12) From that moment on, the ICD has evolved from a simple shock-only box into a full arrhythmia management device. Steady and

remarkable advances in device technology driven by the clinical needs resulted in greater patient safety and comfort.

The first-generation devices were designed to recognize only ventricular fibrillation (VF). It soon became apparent that survivors of cardiac arrest also suffered from unstable ventricular tachycardia (VT) that degenerated into VF. Therefore, second-generation devices had next to VF detection also VT detection incorporated. This early generation of ICDs could not discriminate between atrial and ventricular tachyarrhythmias, resulting in a high incidence of inappropriately delivered shocks, especially for atrial fibrillation.(13) However, interpretation and investigation of the appropriateness of therapy was limited due to the lack of storage of diagnostic information.(14)

The concept of tiered therapy was introduced in third-generation devices. These devices provide bradycardia pacing, antitachycardia pacing (ATP) modalities, as well as low- and high-energy shock therapies. The diagnostic information has been significantly improved by the storage of intracardiac electrograms.(15,16) In order to prevent inappropriate therapy, detection enhancements, like sudden onset and stability, were developed to improve arrhythmia discrimination.(17,18) Despite the advances in arrhythmia discrimination in tiered-therapy ICDs, a significant proportion of patients still experienced inappropriate shocks.(19) With the introduction of dual chamber devices, it was postulated that the specificity of arrhythmia discrimination might improve further with the addition of atrial information.(20,21) The evolution of arrhythmia discrimination continues with further refinement of morphology-based algorithms.

Clinical ICD trials

For several years ICD therapy was limited only to patients who survived 2 episodes of cardiac arrest due to VF.(22) Data from the first ICD implantations showed a low sudden death rate.(23,24) In 1985, the US Food and Drug Administration approved the ICD as a commercial device. At that time, ICD therapy was approved and limited for patients who survived 1 episode of cardiac arrest or patients with recurrent ventricular arrhythmias that were inducible but not suppressible with antiarrhythmic drugs. Studies showed consistently a low sudden death rate in ICD patients. However, in these uncontrolled studies, shock delivery was assumed to represent a life saved. Not all delivered shocks were appropriate, not every arrhythmia would

have been fatal if not terminated.(25) Other cardiac causes of death replaced sudden cardiac death.(26) To investigate the potential benefit of defibrillator therapy both for primary and secondary prevention of sudden cardiac death, randomised, clinical trials were designed. Three trials, Antiarrhythmics Versus Implantable Defibrillators (AVID), the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH), confirmed the use of defibrillator therapy for secondary prevention of potentially fatal ventricular tachyarrhythmias.(27-29) The concept of prophylactic defibrillator therapy for patients at high risk for cardiac arrest made risk stratification necessary. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was based on the risk model of nonsustained VT and low ejection fraction (EF) in postinfarction patients.(30) The results of this trial were supported by the results of the Multicenter Unsustained Tachycardia Trial (MUSTT).(31) In both studies, patients with coronary artery disease, low EF, and nonsustained VT in whom a sustained VT or VF could be induced at electrophysiologic study had survival benefit from defibrillator therapy.

In the second MADIT study (MADIT II), stable post-infarction patients with EF $\leq$ 30% without requirement of nonsustained VT or electrophysiologic study were randomised.(32) The results of this trial again demonstrated a significant reduction in all-cause mortality in patients treated with an ICD. This trial provoked a lot of debate about the issue of adequate risk stratification. Additional data on prophylactic ICD implantation was provided by the results of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).(33) Data from this trial confirmed that amiodarone does not improve survival in patients with depressed EF ($\leq$ 35%) and congestive heart failure. Simple, shock-only ICD therapy improved survival in both ischemic and nonischemic cardiomyopathy patients, beyond the improvement afforded by optimal drug therapy. ICD therapy became an established therapeutic modality for primary and secondary prevention of sudden cardiac death in post-infarction patients.

Although ICD therapy is beneficial among patients with left ventricular dysfunction, it may also result in morbidity, such as inappropriate shocks. Not all patients with depressed left ventricular function should immediately receive an ICD. Adequate risk stratification and device selection for each patient will certainly continue over the next years.

References

1. Prevost JL, Batelli F. La mort par les decharges electriques. I. Conditions physiques. II. Mecanisme de la mort par des decharges electriques isolees. J Physiol Pathol Gen 1899;1:1085-1129.
2. Hooker DR, Kouwenhoven WB, Langworthy OR. The effect of alternating electrical currents on the heart. Am J Physiol 1933;103:444-454.
3. Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. J Am Med Assoc 1947;135:985-986.
4. Kouwenhoven WB, Milnor WR. Treatment of ventricular defibrillation using a capacitor discharge. J Appl Physiol 1954;7:253-257.
5. Zoll PM, Linenthal AJ, Gibson W, Paul MH, Norman LR. Termination of ventricular fibrillation in man by externally applied electric countershock. N Engl J Med 1956;254:727-732.
6. Lown B, Neuman J, Amarasingham R, Berkovits BV. Comparison of alternating current with direct electroshock across the closed chest. Am J Cardiol 1962;10:223-233.
7. Edmark KW. Simultaneous Voltage and Current Waveforms Generated During Internal and External Direct Current Pulse Defibrillation. Surg Forum 1963;14:262-264.
8. Edmark KW, Thomas GI, Jones TW. DC pulse defibrillation. J Thorac Cardiovasc Surg 1966;51:326-333.
9. Kouwenhoven WB. The development of the defibrillator. Ann Intern Med 1969;71:449-458.
10. Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. Lancet 1967;2:271-273.
11. Mirowski M, Mower MM, Langer A, Heilman MS, Schreibman J. A chronically implanted system for automatic defibrillation in active conscious dogs. Experimental model for treatment of sudden death from ventricular fibrillation. Circulation 1978;58:90-94.
12. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322-324.
13. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1992;15:1667-1673.
14. Marchlinski FE, Buxton AE, Flores BF. The automatic implantable cardioverter defibrillator: Followup and complications. In: El-Sherif N, Samet P, editors. Cardiac pacing and electrophysiology. Orlando, FL: Grune and Stratton; 1990. p. 743-758.

15. Marchlinski FE, Gottlieb CD, Sarter B, Finkle J, Hook B, Callans D, Schwartzman D. ICD data storage: Value in arrhythmia management. Pacing Clin Electrophysiol 1993;16:527-534.
16. Hook BG, Callans DJ, Kleiman RB, Flores BT, Marchlinski FE. Implantable cardioverter-defibrillator therapy in the absence of significant symptoms. Rhythm diagnosis and management aided by stored electrogram analysis. Circulation 1993;87:1897-1906.
17. Swerdlow CD, Chen PS, Kass RM, Allard JR, Peter CT. Discrimination of ventricular tachycardia from sinus tachycardia and atrial fibrillation in a tiered-therapy cardioverter-defibrillator. J Am Coll Cardiol 1994;23:1342-1355.
18. Higgins SL, Lee RS, Kramer RL. Stability: an ICD detection criterion for discriminating atrial fibrillation from ventricular tachycardia. J Cardiovasc Electrophysiol 1995;6:1081-1088.
19. Nunain SO, Roelke M, Trouton T, Osswald S, Kim YH, Sosa-Suarez G, Brooks DR, McGovern B, Guy M, Torchiana DF, et al. Limitations and late complications of third-generation automatic cardioverter-defibrillators. Circulation 1995;91:2204-2213.
20. Lavergne T, Daubert JC, Chauvin M, Dolla E, Kacet S, Leenhardt A, Mabo P, Ritter P, Sadoul N, Saoudi N, Henry C, Nitzsche R, Ripart A, Murgatroyd F. Preliminary clinical experience with the first dual chamber pacemaker defibrillator. Pacing Clin Electrophysiol 1997;20:182-188.
21. Nair M, Saoudi N, Kroiss D, Letac B. Automatic arrhythmia identification using analysis of the atrioventricular association. Application to a new generation of implantable defibrillators. Participating Centers of the Automatic Recognition of Arrhythmia Study Group. Circulation 1997;95:967-973.
22. Winkle RA, Thomas A. The automatic implantable cardioverter defibrillator: The US experience. In: Brugada P, Wellens HJJ, editors. Cardiac Arrhythmias: Where To Go From Here? Mount Kisco, NY: Futura Publishing Co.; 1987. p. 663-680.
23. Mirowski M. Prevention of sudden arrhythmic death with implanted automatic defibrillators. Ann Intern Med 1982;97:606-608.
24. Mirowski M, Reid PR, Mower MM, Watkins L, Jr., Platia EV, Griffith LS, Juanteguy JM. Clinical experience with the implantable cardioverter-defibrillator. Ann N Y Acad Sci 1984;427:297-306.
25. Jordaens L, Waleffe A, Derom F, Rodriguez LM, Clement DL, Kulbertus H. Experience with the automatic implantable defibrillator. Acta Clin Belg 1988;43:209-218.
26. Winkle RA, Mead RH, Ruder MA, Gaudiani VA, Smith NA, Buch WS, Schmidt P, Shipman T. Long-term outcome with the automatic implantable cardioverter-defibrillator. J Am Coll Cardiol 1989;13:1353-1361.

27. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
28. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-1302.
29. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748-754.
30. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
31. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882-1890.
32. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
33. Bardy G, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R for the Sudden Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-237.

Part I

Prognosis and Follow-up of Patients with an ICD

Chapter 1

Clinical Benefit, Survival, and Adverse Events in Patients with an Implantable Cardioverter Defibrillator: The Initial Rotterdam Experience

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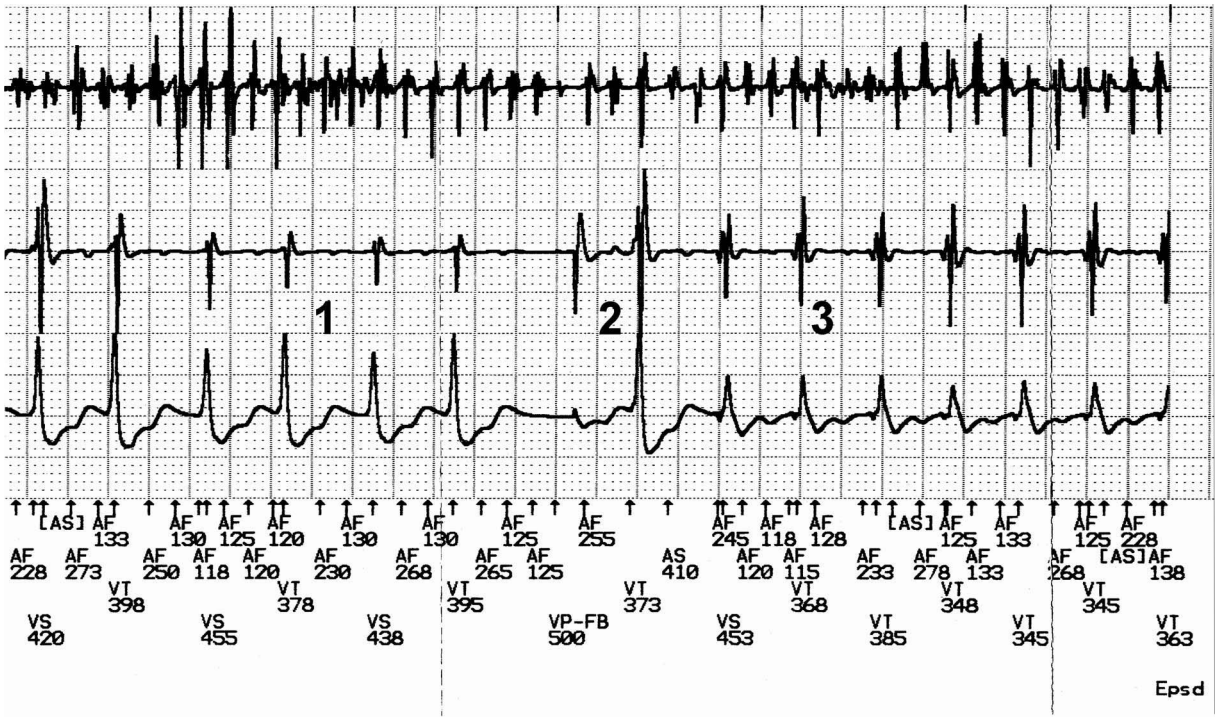
Published: Netherlands Heart Journal 2001;9:216-221.



Abstract

Background: *The implantable cardioverter defibrillator (ICD) has become a widely accepted therapy for patients with severe life-threatening ventricular tachyarrhythmias. The aim of this study was to illustrate the possible advantages of ICDs with respect to survival and clinical events.*

Methods and results: *Between 1998 and 2000, 92 patients (age, 58±15 years; ejection fraction, 36±15%; coronary artery disease, 71%) were treated with an ICD in combination with an endocardial lead system. Benefit of the ICD was estimated as the difference between total cardiac death and the projected death rate of fast ventricular tachyarrhythmias (>200 bpm), assuming that most fast ventricular tachyarrhythmias would have been fatal without termination by the ICD. Adverse events were classified according to European standards.*

The cardiac mortality rate was 5.5% and 9.8%, at 1 and 2 years respectively. The recurrence rate of fast VT (>200 bpm) was 22.4% and 30.2%, at 1 and 2 years respectively. The observed difference between cardiac death and projected death was very significant (P=0.002) and suggests a clear benefit from ICD implantation. Low ejection fraction (<35%) and NYHA class ≥ II correlated with a higher projected death. The most common adverse event was inappropriate therapy (18%).

Conclusion: *The data in our small series supports the existing data that especially patients with poor ejection fraction (<35%) benefit from ICD implantation. The adverse event rate was low. However, inappropriate therapy remains a matter of concern. Given the high workload of correct screening and follow-up, we expect that the actual number of centers in the Netherlands, permitted to implant ICDs, will not be able to cope with the widening spectrum of ICD indications.*

Introduction

The implantable cardioverter defibrillator (ICD) has become a widely accepted therapy for the treatment of patients with severe life threatening ventricular tachyarrhythmias.[1,2] Driven by clinical needs, the evolution of ICD systems into full cardiac arrhythmia management devices continues.[3] Technologic development in device therapy includes increased and improved diagnostics, and comprehensive and specific therapy. Indeed, several shortcomings of conventional ICDs still exist. One of the most important is inappropriate therapy due to supraventricular tachycardia.[4] Several approaches to avoid "spurious" interventions caused by this arrhythmia are possible. One way to avoid unnecessary shocks is to use the atrial signals for decision making, by implanting an additional atrial lead. Reliable sensing of atrial activity also allows the recognition of atrial fibrillation, which then can be treated with more advanced systems as well.[5,6]

The potential of the ICD to prolong life has been challenged by the argument that although the ICD reduces the rate of sudden death, it does not reduce cardiac death or total mortality.[7] The benefit from ICD implantation might last the longest for patients without heart failure or with mild heart failure.[8] On the other hand, post-hoc analysis of the AVID trial suggested that only patients with left ventricular ejection fraction (LVEF) < 35% have benefit.[1]

The aim of this overview of our first 92 patients in whom we implanted an ICD is to illustrate the possible advantages of arrhythmia management devices with respect to survival and clinical events.

Material and Methods

Patients

Between October 1998 and October 2000, 92 consecutive patients were treated with an ICD in combination with an endocardial lead system because of a history of sustained malignant ventricular tachyarrhythmia, aborted sudden death, or syncope attributable to a ventricular tachyarrhythmia.

Implantation method

The ICD pulse generator and endocardial leads were inserted through a single left pectoral incision. We used a left cephalic vein cutdown and/or a left subclavian

puncture for lead insertion. The ventricular lead was placed at the right ventricular apex, while the atrial lead was positioned in the right atrial appendage or lateral free wall by active fixation. In case of a biventricular device, the lead for left ventricular pacing was positioned via the left subclavian vein in one of the tributaries of the coronary sinus. The capture and sensing thresholds of both atrial and ventricular leads were tested. The presence of far-field R wave sensing in the atrial electrogram was to be excluded. If present, the atrial lead was relocated at another location until appropriate sensing could be achieved.
All patients underwent defibrillation threshold testing and a pre-hospital discharge test with reinduction of ventricular fibrillation.

Follow-up

Follow-up started at the time of ICD implantation. Regular follow-up was scheduled at 3-month intervals. In case of therapy delivery by the device, patients were advised to visit the out-patient clinic. Subsequently, the memory of the device was interrogated and the therapy was adapted to the clinical findings if necessary.
All therapeutic device interventions were classified as appropriate or as inappropriate (that is, intervention of the device for events not be a ventricular tachyarrhythmia) according to stored electrograms.

Definitions and classification of events

Cardiac death: cardiac deaths were classified into sudden and nonsudden. Sudden death was defined as death occurring without preceding symptoms or within 1 hour after the onset of or sudden change in symptoms. An unexpected, insufficiently documented, and unwitnessed death was conservatively also classified as sudden.[9]
Electric storm: electric storm was defined as three or more episodes of VT or VF requiring ICD therapy in a 24-h period.[10]
Benefit of the ICD: benefit of the ICD was estimated by the difference between the total cardiac death and the projected death rate of fast ventricular tachyarrhythmias, assuming that most fast ventricular tachyarrhythmias would have been fatal without termination by the ICD. Recorded nonfatal events included fast ventricular tachyarrhythmias were defined as ventricular tachyarrhythmias with cutoff rates of $>$ 200 beats/min and according to Böcker et al. $>$ 240 beats/min.[8]

Adverse event: according to European standards, an “adverse event” was “any undesirable clinical occurrence in a subject whether it was considered to be device related or not.”[11,12] A procedure-related event was defined as being directly or indirectly caused by the implantation procedure. A device-related event was defined as an event related to the implanted ICD system including leads. A non-device-related adverse event was defined as hospital admission.

Statistical analysis

The Kaplan-Meier method was used to generate survival curves. The following end points were used: 1. VT, 2. fast VT (> 200 bpm) or VF, 3. fast VT (> 240 bpm) or VF, 4. total death, and 5. total death plus occurrence of fast ventricular tachyarrhythmias representing projected death. Benefit of the ICD implantation was estimated by the difference between curves for total cardiac death and calculated projected deaths. Fisher´s exact test was used to analyze the difference between Kaplan-Meier curves. Univariate analysis with 95% confidence intervals was used to analyze the influence of various covariates on the occurrence of fast VT and projected death.

Results

Patients

A total of 92 patients were considered for implantation of an ICD in combination with an endocardial lead system. The patient characteristics are summarized in Table 1. There were 75 men (82%) and 17 women (18%) with a mean age of 58 ± 15 years (range 17–82 years). Mean LVEF as determined by nuclear isotopes was 36 ± 15% range (12-74 %). The underlying diseases were coronary artery disease in 71% of the patients, dilated cardiomyopathy in 13%, hypertrophic cardiomyopathy in 2%, and other cardiac diseases in 14%.

Patient deaths

There were 5 patient deaths (5 men, mean age 59 ± 20 years). All deaths except 1 were witnessed in the hospital. One death was classified as “unknown and occurring suddenly” because it was unwitnessed, insufficient information was available, and it occurred outside the hospital. The ICD was not available for interrogation.

Two patients died of progressive heart failure after implantation, and the other 2 patients died of an electric storm, one of them during an exacerbation of heart failure.

Table 1. *Patient Characteristics*

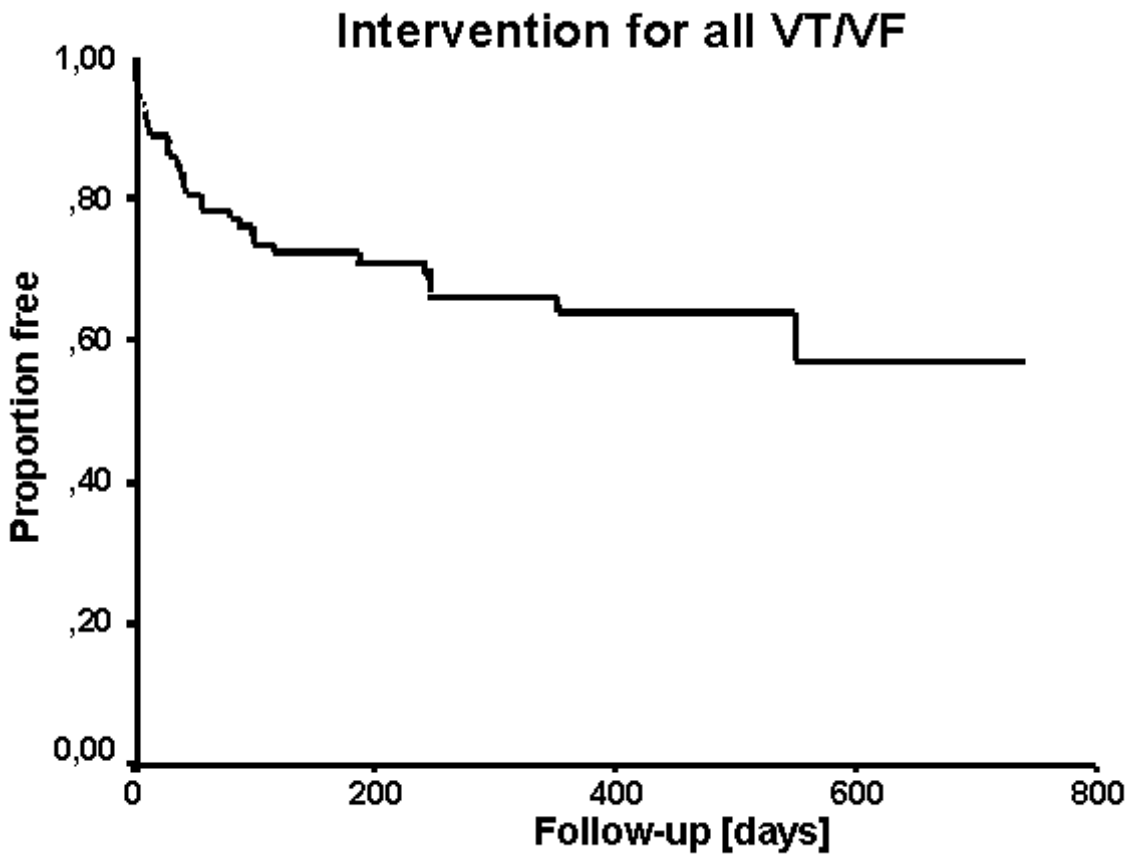
Patient Characteristics	
Gender, M/F	75/17
Age, years	58±15
LV ejection fraction, %	36±15
Antiarrhythmic drug therapy, n	
Amiodarone	32
Sotalol	10
ß-blockade	15
Underlying cardiac disease, n	
CAD	65
CMP	12
History of atrial tachyarrhythmias, n	33
Indication for ICD implantation, n	
SCD, cardiac arrest	38
VT, cardiac arrest	19
VT	30
Other	5
Type of ICD, n	
Single chamber	15
Dual chamber	61
Biventricular	16

LV = left ventricular; CAD = coronary artery disease; CMP = cardiomyopathy; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; VT = ventricular tachycardia

Incidence of all VT/VF

During a mean follow-up of 364 ± 189 days (range 40 – 737 days), 31 (34%) patients had at least 1 episode of ventricular tachyarrhythmia presenting at a median interval of 39 days (range 1 – 550 days) after implantation. The recurrence rate of ventricular tachyarrhythmia was 36% and 43% at 1 and 2 years respectively (Figure 1). All episodes of ventricular tachyarrhythmia were appropriately detected and terminated by the device.

Figure 1. *Actuarial survival rate for freedom of sustained ventricular tachyarrhythmias of any rate requiring intervention of the ICD. VF: ventricular fibrillation; VT: ventricular tachycardia.*

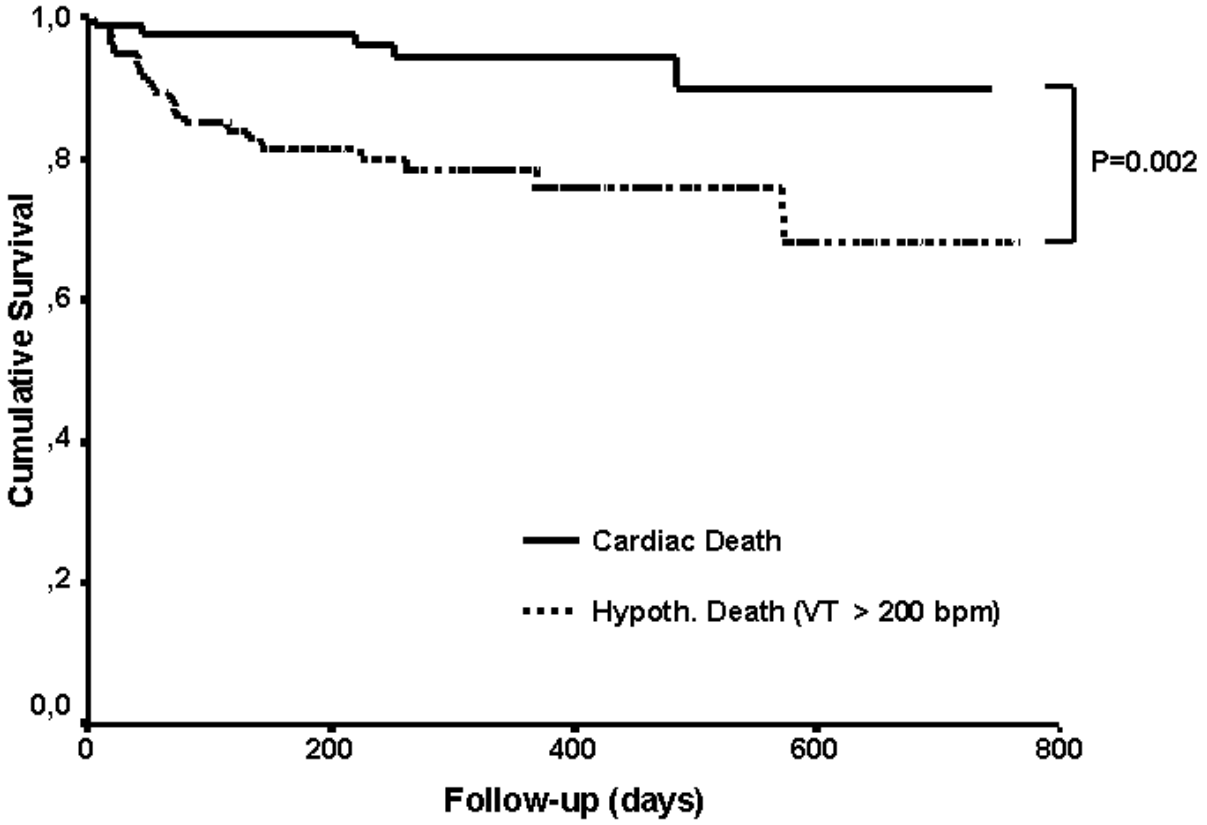


Incidence of fast VT or VF

Twenty patients (22%) had at least 1 episode of fast VT (> 200 bpm) or VF presenting at a median interval of 57,5 days (range 6 – 550 days) after implantation. Fast VT (> 240 bpm) or VF was present in 9 patients (10%) at a median interval of 67 days (range 6 – 550 days) after implantation. The majority of patients in both fast VT groups had NYHA class II. The mean LVEF was 29 ± 12% for patients with fast VT (> 200 bpm) or VF versus 35 ± 15% for patients with fast VT (> 240 bpm) or VF. The actuarial event-free rate for fast VT (> 200 bpm) was 77.6% and 69.8% at 1 and 2 years respectively, whereas the actuarial event-free rate for fast VT (> 240 bpm) was 88% at 1 year and remained than constant.

In a univariate model a lower ejection fraction only correlated with a higher recurrence of fast ventricular tachyarrhythmias with rates > 200 bpm (*P*=0,04). The NYHA class failed to reach significance in both groups of fast VT.

Figure 2. *Actuarial survival rates for freedom from death of cardiac origin and of projected (project.) death due to ventricular tachycardia (VT) with cycle lengths < 300 ms (> 200 bpm) and / or ventricular fibrillation (VF).*



Survival

The total mortality rate was 5.5% and 9.8%, at 1 and 2 years respectively. The projected death rates (total mortality plus occurrence of fast VT or VF) were 24,0% and 33,8% for fast VT (> 200 bpm) and 12.3% and 14.6% for fast VT (> 240 bpm), at 1 and 2 years respectively (Figure 2). For the total group, the estimated benefit from ICD implantation, calculated as the difference between the curves total mortality and the projected death rate, increased from 18,5% (1 year) to 24,0% (2 years) for fast VT (> 200 bpm). The estimated benefit of ICD implantation was 6.8% (1 year) and 4.8% (2 years) in case of the projected death with cutoff rate > 240 bpm.

The estimated benefit of ICD implantation only reached significance in patients with fast VT (> 200 bpm) (*P*=0.002). The difference in benefit of ICD implantation between the groups with fast VT (> 200 bpm versus > 240 bpm) showed a significantly greater benefit for the group with fast VT > 200 bpm (*P*=0.04).

The covariates LVEF (*P*=0,03) and NYHA class (*P*=0,05) correlated with a higher projected death rate for fast VT (> 200 bpm) in a univariate model. Both covariates failed to reach significance for fast VT (> 240 bpm).

Procedure-Related Adverse Events

Adverse events related to the implantation procedure were observed in 12 (13%) patients (Table 2). No perioperative deaths were reported.

The most common adverse events were lead dislodgment (4 pts) and pneumothorax (4 pts). Related with implantation of biventricular devices, the LV lead dislodged most often (n=2, 13% of biventricular devices). The second most frequent adverse event was pneumothorax due to puncture of the left subclavian vein (5% of 77 subclavian punctures).

One patient received inappropriate therapy due to a connector problem, which was resolved the next day by re-operation.

Table 2. *Procedure-Related Adverse Events*

	Number of patients (%)
Pneumothorax	4 (4%)
Coronary sinus dissection	1 (1%)
Fever/sepsis/infection	1 (1%)
Wound/pocket problems	1 (1%)
Lead dislodgment	
Atrial lead	1 (1%)
Right ventricular lead	1 (1%)
Left ventricular lead	2 (2%)
Lead connection	1 (1%)

Device-Related Adverse Events

The event with the highest incidence was inappropriate therapy, which was observed in 17 (18%) patients (Table 3). In 11 patients, this was due to supraventricular tachyarrhythmias which required hospitalization for cardioversion in 6 of them. Subsequently, 2 patients underwent AV node ablation.

T wave oversensing was observed in 6 patients (1 Medtronic, 5 Biotronik). This was resolved by reprogramming the sensitivity.

A decreased sensing efficacy was present in 2 patients. This was corrected by repositioning of the right ventricular lead in 1 patient. The other patient received a

special designed coronary sinus lead with left atrial sensing and pacing capabilities, as in the right atrium no sufficient sensing signals were available.

Table 3. *Device-Related Adverse Events*

	Number of patients
Inappropriate therapy	17
SVT	11*
T wave	6*
Va	1
Sensing problems	2

SVT = supraventricular tachycardia; Va = ventricular arrhythmia
* including patients with more than one different event

Non-Device-Related Adverse Events

In 9 (10%) patients, all presenting with an electric storm, hospitalization was required for adjustment of drug therapy and general measures (Table 4). Five of these patients developed slow ventricular tachycardias (≤ 150 beats/min) and reprogrammation of the device was required. Subsequently, in 2 of them VT ablation was performed to resolve the problem.

Hospitalization for signs of congestive heart failure was required in 6 patients. In 4 of these patients, an electric storm occurred in the presence of heart failure.

Table 4. *Non-Device-Related Adverse Events*

	Number of patients
Hospitalization for CHF	6*
Hospitalization for atrial arrhythmias	7
Hospitalization for ventricular arrhythmias	9*
Electric storm	12*

CHF = congestive heart failure
* including patients with more than one different event

Discussion

The results in this study are in concordance with earlier findings that patients with a history of cardiac arrest or ventricular tachyarrhythmias refractory to drug therapy benefit from ICD implantation. The potential benefit was estimated as the difference between overall mortality and the projected death rate had the device not been implanted. The latter was based on the recurrence of fast and presumably fatal

ventricular tachyarrhythmias without termination by the device. The estimated benefit from ICD implantation is comparable with the benefit as reported by Böcker et al. for the overall group (15.9% and 23.5% at 1 and 3 years respectively.[8] It is hard to imagine such gain in life expectancy might have been obtained with drugs. The AVID trial reported a reduction in mortality of 27% at 2 years in the ICD group compared to the group with antiarrhythmic drug therapy.[1] The recently published CASH trial confirms the superiority of ICD therapy over antiarrhythmic drug therapy as they demonstrated a 37% survival benefit from ICD therapy.[13] However, the mean LVEF of patients in the CASH trial (46%) was higher than in the AVID trial (32%), propably due to a larger population without organic heart disease in CASH. Data from the AVID trial suggested that patients who appear to benefit most from ICD implantation are those with a LVEF < 35%.[1] These data are further supported by the MADIT and MUSTT trial which both focused on patients with low EF.[2,14] In our study, the mean LVEF for the whole group was 36%, and 29% for patients with fast ventricular tachyarrhythmias.

In the present study, there were no perioperative deaths, which is in line with a mortality rate of < 1% associated with implantation of endocardial defibrillation lead systems. If we would have used the American definition for surgical mortality, all mortality within one month would have been identified as such. This would have resulted in 1 death, a mortality rate of 1%. However, it is very difficult to accept this early death as “surgical”, and in this case it should rather be considered as failure of the therapy. The incidence of procedure-related adverse events was low in our series. The observed incidence of lead dislodgments was lower than observed in other studies.[15] The higher incidence of LV lead dislodgment in patients with biventricular devices can be reduced by further improvement of the implantation technique and design of the LV lead.

The second most frequent procedure-related adverse event was pneumothorax which is related to puncture of the left subclavian vein.[16] The observed incidence in our group was low and is line with other reported values.[16,17]

As observed with second-generation ICD therapy with limited programmability, inappropriate therapy was the most frequent event.[4] This inappropriate therapy was most often triggered by atrial fibrillation with rapid ventricular response. Despite enhancements in technology (improved algorithms and/or the addition of atrial

signals), 11 patients (12%) received inappropriate therapy for supraventricular tachyarrhythmias. Also, T wave oversensing may lead to inappropriate tachyarrhythmia detection. During early follow-up, the evaluation of oversensing during sinus rhythm and pacing is necessary to avoid this sensing problem with reprogrammation.[18]

The overall incidence of inappropriate therapy (18%) is in line with other reports emphasizing that inappropriate therapy is the most common adverse event among ICD patients.[15,17]

Limitations of the study

In our study, patients were their own control. As endpoint we used projected death. This was based on the assumption that fast ventricular tachyarrhythmias might have been fatal in the absence of an ICD. Obviously, both underestimation and overestimation of the benefit imposed by ICD therapy cannot be excluded. First, a minority of patients might have died from their ventricular tachyarrhythmia slower than 200 bpm. Especially, for patients with advanced heart failure who might not even tolerate a slower tachycardia or incessant tachycardia. Second, a minority of patients might have survived a fast ventricular tachycardia long enough to obtain medical attention. Further investigation of these patient groups is warranted.

Conclusions

Finally, we were very pleased that we could reproduce the existing data in literature with this small series. This reflects a rigid patient selection with conservative criteria. The complication rate and surgical mortality had a very acceptable prevalence, and this was probably due to the low profile we kept for the procedure (implantation by experienced cardiologists, no general anesthesia). Our follow-up included pre-hospital discharge testing, out-patient technical and medical follow-up, and psychosocial support of patients and family. However, we feel that the attention for individual patient problems is still insufficient at present.

As the Netherlands, with a reported number of 16 new ICD implantations per million per year in 1997 are not even reaching the implantation figures of other European countries such as Belgium (28/mil.), Denmark (33/mil.), and Germany (49/mil.), the

recent increase of implantation centers in the Netherlands was certainly justified[19]. In fact, the National Health Service of the United Kingdom anticipates that 50 per million inhabitants, will be the actual, desirable target.[20] From these figures, it seems very unlikely that the actual number of centers in the Netherlands will be able to cope with the widening spectrum of indications. In particular, patients with the most evident benefit ("MADIT" and "MUSTT") are not treated today under the regulations of the Ministry of Health. A solution could be that ´peripheral centers`, rather 'satellite centers', will start again with more rigid screening for those patients considered at high risk. As a consequence, facilities for clinical electrophysiology should be offered to these centers, which however, is impossible for budgetary reasons at present.

References

1. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
2. Moss A, Hall W, Cannom D, Daubert J, Higgins S, Klein H, et al. Improved survival with an implanted defibrillator in patients coronary artery disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
3. Kenknight B, Jones B, Thomas A, Lang D. Technological advances in implantable cardioverters-defibrillators before the year 2000 and beyond. Am J Cardiol 1996;78(suppl 5A):108-115.
4. Grimm W, Flores B, Marchlinski F. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1992;15:1667-1673.
5. Elliott L, Gilkerson J. Advances in dual-chamber implantable cardioverter/defibrillators. J Interven Cardiol 1998;11:187-196.
6. Swerdlow C, Schšls W, Dijkman B, Jung W, Sheth N, Olson W, et al. Detection of atrial fibrillation and flutter by a dual-chamber implantable cardioverter-defibrillator. Circulation 2000;101:878-885.
7. Saksena S, Madan N, Lewis C. Implanted cardioverter-defibrillators are preferable to drugs as primary therapy in sustained ventricular tachyarrhythmias. Prog Cardiovasc Dis 1996;38:445-454.
8. Böcker D, Bänsch D, Heinecke A, Weber M, Brunn J, Hammel D, et al. Potential benefit from implantable cardioverter-defibrillator therapy in patients with and without heart failure. Circulation 1998;98:1636-1643.
9. Jordaens L. The classification of sudden death in clinical trials. In: Aliot E CJ, Prystowsky EN, editors. Fighting sudden cardiac death: a worldwide challenge. Armonk: Futura; 2000. p. 29-39.
10. Greene M, Newman D, Geist M, Paquette M, Heng P, Dorian P. Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias. Europace 2000;2:263-269.
11. EN540, European standard. Clinical Investigation of Medical Devices for Human Subjects. Brussels, Belgium: European Committee for Standardization; 1993.
12. ISO 14155, International Standard for Clinical Investigation of Medical Devices. Geneva, Switzerland: International Organization for Standardization; 1996.

13. Kuck K, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748-754.
14. Buxton A, Lee K, Fisher J, Josephson M, Prystowsky E, Hafley G, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-1890.
15. Rosenqvist M, Beyer T, Block M, den Dulk K, Minten J, Lindemans F. Adverse events with transvenous implantable cardioverter-defibrillators: A prospective multicenter study. Circulation 1998;98:663-670.
16. Parsonnet V, Roelke M. The cephalic vein cutdown versus subclavian puncture for pacemaker/ICD lead implantation. Pacing Clin Electrophysiol 1999;22:695-697.
17. Grimm W, Menz V, Hoffmann J, Timmann U, Funck R, Moosdorf R, et al. Complications of third-generation implantable cardioverter therapy. Pacing Clin Electrophysiol 1998;22:206-211.
18. Callans D, Hook B, Kleiman R, Mitra R, Flores B, Marchlinski F. Unique sensing errors in third-generation implantable cardioverter-defibrillators. J Am Coll Cardiol 1993;22:1135-1140.
19. Ector H, Rickards AF, Kappenberger L, Vardas P, Oto A, Santini M, et al. The registry of the European working group on cardiac pacing (abstract). Europace 2000;1(suppl. D):194.
20. Guidance on the use of implantable cardioverter defibrillators for arrhythmias. London, United Kingdom: National Institute for Clinical Excellence; 2000.

Chapter 2

Defibrillation Efficacy Testing – Long-term Follow-up and Mortality

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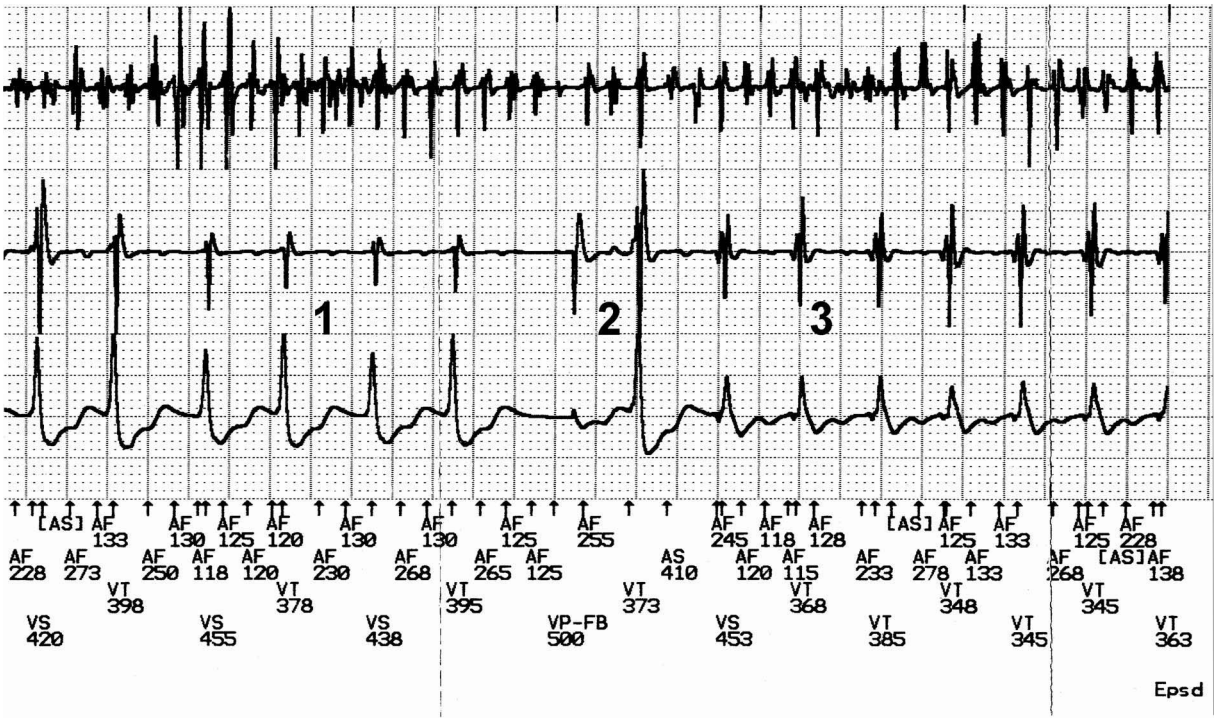
Accepted for publication.



Abstract

Aims: *Defibrillation threshold testing is no longer routinely performed as devices became more effective. We assessed the lowest effective defibrillation (LED) level at implantation and before hospital discharge and related this with outcome.*

Methods and results: *146 consecutive patients with biphasic shock, active can devices were studied. Both intraoperative and predischarge tests were completed in 127 patients, of whom 67 had ≥ 3 VF inductions at implant. Improvement was defined when LED decreased with ≥ 3 J. The LED was significantly higher at implantation compared to predischarge (P < 0.001). Improvement was seen in 73/127 patients (58%). In the group with ≥ 3 VF inductions, an implantation LED > 9 J was related with a lower LVEF (P < 0.01); 34 patients (51%) had improvement in LED. During follow-up, 18 patients died, 4 received heart transplantation. No different outcome was observed in patients with and without improvement. However for those with ≥ 3 VF inductions, an independent predictor of mortality was implantation LED > 9 J without improvement at the second test.*

Conclusion: *Repeated defibrillation efficacy testing before hospital discharge may confirm that a relatively high defibrillation energy is required. This is related to a higher mortality in long-term follow-up.*

Introduction

The implantable cardioverter-defibrillator (ICD) became widely accepted for the treatment of patients with severe life threatening ventricular tachyarrhythmias(1-3). The functions of the ICD and the shock lead integrity are usually tested after implantation or prior to hospital discharge(4). Device related problems leading to ICD malfunction have become less common due to advances in ICD technology. Improvements in lead technology have reduced the risk of lead malfunction(5,6). The introduction of biphasic shock waveforms and active can devices improved the defibrillation efficacy(7-10). These enhancements have led to a general feeling that defibrillation threshold or efficacy testing is no longer important. In order to determine the necessity of predischarge testing, the results of ICD testing at implant and predischarge were studied and related to patient outcome.

Methods

Patients

The study population consisted of 127 patients who received an ICD in combination with an endocardial lead system. Baseline clinical characteristics, including age, gender, left ventricular ejection fraction (LVEF), the presence of coronary artery disease (CAD), cardiomyopathy, cardiothoracic (CT) ratio, presenting arrhythmia, and pharmacologic treatment were documented. The patient characteristics are shown in Table 1.

ICD implantation

The implantation procedure was performed in the electrophysiology laboratory under local anesthesia. The biphasic shock, active can ICD pulse generator and the transvenous lead system were inserted through a single left pectoral incision. A left cephalic vein cutdown and/or a left subclavian puncture were used for lead insertion. The atrial lead was located at the right atrial appendage or lateral free wall by active fixation. The right ventricular lead was placed in the right ventricular apex by active fixation. The right ventricular lead had either one defibrillation coil or two defibrillation coils. For biventricular devices, the left ventricular lead was placed in a tributary of the coronary sinus. The ICD pulse generators and defibrillation leads are summarised in Table 2.

Table 1. *Baseline clinical and demographic data*

Characteristic	
Number of cases	127 (100%)
Gender (Male)	105 (83%)
Age (years)	59 ± 14
LVEF	0.35 ± 0.15
Underlying disease	
Coronary artery disease	92 (72%)
Dilated cardiomyopathy	21 (17%)
Hyperthrophic cardiomyopathy	4 (3%)
NYHA functional class	
I – II	94 (72%)
III – IV	36 (28%)
Cardiothoracic ratio	0.54 ± 0.06
Index arrhythmia	
VF	46 (36%)
SMVT	70 (55%)
NSVT	11 (9%)
Medications	
Amiodarone	46 (36%)
Beta-blocker	49 (39%)
Digoxin	26 (20%)
ACE inhibitor	88 (70%)
Diuretics	70 (56%)

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SMVT = sustained monomorphic ventricular tachycardia; VF = ventricular fibrillation

Defibrillation efficacy testing

During the implantation procedure, defibrillation efficacy was tested with the use of a step-down defibrillation protocol. The initial delivered shock energy for testing was 15 J. If successful, the energy was decreased with steps of 3 J on successive trials until defibrillation failed. In case of failure of the initial 15-J shock, the energy was increased in 3-J steps on subsequent trials until defibrillation was successful. Testing was performed under short-lasting deep sedation by the administration of diazepam combined with etomidate. The lowest energy, successful to convert ventricular fibrillation to sinus rhythm, was defined as the lowest effective defibrillation (LED). For acceptance of the configuration, the LED had to be equal or less than the maximum defibrillation energy of the device minus a safety margin of 10 J. Ventricular fibrillation was induced via the test program of the ICD by a 50-Hz burst or a T wave shock(11). Ventricular fibrillation was defined as a fast polymorphic ventricular rhythm with a cycle length < 250 ms that resulted in no phasic blood pressure. In case of non-successful defibrillation, an internal rescue shock with the

maximum energy of the device or an external maximal shock from a precharged defibrillator with the use of epicutaneous self-adhesive patches was delivered. In patients with severe LV dysfunction, the procedure was shortened to demonstrate that 2 consecutive shocks with a safety margin of 10 J were successful.

An improvement in LED was defined as a decrease in defibrillation energy of $\geq$ 3 J at the predischarge test.

Table 2. *Implanted ICD systems*

ICD system	Number
Biotronik	(44)
DC – ICD	44
Single coil defibrillation lead	44
Guidant/CPI	(34)
SC – ICD	27
BV – ICD	7
Single coil defibrillation lead	1
Dual coil defibrillation lead	33
ELA Medical	(8)
DC – ICD	8
Single coil defibrillation lead	8
Medtronic	(60)
SC – ICD	16
DC – ICD	28
BV – ICD	16
Single coil defibrillation lead	45
Dual coil defibrillation lead	15

BV – ICD = biventricular implantable cardioverter defibrillator;
DC – ICD = dual chamber implantable cardioverter defibrillator;
SC – ICD = single chamber implantable cardioverter defibrillator.

Numbers between brackets indicate the total number for a specific brand

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Chi-square testing was used for analysis of categorical variables, and Student's *t* test was used for analysis of continuous variables. Kaplan-Meier actuarial method was used to calculate the survival rate over time. Survival analysis was initiated at the time of ICD implantation. Differences between pairs of survival curves were tested by log-rank test. Cox proportional hazards model was used to identify independent predictors of mortality. Patients who received cardiac transplantation were censored at the time of cardiac transplantation. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Of the 146 consecutive patients, 19 were excluded from analysis as they were not tested at both occasions. The study population consisted of 127 patients. The clinical characteristics of these patients are summarised in Table 1. The mean age of the patients was 59 ± 14 years (range: 20-82 years). The mean LVEF was 0.35 ± 0.15 (range: 10-76%). Cardiomyopathy was present in 25 (20%) patients, 21 (17%) patients had dilated cardiomyopathy and 4 (3%) had hyperthrophic cardiomyopathy. Indications for ICD therapy were as follows: NSVT with subsequent inducible sustained ventricular tachyarrhythmias in 11 (9%) patients, spontaneous sustained VT in 70 (55%), and VF in 46 (36%).

Survival

During a mean follow-up of 38 ± 14 months, 18 patients died (17 men, mean age 60 ± 16 years). The mortality rates were 4.7%, 9.6%, and 25.1%, at 1, 2, and 5 years respectively. Deaths were considered to be sudden cardiac in 4 (22%) and non-sudden cardiac in 10 (55%). In 1 case, death was attributed to non-cardiac cause. Three cases (17%) were un-witnessed deaths. There were no deaths related to ICD implantation. Four (3%) patients underwent cardiac transplantation. The mean interval of cardiac transplantation after ICD implantation was 21 months.

Defibrillation data at implantation

A total number of 93 patients (73%) had an LED ≤ 15 J at this test. The proportion of patients with LED ≤ 12 J, ≤ 9 J, and ≤ 6 J was 53%, 38%, and 14%, respectively.

Defibrillation data prior to hospital discharge

A total number of 108 patients (85%) had an LED ≤ 15 J at this test. This test was performed after a median of 1 day after implantation. The proportion of patients with LED ≤ 12 J, ≤ 9 J, and ≤ 6 J was 75%, 62%, and 34%, respectively. Overall, the LED at implantation was significantly higher compared to the LED at predischarge testing (12.9 ± 4.9 J versus 10.4 ± 5.0 J; P < 0.001). A total number of 73 patients (57%) had an improvement of ≥ 3 J.

Variables in relation to LED

There was no significant difference in LED between patients with a single coil defibrillation lead (n=88) and patients with a dual coil defibrillation lead (n=39) at implantation (12.7 ± 4.8 J vs 13.3 ± 4.9 J) and at predischarge testing (10.2 ± 5.0 J vs 10.7 ± 5.0 J). The shock impedance for all patients significantly decreased from 56 ± 12 Ω at implantation to 51 ± 10 Ω at predischarge (P < 0.001). At predischarge, the shock impedance significantly decreased in patients with a single coil defibrillation lead as well as in patients with a dual coil defibrillation lead.

Subanalysis of patients with at least 3 VF inductions at implantation

For this group (n=67), the average LED was 11.8 ± 5.7 J. In Table 3, the clinical characteristics are summarised for 2 subgroups, dichotomized at an LED value 9 J. There were no significant differences between the two patient groups with regard to clinical data as age, amiodarone use, coronary artery disease, and CT ratio. Only the LVEF was significantly different (P < 0.01). An improvement of ≥ 3 J was observed in 34 patients (50.7%). In the 30 patients with implantation LED > 9 J, the LED improved from 16.9 ± 4.4 J to 13.9 ± 5.1 J at predischarge (P < 0.001). In the 37 patients with implantation LED ≤ 9 J, it remained unchanged.

Factors related to mortality

This is presented in table 4. In the group tested at 2 occasions, mortality was similar in patients with and without improvement in LED. In the group with 3 VF inductions at baseline, the difference for those without improvement was borderline significant. Subgroup analysis for those with an implantation LED > 9 J, revealed a significantly higher mortality when no improvement was observed at the second test (P = 0.02) (Figure 1). Cox proportional hazard analysis in the total group of 67 patients revealed a baseline LED > 9 J and no improvement at the second test as independent predictors of mortality (P < 0.03). The presence of coronary artery disease, cardiomyopathy, and LVEF were not identified as predictors of mortality.

Table 3. *Patients with 3 VF inductions at implantation*

Patient characteristics	**LED ≤ 9 J**	**LED > 9 J**	**p value**
Gender (M/F)	34/3	24/6	NS
Age (years)	60,5 ± 13,6	60,0 ± 14,4	NS
LVEF (%)	37,4 ± 14,0	26,8 ± 12,7	< 0,01
Underlying cardiac disease (n)			
CAD	26	22	NS
CMP	8	8	NS
CT ratio	0,54 ± 0,06	0,55 ± 0,05	NS
Antiarrhythmic drug therapy (n)			
Amiodarone	13	12	NS
β-blockers	7	8	NS
Sotalol	6	3	NS
None	11	7	NS
Shock impedance (Ω)	59 ± 12	52 ± 12	< 0,05
Mortality (n)	4/37	5/30	NS

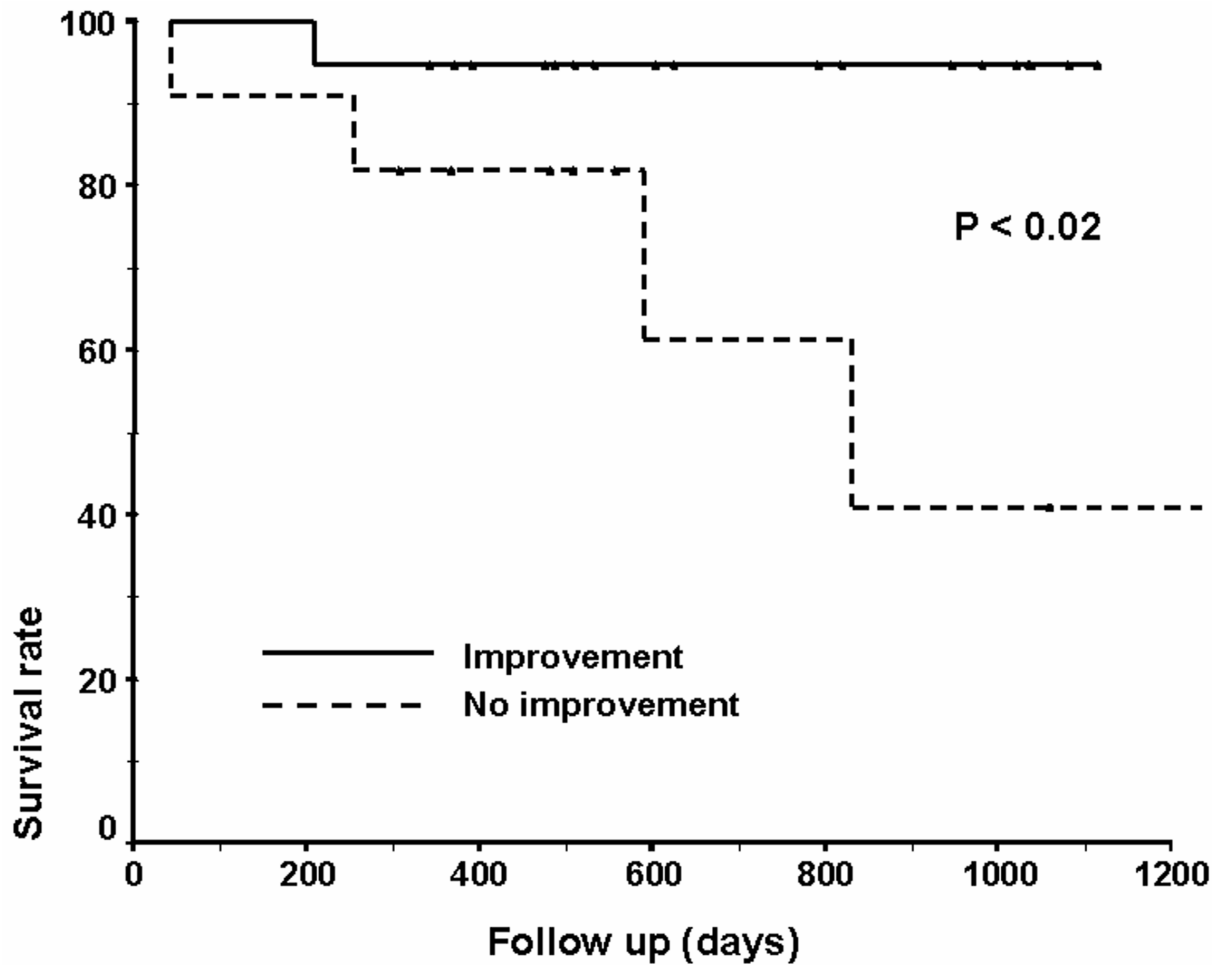
CAD = coronary artery disease; CMP = cardiomyopathy; CT = cardiothoracic; F = female; LED = lowest effective defibrillation; LVEF = left ventricular ejection fraction; M = male; NS = not significant

Table 4. *Mortality*

		Subgroup of patients		
		Improvement	No improvement	
	Total mortality	**Mortality**	**Mortality**	**p value**
Total group	18/127	8/73	10/54	NS
3 VF inductions	9/67	2/34	7/33	P = 0.07
LED ≤ 9J	4/37	1/15	3/22	NS
LED > 9J	5/30	1/19	4/11	P = 0.02

LED = lowest effective defibrillation; NA = not applicable; NS = not significant

Figure 1. *Kaplan-Meier curves for total mortality in patients (n=30) with 3 VF inductions at implantation, and a baseline defibrillation threshold > 9 J. Improvement in defibrillation efficacy at the second test versus no improvement.*



Discussion

This study has both technical and clinical implications. The major findings are that patients without improvement of defibrillation efficacy at the second test tended to have a higher mortality, especially if implantation LED was > 9 J. From a technical point of view repeated testing of defibrillation efficacy is no longer necessary in the majority of patients. However, the finding that a relatively high energy level to convert VF is required, suggests that such a patient has a worse prognosis if this is confirmed during repeated testing.

Technical aspects of defibrillation efficacy testing

Finding a low effective energy level for conversion of VF to sinus rhythm means that the probability that a patient will be safely converted during future events is high(12,13). The primary function of defibrillation threshold testing is to confirm that the safety margin for defibrillation is adequate. A difference of ≥ 10 J between the maximum output of a device and the lowest effective energy level has been accepted as an adequate safety margin(14). However, these early studies were conducted in devices with an epicardial lead system and monophasic waveforms. The idea that such finding is predictive for successful therapy was also confirmed with transvenous devices(13). The development of active pectoral pulse generators, transvenous lead systems, and biphasic waveforms resulted in lower and more stable defibrillation thresholds. On the other hand, an absolute safety margin of 10 J does not provide a 100% probability of successful defibrillation(15). The results of the Low-Energy-Endotak-Trail (LEET) demonstrated that a relative safety margin is just as safe and effective as an absolute safety margin(16). The rate of successful defibrillation at twice the energy level of the DFT was 99.5%. During follow-up, this study demonstrated no significant difference in conversion rate between twice the DFT and maximum output as first-shock energy. These results were recently confirmed in the Low Energy Safety Study(17). A safety margin of 5 J was found to be adequate and safe with a dual-coil lead and active can device. However, to determine a much more accurate value, a step-up/down protocol with multiple induced VF episodes must be used(17).

Clinical aspects of defibrillation efficacy

Clinical long-term follow-up data have reported potential adverse consequences of an elevated defibrillation threshold(18,19). A higher sudden cardiac death rate was reported in the presence of a low safety margin(18,19). Arrhythmic death, accounting for 42% of total mortality in the ICD group, could be attributed to failing conversion in patients with a high DFT(20). Several studies were designed to identify characteristics that may predict the finding of an elevated defibrillation threshold. Amiodarone therapy, body surface area, and left ventricular dilation were the predictors of high thresholds for nonthoracotomy defibrillation with monophasic as well as biphasic waveforms(21-23). In a recent study, clinical parameters were of limited use for predicting DFTs in a dual coil active can system(24). None of the recent studies showed a correlation between LVEF and DFTs. In our study, the LVEF was significantly lower in patients with a LED > 9 J.

Changes in defibrillation efficacy

Long-term stability of the defibrillation efficacy is important, especially among patients with a high DFT and a low safety margin. Changes in DFT are influenced by several factors, such as the lead system and the defibrillation waveform. A long-term increase in DFT was observed with the use of monophasic defibrillation waveforms in combination with a transvenous lead system(25). This was also detected in a biphasic series with lead-only and subcutaneous patch configurations(26). In contrast to these data, biphasic active can devices combined with a transvenous lead system prevented such rise(27). Recently, a significant decrease of DFTs over time with a dual-coil, active pectoral lead system was reported(28). In our study, the LED was significantly lower at the second test. The LED at implantation can not have been influenced by a long lasting anesthesia, as was usual in the era of thoracotomy. However, the implantation values can have been influenced by surgical variables, such as stress and the presence of a loose pocket. The finding that the impedance changed between both tests is another argument to believe that the predischarge test is a more “reliable” measurement.

With the advances in technology, defibrillation thresholds are lower and remain stable. The risk to find an increased defibrillation threshold becomes lower than in previous times, and good safety margins are usually obtained in almost all patients. Even if the safety margin is low, consecutive shocks usually convert the arrhythmia to

a normal rhythm, and patients are saved from instantaneous arrhythmic death. The fact that our patients with marginal findings had similar mortality as the others confirms the idea, that we are faced with the problem of heart failure rather than with an arrhythmic problem. The role of a second defibrillation threshold test after implantation can than be questioned. Our study shows that despite the current generation of biphasic shock, active can pectoral ICDs, a subset of patients requires a second defibrillation test. With this second test, patients with a worse prognosis can be identified.

Study limitations

This study was not designed as a prospective trial. However, the data used were based on a continuously updated and a prospective complete database. We did not assess the LED at longer intervals after implantation, but limited the study to predischarge testing. The data must be interpreted with caution, as the number of patients with at least 3 VF inductions is small.

Conclusion

From a technical point of view, defibrillation efficacy testing at predischarge is no longer necessary in experienced hands, in conventional situations(29,30). With the advances in technology, defibrillation thresholds are low and stable. A predischarge test is probably more correct for patients who required relatively high defibrillation energy to convert the arrhythmia to normal sinus rhythm. The confirmation that relatively high defibrillation energy is required during repeated testing suggests that mortality is higher during follow-up for these patients.

References

1. Echt DS, Armstrong K, Schmidt P, Oyer PE, Stinson EB, Winkle RA. Clinical experience, complications, and survival in 70 patients with the automatic implantable cardioverter/defibrillator. Circulation 1985;71:289-296.
2. Moss AJ, Hall WJ, 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. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
3. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
4. Winkle RA, Bach SM, Mead RH, Gaudiani VA, Stinson EB, Fain ES, et al. Comparison of defibrillation efficacy in humans using a new catheter and superior vena cava spring-left ventricular patch electrodes. J Am Coll Cardiol 1988;11:365-370.
5. Brady PA, Friedman PA, Trusty JM, Grice S, Hammill SC, Stanton MS. High failure rate for an epicardial implantable cardioverter- defibrillator lead: implications for long-term follow-up of patients with an implantable cardioverter-defibrillator. J Am Coll Cardiol 1998;31:616-622.
6. Mattke S, Muller D, Markewitz A, Kaulbach H, Schmockel M, Dorwarth U, et al. Failures of epicardial and transvenous leads for implantable cardioverter defibrillators. Am Heart J 1995;130:1040-1044.
7. Bardy GH, Ivey TD, Allen MD. A prospective randomized evaluation of biphasic versus monophasic waveform pulses on defibrillation efficacy in humans. J Am Coll Cardiol 1989;14:728-733.
8. Block M, Hammel D, Bocker D, Borggrefe M, Budde T, Isbruch F, et al. A prospective randomized cross-over comparison of mono- and biphasic defibrillation using nonthoracotomy lead configurations in humans. J Cardiovasc Electrophysiol 1994;5:581-590.
9. Haffajee C, Martin D, Bhandari A, Bardy GH, Desouza C, Kuehlkamp V, et al. A multicenter, randomized trial comparing an active can implantable defibrillator with a passive can system. Pacing Clin Electrophysiol 1997;20:215-219.
10. Sticherling C, Klingenheben T, Cameron D, Hohnloser SH. Worldwide clinical experience with a down-sized active can implantable cardioverter defibrillator in 162 consecutive patients. Worldwide 7221 ICD Investigators. Pacing Clin Electrophysiol 1998;21:1778-1783.

11. Jordaens L, Vertongen P, Provenier F, Trouerbach JW, Poelaert J, Herregods L. A new transvenous internal cardioverter-defibrillator: implantation technique, complications, and short-term follow-up. Am Heart J 1995;129:251-258.
12. Rattes MF, Jones DL, Sharma AD, Klein GJ. Defibrillation threshold: A simple and quantitative estimate of the ability to defibrillate. Pacing Clin Electrophysiol 1987;10:70-77.
13. Lindemans FW, van Berlo AMW, Bourgeois IM. Summary of PCD clinical study results. in Kappenberger LJ, Lindemans FW (eds): Practical aspects of staged therapy defibrillators. Mount Kisco, Futura, 1992:103-111.
14. Marchlinski FE, Flores B, Miller JM, Gottlieb CD, Hargrove WC. Relation of the intraoperative defibrillation threshold to successful postoperative defibrillation with an automatic implantable cardioverter defibrillator. Am J Cardiol 1988;62:393-398.
15. Strickberger SA, Daoud EG, Davidson T, Weiss R, Bogun F, Knight BP, et al. Probability of successful defibrillation at multiples of the defibrillation energy requirements in patients with an implantable defibrillator. Circulation 1997;96:1217-1223.
16. Neuzner J, Liebrich A, Jung J, Himmrich E, Pitschner HF, Winter J, et al. Safety and efficacy of implantable defibrillator therapy with programmed shock energy at twice the augmented step-down defibrillation threshold: results of the prospective, randomized, multicenter low-energy Endotak trial. Am J Cardiol 1999;83:34D-39D.
17. Gold MR, Higgins S, Klein R, Gilliam FR, Kopelman H, Hessen S, et al. Efficacy and temporal stability of reduced safety margins for ventricular defibrillation: primary results from the Low Energy Safety Study (LESS). Circulation 2002;105:2043-2048.
18. Lehmann MH, Thomas A, Jackson K, Steinman RT, Shah M, Schuger C, et al. Long-term outcome with implantable cardioverter defibrillator (ICD) therapy in a multicenter investigator-edited database. (abstract). Circulation 1990;80(Suppl III):III-166.
19. Pinski SL, Vanerio G, Castle LW, Morant VA, Simmons TW, Trohman RG, et al. Patients with a high defibrillation threshold: Clinical characteristics, management, and outcome. Am Heart J 1991;122:89-95.
20. Epstein AE, Ellenbogen KA, Kirk KA, Kay GN, Dailey SM, Plumb VJ. Clinical characteristics and outcome of patients with high defibrillation thresholds. A multicenter study. Circulation 1992;86:1206-1216.
21. Brooks R, Garan H, Torchiana D, Vlahakes GJ, Jackson G, Newell J, et al. Determinants of successful nonthoracotomy cardioverter-defibrillator implantation: experience in 101 patients using two different lead systems. J Am Coll Cardiol 1993;22:1835-1842.

22. Schwartzman D, Concato J, Ren JF, Callans DJ, Gottlieb CD, Preminger MW, et al. Factors associated with successful implantation of nonthoracotomy defibrillation lead systems. Am Heart J 1996;131:1127-1136.
23. Khalighi K, Daly B, Leino V, Shorofsky SR, Kavesh NG, Peters RW, et al. Clinical predictors of transvenous defibrillation energy requirements. Am J Cardiol 1997;79:150-153.
24. Hodgson DM, Olsovsky MR, Shorofsky SR, Gold MR. Clinical predictors of defibrillation thresholds with an active pectoral pulse generator lead system. Pacing Clin Electrophysiol 2002;25:408-413.
25. Kirk MM, Shorofsky SR, Khalighi K. Chronic rise in monophasic defibrillation thresholds with a transvenous lead system. Am J Cardiol 1997;79:502-505.
26. Martin DT, John R, Venditti, FJ. Increase in defibrillation threshold in non-thoracotomy implantable defibrillators using a biphasic waveform. Am J Cardiol 1995;76:263-266.
27. Gold MR, Kavesh NG, Peters RW. Biphasic waveforms prevent the late rise of defibrillation thresholds with a transvenous lead system. J Am Coll Cardiol 1997;30:233-236.
28. Rashba EJ, Olsovsky MR, Shorofsky SR, Kirk MM, Peters RW, Gold MR. Temporal decline in defibrillation thresholds with an active pectoral lead system. J Am Coll Cardiol 2001;38:1150-1155.
29. Strickberger SA, Klein, GJ. Is defibrillation testing required for defibrillator implantation. J Am Coll Cardiol 2004;44:88-91.
30. Swerdlow CD. Reappraisal of implant testing of implantable cardioverter defibrillators. J Am Coll Cardiol 2004;44:92-94.

Chapter 3

Feasibility of Home Monitoring in ICD Therapy

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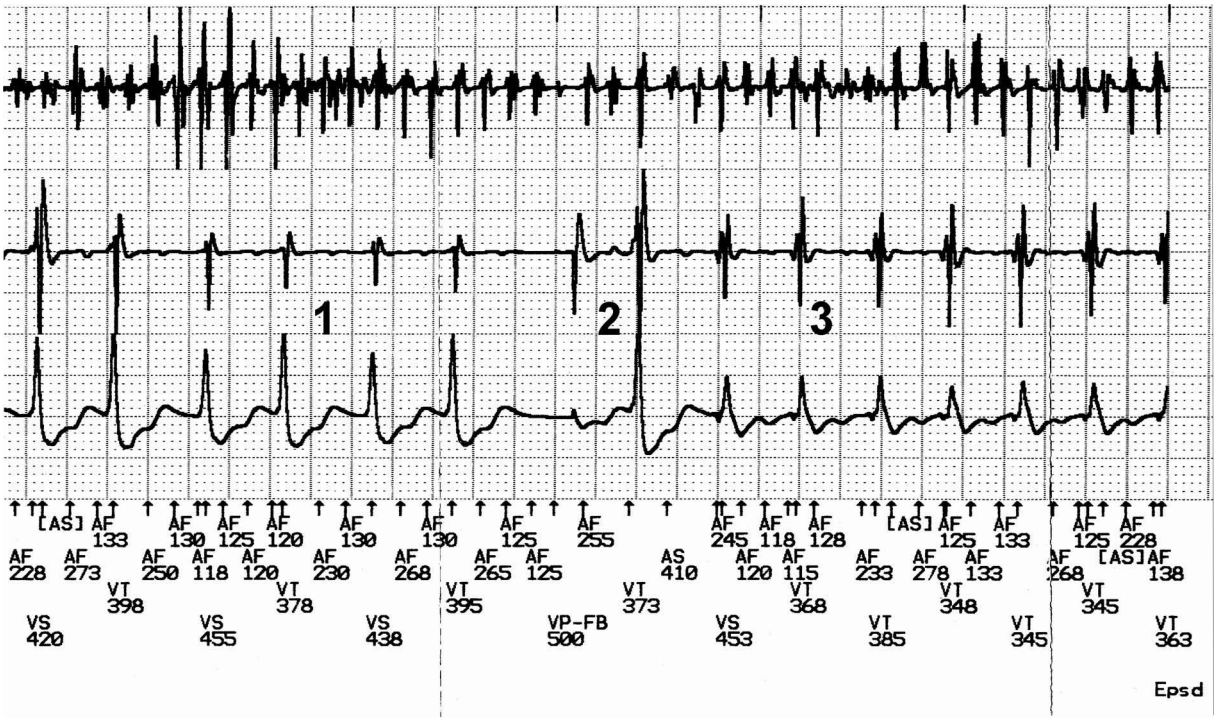
Published: Europace 2003;5:139-142.



Abstract

The expanding indications for ICD therapy and the complexity of current devices will have impact on follow-up policy. The application of ICD therapy requires an elaborate attention to on technical aspects, arrhythmias, and the clinical course of the underlying disease. Currently, the quality of medical supervision is dependent on scheduled regular follow-up visits. A disadvantage of long intervals can be a delay in the physician's or patient's awareness of changes in the clinical status. Some patients will need more intensive follow-up while others will have the device as an innocent bystander and only need technical follow-up. A possibility to address this situation, is the transmission of data, already stored in the implanted device. This will guarantee a continuous patient surveillance and could possibly help to avoid unnecessary control visits.

Introduction

The implantable cardioverter defibrillator (ICD) is an effective therapy as shown in prospective, randomized trials for primary and secondary prevention of cardiac death(1-4). The workload involved in ICD implantation and follow-up is increasing, due to expanding indications and socioeconomic factors. Furthermore, improvement in ICD technology is rapidly advancing. Recent developments are the management of supraventricular tachyarrhythmias and devices incorporating cardiac resynchronization therapy(5, 6). Despite this technical progress, modern ICD application continues to require careful and more elaborate attention with respect to the many variables of the arrhythmias and the clinical course of the underlying disease.

Normal follow-up after ICD implantation

Regular technical follow-up visits, usually scheduled at 3-monthly intervals were initially intended for capacitor reformation. The feature of automatic capacitor reformation allowed to concentrate on other items which included battery status, shock impedance, therapy history, bradycardia pacing parameters, and stored electrograms(7, 8). With these technical improvements it becomes theoretically possible to increase the follow-up interval.

A disadvantage of long intervals can be a delay in the physician's or patient's awareness of changes in the clinical status. As a result, prevention of disease progression and the inherent optimization of therapy can face a setback, e.g. in patients who are at high-risk for developing congestive heart failure. Some guidelines on ICD therapy recognized this potential problem while others did not address the necessity for frequent follow-up(9, 10).

In spite of this rigid follow-up scheme, unscheduled visits will occur, e.g. after ICD discharges. Some patients will indeed need very intensive follow-up with reprogramming, adaptation of drug therapy (for heart failure, ischemic events or arrhythmias), psychological and social support while others will have the device as an innocent bystander and need only minimal technical and clinical check-up. Another major concern is that a large subset of interventions may be inappropriate, especially in the primary prevention setting(4). Therefore, the workload for an electrophysiology department will increase over the next decade.

A possibility to address this situation, is the transmission of data which is already stored in the implanted device. This will allow an almost continuous patient surveillance.

History of Remote or Home Monitoring

In the early 1970's, the concept of TransTelephonic Monitoring (TTM) was introduced to monitor the longevity of pacemakers(11). In the late 1970's and 1980's, the usefulness of TTM as a diagnostic tool has expanded to other problems including sensing, capture, lead defects, and arrhythmias(12, 13). The clinical utility of TTM was confirmed in the 1990's(14). Transtelephonic interrogation of pacemakers is common in the USA but has never gained acceptance in Europe. Transtelephonic monitoring is dependent on the active coorperation of the patient, as the patient has to place a special device over his/her pacemaker. This arrangement cannot be expected to work properly for the majority of patients. A new concept of monitoring which relies to a minor extent on the patients cooperation has now been implemented in pacemaker therapy. The results are beneficial with respect to supraventricular arrhythmia detection and monitoring of AV conduction(15). The reported transmission success of messages was high, approximately 92%. The patient satisfaction with the convenience, handling, and reliability of the home monitoring system ranged from 93 to 97% in SF-36 surveys(16). The cost effectiveness of home monitoring was calculated and home monitoring in pacemaker patients could result in a significant reduction of 20% in Medicare costs(17).

Home Monitoring System

A device which is suitable for remote monitoring has the ability to transmit a periodic message and in some devices also patient-activated messages. Such transmission can be done in several ways, transtelephonic or other networks (e.g. via satellite). In a recent commercially avialable model, the data are received by a patient device, which transmits an encrypted message to a "Home Monitoring Service Center". There, the message is decrypted and forwarded via fax to the attending physician. This message is called "Cardio Report" which contains diagnostic information.

The first available system for ICD's is a single-chamber rate adaptive ICD, Belos VR-T (Biotronik, Berlin, Germany), in combination with a patient device RUC 1000-A (Biotronik, Berlin, Germany). The patient device is a dedicated GSM-telephone,

which transfers the message to the service-center, when GSM-network service is available in the living area of the patient.

***Table 1**. Possibilities of diagnostic and therapeutic information with home monitoring with actual arrhythmia devices*

Clinical Information	*General* – Electrogram in actual rhythm – Heart rate – Heart rate variability *Pacing related* – Percentage atrial pacing – Percentage AV synchrony – Percentage ventricular pacing – Number of mode switches *Tachyarrhythmia related* – Number of AT episodes – Number of AF episodes – Number of VT episodes – Number of VF episodes – Number of nonsustained episodes – Number of delivered ICD therapies – Number of aborted ICD therapies – Electrogram of arrhythmia *Sensor related* – Motion – Respiration – Pressure
Technical Information	Battery status and voltage Shock impedance P- and R-wave amplitudes Autocapture thresholds Impedance of pace / sense leads

Applications of home monitoring in ICD therapy

Follow-up or guidance of therapy at a distance from the patient has been realised for several diagnostic and therapeutic procedures. When applied to ICD therapy, supervion of both clinical and technical aspects becomes possible. Table 1 gives an indication of what might be possible on short term. Some of these features are already possible with currently available ICD's, some as remote reprogramming are still to be implemented (Table 2).

Table 2.

Possibility of Bidirectional Transmission
- device interrogation
- device (re)programmation

Clinical aspects

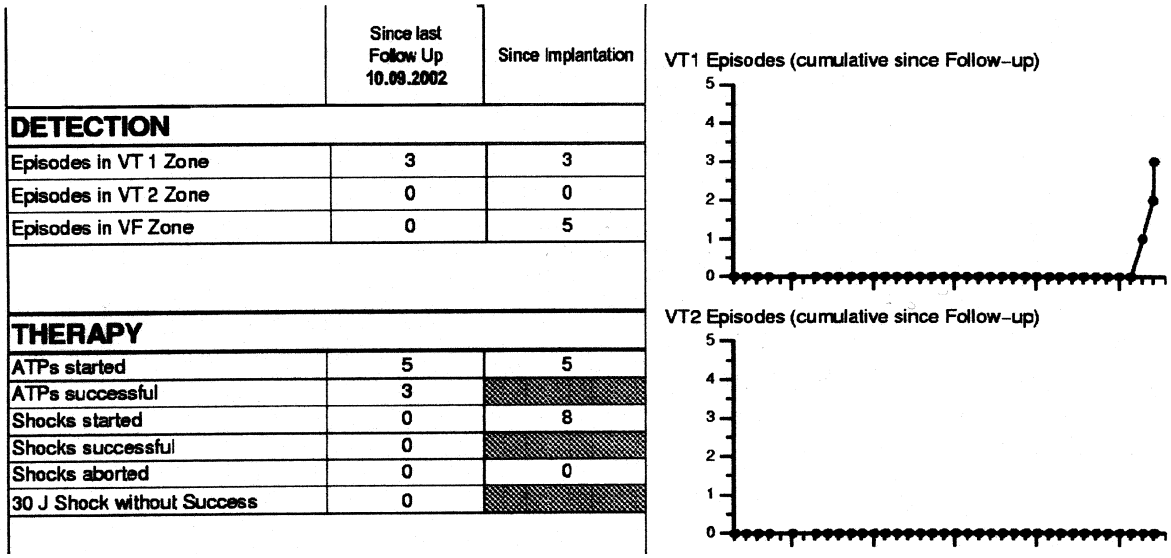
Tachyarrhythmias

Diagnostic data such as the numbers of aborted and delivered ICD therapies are an indicator of the total incidence of tachyarrhythmias (Figure 1). Frequently recurring episodes of ventricular tachyarrhythmias in patients may indicate increasing instability and progression of cardiac disease(18, 19). Treatment of the underlying cardiac disease can be optimized by device reprogrammation and/or additional antiarrhythmic drug therapy.

Congestive heart failure

An indication of progression of congestive heart failure can be reflected by physiologic parameters as heart rate (e.g. averaged over several days) or in the incidence of arrhythmias. Mild heart failure can deteriorate into severe heart failure by means of ischemia, or by atrial or ventricular arrhythmias. The arrhythmias may lead to ischemia and remodeling(20). Arrhythmias may also drive the progression of heart failure, particularly atrial fibrillation(21). Atrial fibrillation has been associated with a higher incidence of recurrent ventricular arrhythmias(22).

Figure 1. *Data from the Cardio Report showing the tables and graphs for detection of VT and delivered VT therapies. Cardio Report (Biotronik, Berlin, Germany).*
ATP = antitachycardia pacing; VF = ventricular fibrillation; VT = ventricular tachycardia



	Since last Follow Up 10.09.2002	Since Implantation
DETECTION		
Episodes in VT 1 Zone	3	3
Episodes in VT 2 Zone	0	0
Episodes in VF Zone	0	5
THERAPY		
ATPs started	5	5
ATPs successful	3	
Shocks started	0	8
Shocks successful	0	
Shocks aborted	0	0
30 J Shock without Success	0	

Inappropriate therapy

Aborted or delivered ICD therapies can either be appropriate or inappropriate. Inappropriate therapy due to supraventricular tachyarrhythmias is a well-known problem in ICD therapy(23-26). Frequent ICD therapies, appropriate and inappropriate, result, in addition to patient's inconvenience, in earlier battery depletion and decrease device longevity. Further, ICD therapy has a proarrhythmic potential(27).

Technical aspects: lead and generator

Failure of the ICD can be catastrophic because the device must be lifesaving. Technical failures which are lead- or generator-related are not rare(28). Technical monitoring of an elementary (shock only) device at intervals of 3 months in the office was usually sufficient for routine follow-up. However, the increasing complexity of devices with additional technical features (e.g. capture of a left ventricular pacing lead in the coronary sinus) warrants other ways of monitoring. If this can be done continuously out off the office, failures of the implanted system will be immediately detected.

Impact and cost-effectiveness of home monitoring

A multicenter trial in Europe and the USA is designed to investigate the diagnostic potential of transmitted data with regard to the necessity for patient follow-up. The primary goal is to individualize patient follow-up with home monitoring. The secondary goals are therapy optimization, acceptance of the home monitoring service, and a change of the cost-effectiveness ratio.

Future perspectives

A next step has to be taken when it will become evident that such transmission is reliable and safe. The potential to correct or improve programming is there. More complicated devices with additional sensors (e.g. thorax impedance, ventricular wall pressure) will allow more sophisticated physiological information to be measured, stored, and transmitted, to improve patient care.

References

1. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
2. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
3. Buxton A, Lee K, Fisher J, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-1890.
4. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
5. Schoels W, Swerdlow CD, Jung W, Stein KM, Seidl K, Haffajee CJ. Worldwide clinical experience with a new dual-chamber implantable cardioverter defibrillator system. J Cardiovasc Electrophysiol 2001;12:521-528.
6. Kuhlkamp V. Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. J Am Coll Cardiol 2002;39:790-797.
7. Jordaens L, Olsson O, Van de Bruaene F, Fiers T. Implantable cardioverter defibrillator: data storage and retrieval with Patientlog. Pacing Clin Electrophysiol 1991;14:317-321.
8. Sarter BH, Callans DJ, Gottlieb GD, Schwartzman DS, Marchlinski FE. Implantable defibrillator diagnostic storage capabilities: evolution, current status, and future utilization. Pacing Clin Electrophysiol 1998;21:1287-1298.
9. Gregoratos G, Cheitlin A, Epstein AE, et al. ACC/AHA Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. J Am Coll Cardiol 1998;31:1175-1209.
10. Hauer RN, Aliot E, Block M, et al. Indications for implantable cardioverter defibrillator (ICD) therapy. Europace 2001;3:169-176.
11. Furman S, Escher DJW. Transtelephone pacemaker monitoring. In: Schaldach M, Furman S (editors). Advances in pacemaker technology. Berlin:Springer. 1975:177-194.
12. Griffin JC, Schuenemeyer TD, Hess KR. Pacemaker follow-up: Its role in the detection and correction of pacemaker system malfunction. Pacing Clin Electrophysiol 1986;9:387-391.

13. Vallario LE, Leman RB, Gillette PC. Pacemaker follow-up and adequacy of Medicare guidelines. Am Heart J 1988;116:11-15.
14. Gessman LJ, Vielbig RE, Waspe LE, Moss L, Damm D, Sundeen F. Accuracy and clinical utility of transtelephonic pacemaker follow-up. Pacing Clin Electrophysiol 1995;18:1032-1034.
15. Igidbashian D, Stellbrink C, Hartmann A, Gill JS, Wunderlich E, Santini M. Benefit of permanent pacemaker follow-up with home monitoring (abstract). Pacing Clin Electrophysiol 2002;24:534.
16. Dressing TJ, Schott R, McDowell C, et al. Transtelephonic ICD follow-up is better: more comprehensive, less intrusive and more desirable (abstract). Pacing Clin Electrophysiol 2002;24:577.
17. Chan AQ, Chun S. Cost effectiveness of wireless home monitoring pacemaker compared to conventional pacemaker (abstract). Pacing Clin Electrophysiol 2002;24:534.
18. Greene M, Newman D, Geist M, Paquette M, Heng P, Dorian P. Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias. Europace 2000;2:263-269.
19. Grom A, Baron TW, Faber TS, Brunner M, Bode C, Zehender M. Clusters of life-threatening ventricular arrhythmias in patients with implanted cardioverter-defibrillators: prevalence, characteristics, and risk stratification. Clin Cardiol 2001;24:330-333.
20. Cleland JG. From left ventricular dysfunction to heart failure. Arch Mal Coeur Vaiss 1996;89:1397-402.
21. Khand AU, Gemmell I, Rankin AC, Cleland JGF. Clinical events leading to the progression of heart failure: Insights from a national database of hospital discharges. Eur Heart J 2001;22:153-164.
22. Gronefeld GC, Mauss O, Li YG, Klingenheben T, Hohnloser SH. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. J Cardiovasc Electrophysiol 2000;11:1208-1214.
23. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1992;15:1667-1673.
24. Kühlkamp V, Dörnberger V, Mewis C, Suchalla R, Bosch R, Seipel L. Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. J Cardiovasc Electrophysiol 1999;10:905-915.
25. Theuns DAMJ, Klootwijk APJ, Kimman GP, Simmoons ML, Roelandt JRTC, Jordaens LJLM. Clinical benefit, survival, and adverse events in patients with an implantable

cardioverter defibrillator: The initial Rotterdam experience. Netherlands Heart J 2001;9:216-221.

26. Theuns D, Klootwijk AP, Kimman GP, Szili-Torok T, Roelandt JR, Jordaens L. Initial clinical experience with a new arrhythmia detection algorithm in dual chamber implantable cardioverter defibrillators. Europace 2001;3:181-186.
27. Pinski S, Fahy G. The proarrhythmic potential of implantable cardioverter-defibrillators. Circulation 1995;92:1651-1664.
28. Hauser RG, Hayes DL, Almquist AK, et al. Unexpected ICD pulse generator failure due to electronic circuit damage caused by electrical overstress. Pacing Clin Electrophysiol 2001;24:1046-1054.

Chapter 4

Twiddler's Syndrome Detected by Home Monitoring Device

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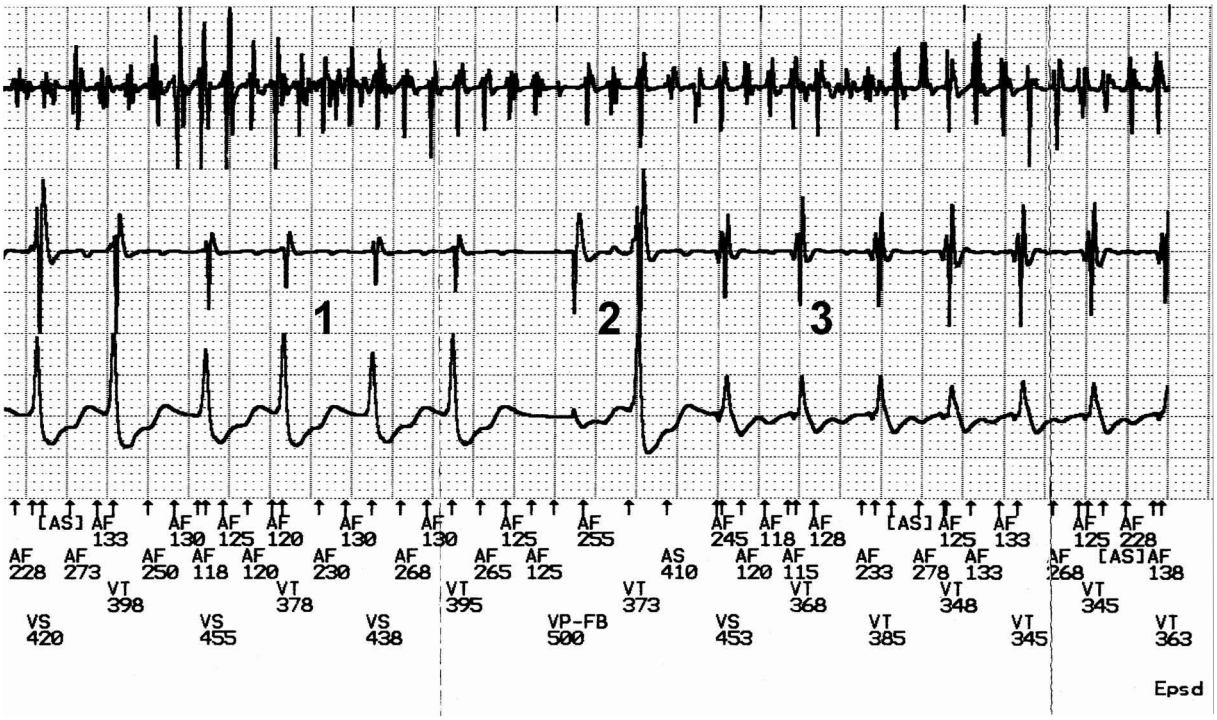
Published: Pacing and Clinical Electrophysiology 2004;27:1151-1152.



Abstract

Lead fracture due to Twiddler's syndrome, was detected in a 68-year-old patient 1 month after implantation of an ICD by means of the incorporated home monitoring system. The patient was admitted and the lead replaced. This case illustrates the clinical benefit of the home monitoring system.

Introduction

Twiddler's syndrome as a pacemaker complication was first described by Bayliss et al in 1968.[1] In these cases the pacemaker is turned over and over, such that the lead is wound around itself. This syndrome has also been described in implantable defibrillator cardioverter (ICD) patients.[2] This report describes a patient in whom the diagnosis of twiddler's syndrome was made after a report from the home monitoring system of the ICD implanted in this patient.

Case report

A 68-year-old man had an ICD implanted in August 2003. In 2001 the patient experienced an inferior wall myocardial infarction. In July 2003 he developed progressive angina and a coronary angiogram was performed. His ejection fraction was 45% and triple vessel disease was found. He underwent coronary artery bypass grafting (CABG) (LIMA graft-LAD, saphenous vein graft-MO-RDP) without complications. One day after the CABG he was resuscitated due to very rapid monomorphic VT with a frequency of 240 beats/min. In the days thereafter, multiple episodes of nonsustained VT were recorded. Programmed stimulation was performed 18 days after the CABG and a sustained monomorphic VT could be repeatedly induced. It was decided to implant an ICD. The patient gave informed consent for participation in the international Home Monitoring Technology for ICD therapy study. The medical ethical committee of the hospital approved the protocol of this study. In this study the Belos VR-T ICD (Biotronik GmbH, Berlin, Germany) is used. Due to its integrated long-distance telemetry, this ICD is capable of periodically transmitting therapy and status data to the patient device RUC 1000-a (Biotronik), usually placed on the bedside cabinet of the patient, and then to a dedicated service center. The service center decodes the data and faxes it to the physician at specified

time intervals. The purpose of the study is to find the diagnostic power of telemetrically transmitted data.

After local anesthesia, the cephalic vein was located and an electrode (Medtronic Sprint 6945, Medtronic Inc, Minneapolis, MN, USA) was introduced and positioned in the right ventricular apex. This lead was connected to a Belos VR-T ICD (Biotronik) which was placed in a left subcutaneous pocket. After successful testing of the implanted system, the patient was discharged the following day. Forty-three days after the implantation, a home monitoring report was received (Fig. 1). This report showed a steep increase in impedance after an initial period of low impedance. A lead rupture was suspected. The patient was called for an urgent check-up. A chest X-ray was done (Fig. 2) and the diagnosis of twiddler's syndrome was made. A second procedure was scheduled. After opening of the wound, the tightly wound lead was clearly visible (Fig. 3). Further dissection disclosed a complete fracture of the lead. The lead had to be cut more distally to advance a stylet. With gentle traction the lead could be extracted. A new lead (Medtronic Sprint 6945, Medtronic Inc.) was introduced through the left subclavian vein and connected to the ICD, which was secured in the pocket with a suture.

Discussion

Twiddler's syndrome early after implantation has been described before.[3] This case clearly demonstrates the potential of the home monitoring system. However since the report was only seen a few days after the acute increase in impedance one feels the need for an automatic warning feature. Technical features of the home monitoring system have been previously described[4] and are promising, at least in areas with sufficient net coverage.

Figure 1. *Home monitoring report showing a decline in impedance (09/25/03) followed a few days later by a steep rise in impedance*

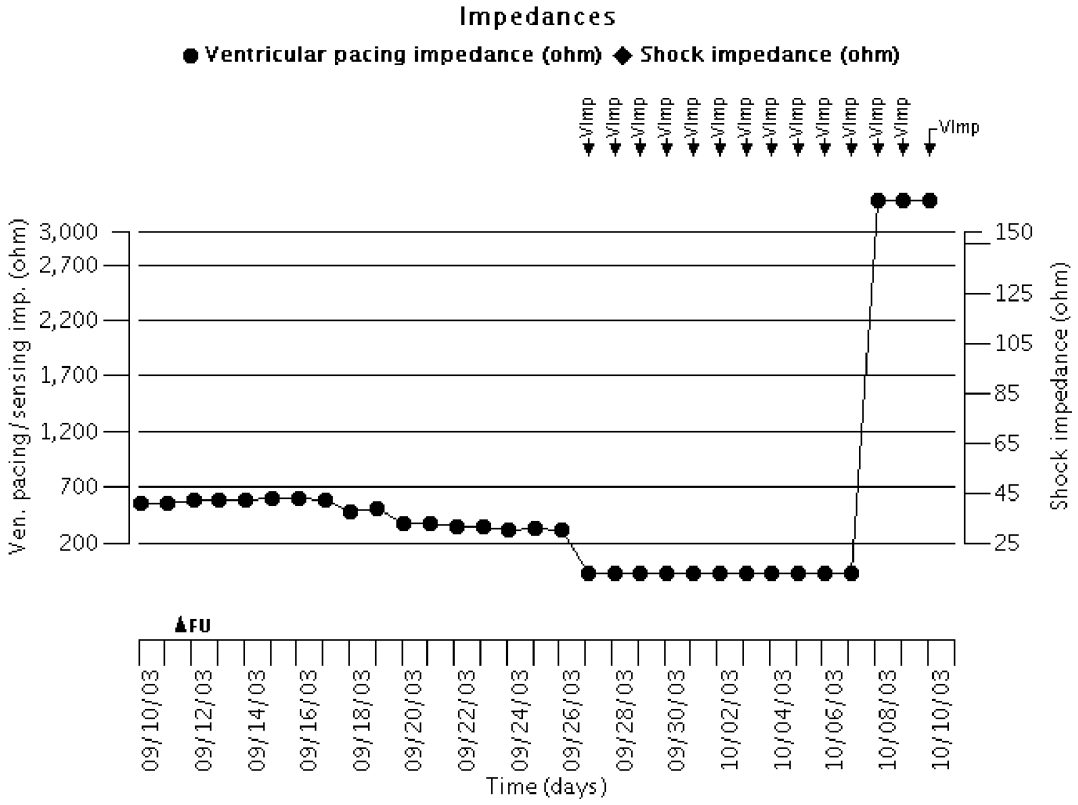


Figure 2. *Chest X-Ray of the patient shows a tightly wound lead.*

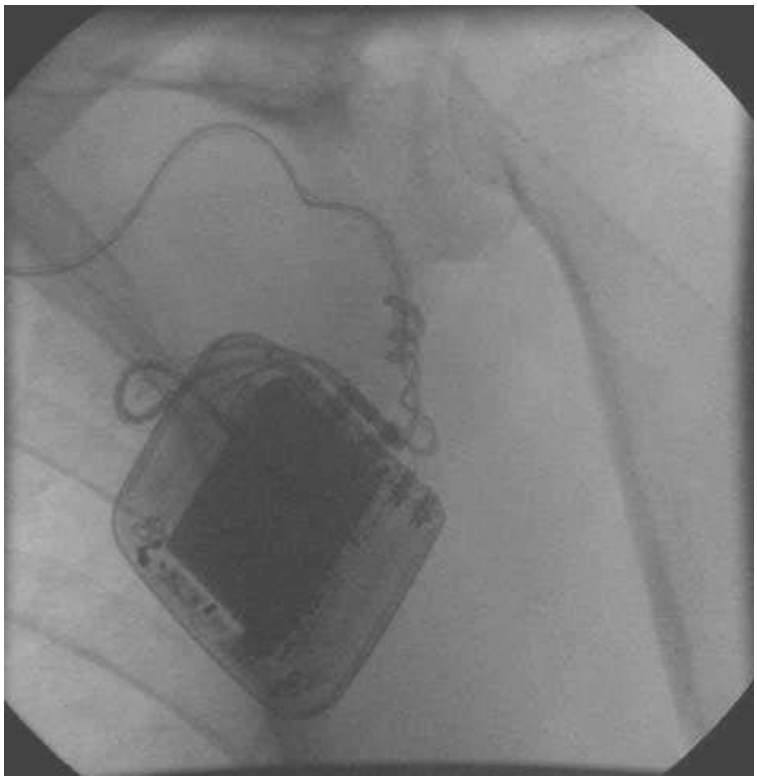
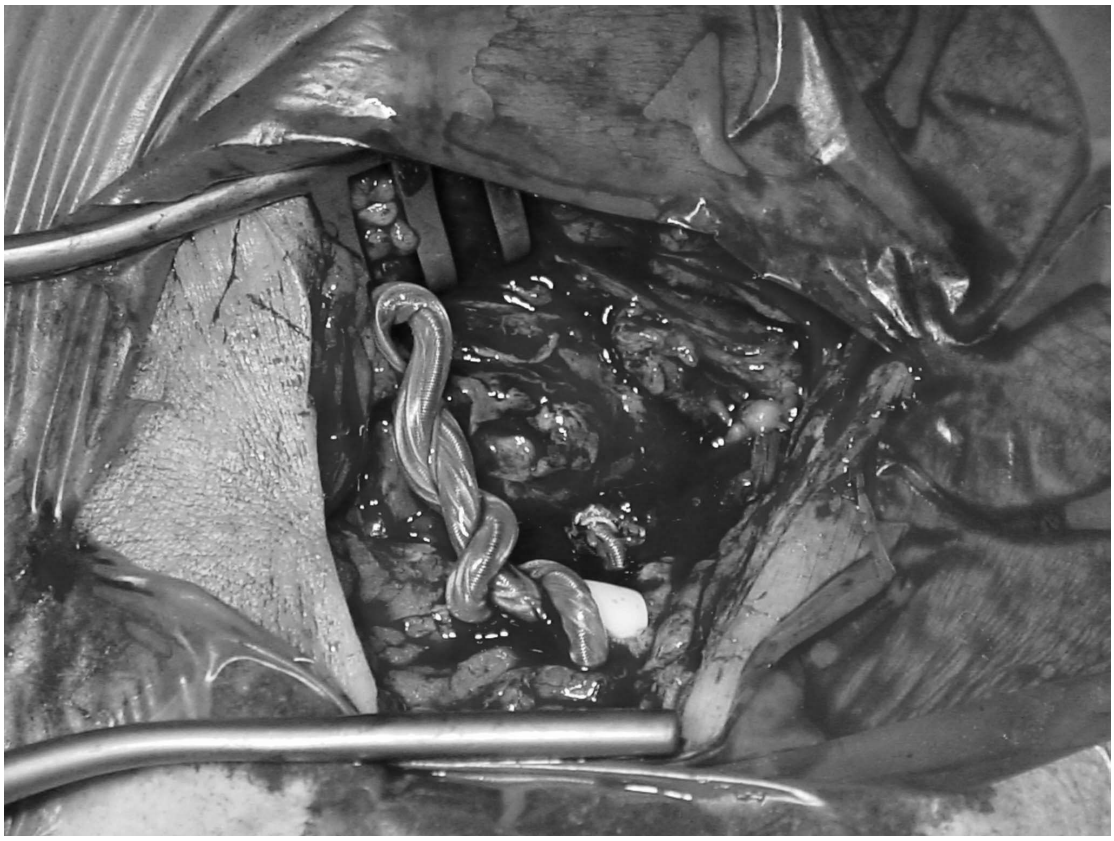


Figure 3. *After opening the pocket the twisted lead is clearly seen.*



References

1. Bayliss CE, Beanlands DS, Baird RJ. The pacemaker-twiddler's syndrome: a new complication of implantable transvenous pacemakers. Can Med Assoc J 1968;99(8):371-3.
2. Defaye P, Ormezzano O, Deharo JC, Denis B. [A rare cause of inappropriate shocks of an implantable automatic defibrillator.Twiddler syndrome]. Arch Mal Coeur Vaiss 1997;90(7):999-1002.
3. Fahraeus T, Hoijer CJ. Early pacemaker twiddler syndrome. Europace 2003;5(3):279-281.
4. Wallbruck K, Stellbrink C, Santini M, Gill J, Hartmann A, Wunderlich E. The value of permanent follow-up of implantable pacemakers--first results of an European trial. Biomed Tech (Berl) 2002;47 Suppl 1 Pt 2:950-953.

Part II

Rhythm Discrimination by the ICD

Chapter 5

Apparent Induction of Ventricular Tachycardia after "Appropriate Pacing" by an Implantable Dual Chamber Defibrillator: Confusing ICD Electrograms

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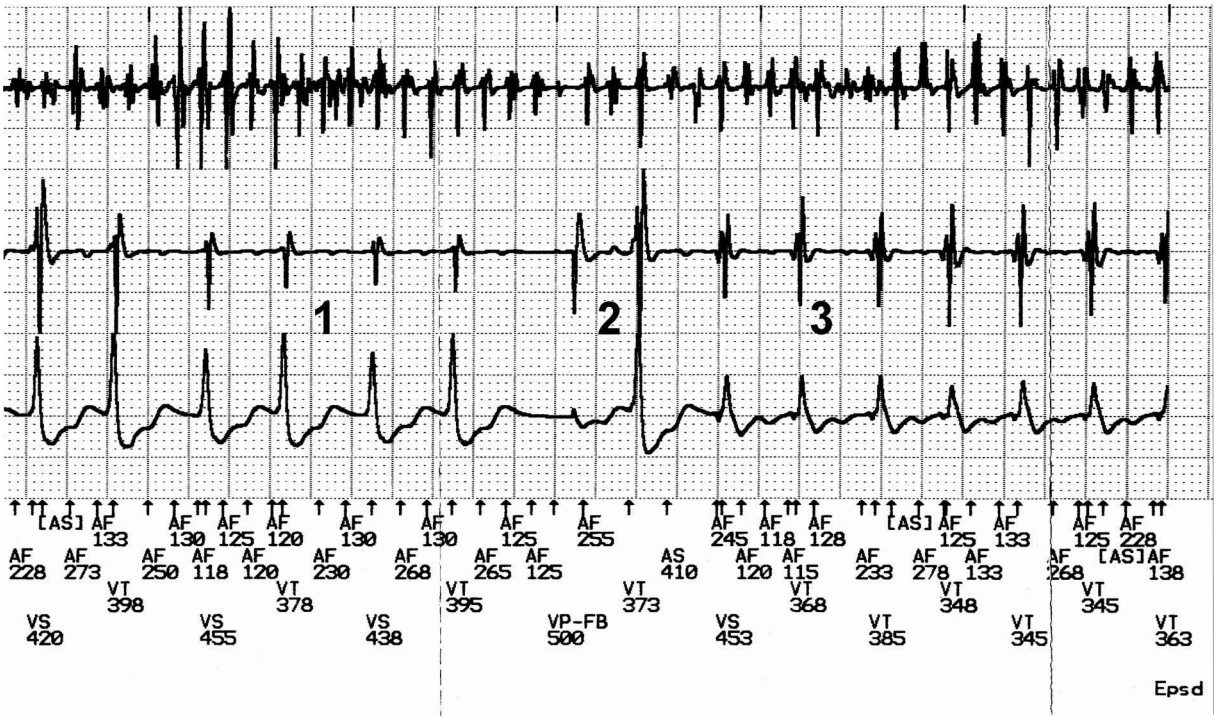
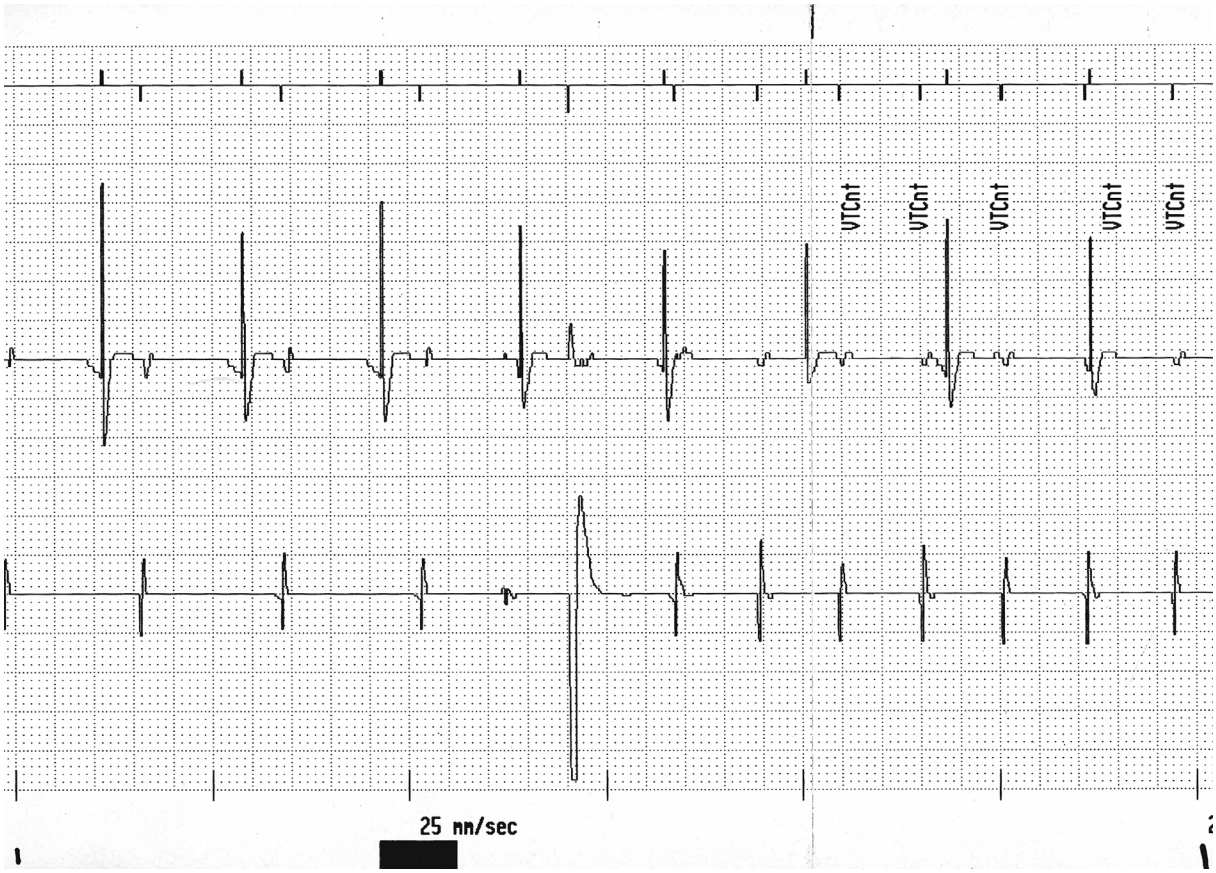


A 38-year-old male patient with a recent large anterior wall myocardial infarction had sustained monomorphic ventricular tachycardia with a rate of 142 beats/minute causing palpitations and signs of congestive heart failure. A Biotronik Phylax AV pulse generator (Biotronik, Berlin, Germany), a Kainox RV 75 electrode (Biotronik, Berlin, Germany), and a Medtronic model 4568 electrode (Medtronic Inc., Minneapolis, MN, USA) were implanted.

Two months after implantation he received his first shock. Endocardial electrograms suggested that the episode of ventricular tachycardia was initiated by a paced ventricular complex (the long downward spike in channel 1) following a sudden delay in the AV conduction. The tachycardia was detected by the ICD and antitachycardia pacing was given. The figure shows a stored endocardial electrogram – upper tracing: marker channel (atrial/ventricular); second tracing: atrial intracardiac electrogram; lower tracing: ventricular intracardiac electrogram. Sinus rhythm, cycle length 710 ms, with a sudden delay in the AV node (250 ms), a ventricular paced beat followed by ventricular tachycardia, cycle length 420 ms; A, artefact.

In the tracing an artefact in the lower ventricular electrogram (channel 3) falling before the P wave in the atrial electrogram (channel 2) is observed. As our patient had premature ventricular beats, we hypothesise that this artefact presumably represents a premature ventricular beat with an amplitude that is different from the preceding sinus beats and the beats during ventricular tachycardia. Its timing in the atrial and ventricular electrogram coincides perfectly with the ventricular tachycardia, and what we initially considered as a ventricular paced beat is probably a fusion of the ventricular pacing synchronous with the ventricular tachycardia, without an apparent reset of this tachycardia. Furthermore, it is not uncommon that sustained monomorphic ventricular tachycardia is initiated by beats with another morphology. Whether the electrogram really reflects the signals as recorded by the amplifiers can be discussed, they certainly misled us in our initial interpretation.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Chapter 6

Initial Clinical Experience with a New Arrhythmia Detection Algorithm in Dual Chamber Implantable Cardioverter Defibrillators

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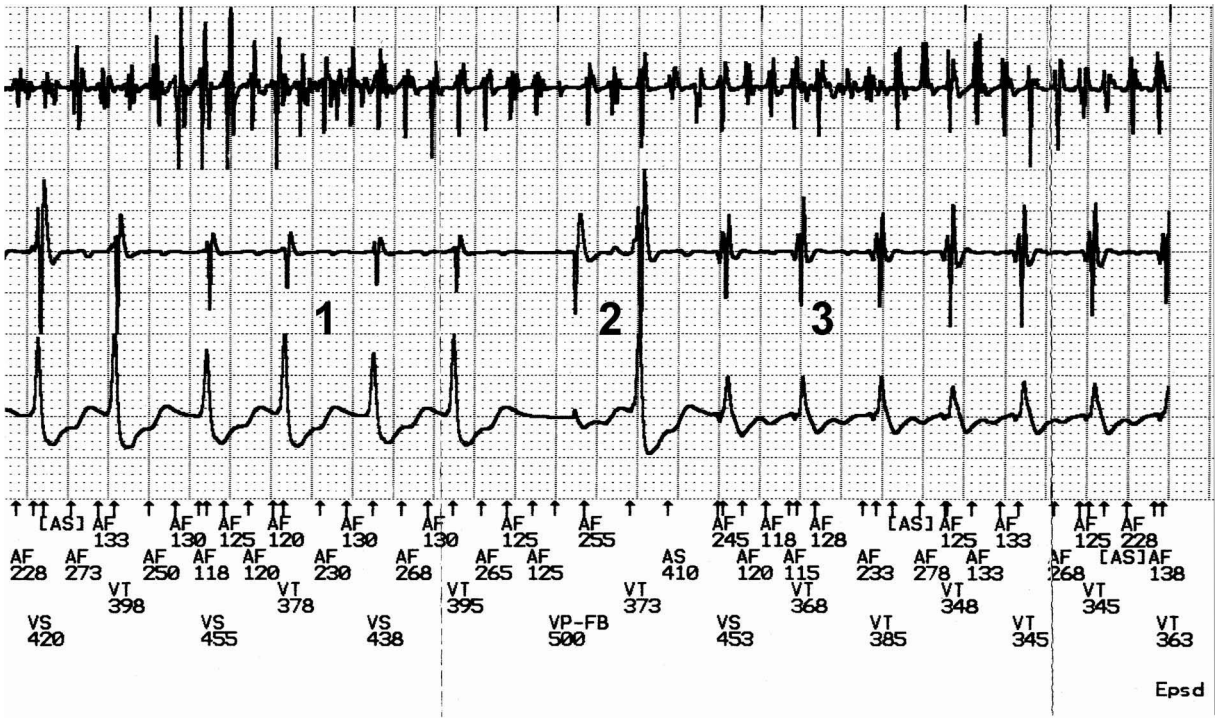


Abstract

Aim: *Inappropriate therapy, due to poor discrimination of supraventricular tachycardia (SVT) and ventricular tachycardia (VT) remains a major problem in patients with an implantable cardioverter defibrillator (ICD). Theoretically, the addition of atrial sensing in discrimination algorithms should improve this differentiation. The aim of the study is to evaluate the performance of a new tachycardia discrimination algorithm, SMART Detection™.*

Methods and results: *Twenty-six patients received a nonthoracotomy ICD system (Phylax AV, Biotronik, Germany). All documented spontaneous arrhythmia episodes were analyzed.*

During a mean follow-up of 8 months, a total number of 139 events with stored electrograms were recorded in 12 patients. The final diagnosis was ventricular fibrillation (VF) or polymorphic VT (n=20), monomorphic VT (n=69), SVT (n=26), other ventricular arrhythmia (n=3) and T wave oversensing (n=21). In 6 episodes a dual tachycardia was present. Considering SVT episodes, inappropriate therapy occurred in 2 cases of atrial flutter due to stable ventricular rate (<30 ms), 1 case of atrial tachycardia and 2 cases of sinus tachycardia due to a sudden onset (>10 %).

Conclusion: *With the SMART Detection™ algorithm, discrimination of VT from SVT achieved a sensitivity of 100%, with an accuracy of 95,6% for all ventricular arrhythmias. In case of SVT, the algorithm appropriately detected and inhibited therapy in 88% of atrial fibrillation.*

Introduction

The implantable cardioverter defibrillator (ICD) has become a widely accepted therapy for the treatment of patients with severe life-threatening ventricular tachycardia (VT) and ventricular fibrillation (VF)[1,2]. However, inappropriate therapy delivered by ICDs for supraventricular tachyarrhythmias remains a clinical problem and has been reported to affect 16-22% of the patients[3,4]. Enhanced detection criteria, such as onset, stability, and morphology template matching might improve the specificity of ICD therapy[5,6,7]. Arrhythmia discrimination is improved further by comparing the timing of atrial and ventricular signals in dual chamber ICDs[8,9]. Accordingly, a new tachycardia discrimination algorithm, SMART Detection™ (Biotronik, Berlin, Germany) which is used in the Phylax AV defibrillators (Biotronik, Berlin, Germany), was developed to discriminate between supraventricular and ventricular arrhythmias by performing a stepwise analysis of the atrial and ventricular events with regard to their rate, regularity and patterns of AV relationship.

This report describes the initial experience with the SMART Detection™ algorithm incorporated in the Phylax AV dual chamber ICD.

Methods

Patient population

During the period between October 1998 and April 2000, 26 patients underwent implantation of a Phylax AV dual chamber ICD. The devices were implanted with endocardial leads. Indications for ICD therapy included (1) 13 patients with out-of-hospital cardiac arrest due to VF, (2) 11 patients with poorly tolerated sustained monomorphic VT and 2 patients with sustained polymorphic VT (pVT).

Implantation technique

The ICD pulse generator and endocardial leads were inserted through a single left pectoral incision. We used a left cephalic vein cutdown or a left subclavian puncture for lead insertion. The ventricular leads were placed at the right ventricular apex, while the atrial leads were located at the right atrial appendage or lateral free wall by active fixation. The capture and sensing thresholds of both atrial and ventricular leads were tested. Far-field R wave sensing in the atrial electrogram was to be

excluded. If present, the atrial lead was relocated at another location until appropriate sensing could be achieved.

Device overview

The Phylax AV is a tiered-therapy dual chamber ICD that provides dual chamber sensing and pacing in standard and post-shock situations, antitachycardia pacing (ATP) modalities, as well as low- and high-energy shock therapies. The device is an 'active can' model and applies onset, stability and the SMART Detection™ algorithms for tachyarrhythmia classification. The criteria onset and stability are applied in conjunction with the SMART Detection™ algorithm.

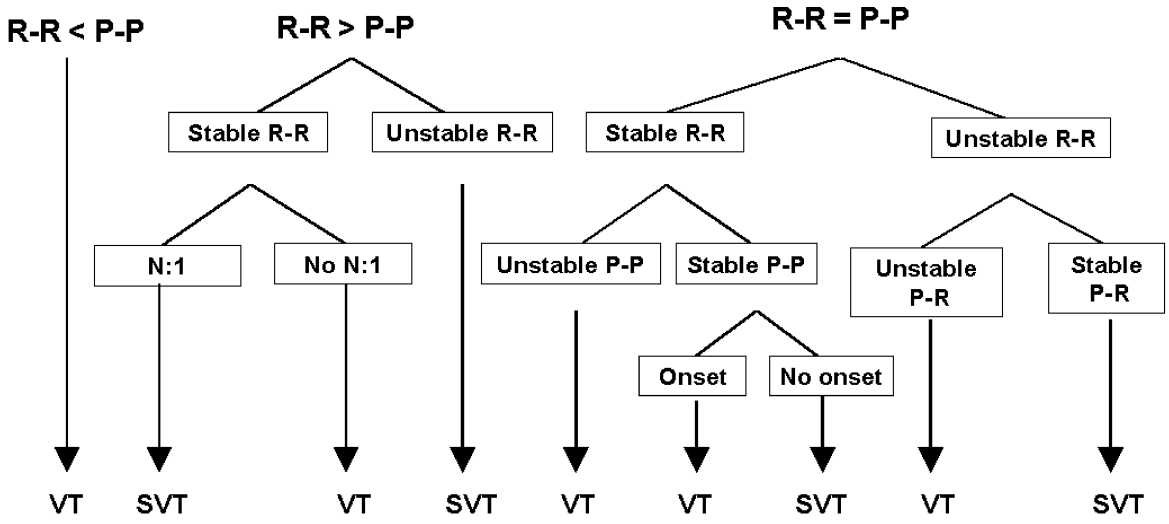
The defibrillation leads used were Kainox RV 75 and Kainox RV-S 75 (Biotronik, Berlin, Germany) endocardial ventricular leads with an integrated pace/sense and defibrillation function. The Kainox RV 75 is a tripolar, tined lead with pace/sense and defibrillation function with one distal defibrillating coil. The Kainox RV-S 75 has the same features, but comes with an active fixation tip. The endocardial lead used for the right atrium was a bipolar active-fixation lead, with an interelectrode spacing of 8.9 mm or 17.8 mm (Model CapsureFix 6940 and 4568, Medtronic Inc., USA).

SMART Detection™ algorithm and sensing function

The SMART Detection™ algorithm is only applied to the VT detection zone to discriminate between supraventricular and ventricular tachyarrhythmias. The algorithm detects and analyzes atrial and ventricular events to determine their averaged rate, stability, and their relationship patterns (Fig. 1). The AV relationship is analyzed by applying the following evaluation criteria, multiplicity and P-R monotonicity. Multiplicity is the numerical relationship of atrial signals to ventricular signals. P-R monotonicity is the degree of change in the timing relationship of atrial events to ventricular events. The RR stability was programmed to 50 msec and onset to 10-15% for all patients. The VF and VT detection zones were individualized at the physicians' discretion.

The initial sensing setting was programmed to 0.375 mV and 0.5 mV for the atrium and ventricle respectively. In all patients, the post ventricular atrial refractory period (PVARP) was programmed to the nominal value of 240 msec.

Figure 1. *The SMART Detection™ algorithm based on averaged atrial and ventricular rate, stability, and atrioventricular (AV) relationship. Initial arrhythmia detection is based on the continuous analysis of the average atrial and ventricular rate. If the ventricular rate exceeds the atrial rate, i.e. RR < PP, the device delivers therapy for VT if the VT sample count is fulfilled. In case of RR > PP, the device recognizes the rhythm as a possible SVT. The device analyses the RR stability and the numerical relationship of atrial to ventricular signals. In case of 1:1 conduction, RR = PP, at the first level the RR stability is verified. Depending on RR stability, the system analyzes either the PP intervals or the PR intervals for stability.*



Follow-up

For all patients regular follow-up was arranged at our out-patients' facility every 3 months or after spontaneous ICD discharges. The event counters and the stored intracardiac electrograms were retrieved. Only events with stored electrograms were included in this analysis in order to detect errors of the SMART Detection™ algorithm resulting in the delivery of inappropriate therapy.

Data analysis

All data are presented as mean values ± standard deviation, unless otherwise specified. Student's t-test was used to compare discrete variables where appropriate. A two-tailed *P* value < 0.05 was considered to be significant.

Results

Patient population

The patients included in this study are summarized in Table 1. Most of the patients were male (77%) and had coronary artery disease (77%). Seven patients (27%) had amiodarone as antiarrhythmic drug therapy. All patients were in sinus rhythm at the time of implant. Paroxysmal atrial fibrillation was documented in 5 patients (19%). One patient had sinus node dysfunction.

Sixteen patients (62%) received the Kainox RV-S 75 tripolar lead with active fixation. In 10 patients (38%) the Medtronic 6940 atrial lead and in 16 patients the Medtronic 4568 atrial lead was implanted. In one patient, both leads were tunnelled from the left to the right side as severe thrombosis was present in the left subclavian vein. During follow-up there was no significant difference in the amplitude of the atrial electrogram. The amplitude of the atrial electrogram at implant was 2.6 $\pm$ 1.3 mV and at follow-up (9 months) 3.4 $\pm$ 2.0 mV. In one patient, the SMART Detection^{TM} algorithm was programmed off due to loss of atrial sensing. This patient had no spontaneous arrhythmia with the deactivated SMART Detection^{TM} algorithm. One patient died from progressive heart failure.

Table 1 *Patient characteristics*

No. of patients	26
Gender M/F	20/6
Age (years)	59 $\pm$ 15
Structural heart disease	
CAD	20
DCM	2
HCM	2
Idiopathic ventricular fibrillation	2
LVEF (%)	38 $\pm$ 16
Clinical arrhythmia	
VF	13
MVT	11
PVT	2
Documented AF	5
Amiodarone	7

AF = atrial fibrillation; CAD = coronary artery disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; VF = ventricular fibrillation; VT = ventricular tachycardia.

Arrhythmia recurrence during follow-up

During a mean follow-up of 8 ± 5 months (range 1 to 17 months), 12 patients (46%) experienced a total of 139 episodes. In all cases, the electrograms with the underlying arrhythmias or events could be analyzed and diagnosed (Table 2). Eighty-nine episodes of ventricular tachyarrhythmias were documented in 8 patients; 26 episodes of supraventricular tachyarrhythmias in 5 patients; 3 episodes of ventricular arrhythmia in 1 patient, and 21 episodes of T wave oversensing in 4 patients.

Table 2 *Number of documented episodes of arrhythmias*

Device diagnosis	Investigator diagnosis	# Episodes
SVT	SVT	21
	VT	0
	VF	0
VT	SVT	5
	VT	69
	VF	0
	V. bigeminy	3
VF	SVT	0
	VT/VF	20
Total		118

SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia
If the device withholds therapy, the rhythm is classified by the device as no ventricular tachyarrhythmia. T wave oversensing was diagnosed in 21 episodes.

Ventricular tachyarrhythmias

During a mean follow-up of 8 ± 5 months (range 1 to 17 months), 20 episodes of pVT/VF with stored electrograms occurred in 4 patients (1 to 7 episodes per patient). In all episodes the ventricular rate was faster than the atrial rate (RR < PP). The device terminated all but 10 episodes with shock therapy. The remaining 10 episodes (50%) were recorded in 4 patients (1 to 7 episodes per patient). The device correctly detected the episodes and, according to the VF confirmation algorithm, therapy was aborted in these cases of nonsustained pVT/VF.

Eight patients experienced a total of 69 episodes of VT with corresponding stored electrograms (1 to 36 episodes per patient). In 6 episodes (9%) atrial fibrillation was present (RR > PP). RR stability during these episodes was 5.8 ± 4.6 msec (range 3-

35 msec). All episodes were correctly identified and terminated with ATP by the device. In 5 cases (7%), 1:1 retrograde conduction was present (RR = PP). These episodes were correctly identified by the SMART Detection™ algorithm. All episodes were terminated with ATP by the device. In 58 episodes (84%), the ventricular rate was faster than the atrial rate (RR < PP). All but 13 episodes were treated by the device by ATP (n=41, 71%) or shock therapy (n=4, 7%). ATP therapy was withheld in the remaining 13 episodes of nonsustained VT. In 2 cases, the ATP therapy accelerated the VT into VF and shock therapy by the device terminated the arrhythmia.

Supraventricular tachyarrhythmias

Five patients (19%) experienced a total number of 26 episodes of SVT with a stored electrogram. Two (8%) of these episodes were sinus tachycardia (occurring in 2 patients). One episode of atrial tachycardia occurred in 1 patient. In 23 (88%) cases, the arrhythmia was atrial fibrillation or atrial flutter (occurring in 2 patients). The RR stability during the episodes of atrial fibrillation or atrial flutter ranged from 2 to 266 msec (mean 60 ± 56 msec). No episode of atrial fibrillation or atrial flutter was recorded in the VF zone. In the VT zone, 2 (9%) episodes of atrial flutter were treated by shock therapy due to stable RR intervals (mean 12 ±.9 msec). In the remaining 21 episodes, the device withheld therapy. The 3 episodes of sinus tachycardia and atrial tachycardia were treated by antitachycardia pacing.

With the SMART Detection™ algorithm discrimination of VT from SVT achieved a sensitivity of 100% with a specificity of 80.7% and accuracy of 95.6% for all ventricular tachyarrhythmias.

Incidence of inappropriate ICD therapies

A total number of 29 episodes (21%) were misclassified as ventricular arrhythmia after the initial detection period (8 patients, range 1 to 6 episodes per patient). Twenty-one of these episodes were T wave oversensing (4 patients, range 2 to 7 episodes per patient). In 14 episodes, an inappropriate shock by the device was delivered. In the remaining 7 episodes, shock therapy was aborted. In 1 patient, 3 episodes of ventricular bigeminy were present. The patient received inappropriate ATP therapy in all episodes. The remaining episodes were 5 cases of SVT (see supraventricular arrhythmias). With respect to the performance of the SMART

Detection™ algorithm, T wave oversensing and ventricular bigeminy are problems which are not related to the detection algorithm.

In addition, during the redetection period no coincidently induced atrial fibrillation was present. However, in 2 episodes (1 patient) sinus tachycardia was present after appropriate therapy for VF. The sinus tachycardia had cycle lengths shorter than the maximum programmed cycle length of the VT detection zone. Due to zone merging during the VF redetection period, the patient experienced inappropriate shocks for sinus tachycardia. In 1 episode VF was induced by an ICD shock delivered during sinus tachycardia in the VF redetection period. This VF was terminated by a further ICD shock. The SMART Detection™ algorithm during the redetection is only applied to detect coincidently induced atrial fibrillation.

Discussion

This article presents an early experience with a new arrhythmia detection algorithm incorporated in a dual chamber ICD. This study primarily evaluates the performance of the algorithm in discriminating between supraventricular and ventricular tachyarrhythmias.

A concern with 'enhanced' discrimination of supraventricular from ventricular tachyarrhythmias in dual chamber defibrillators is the underdetection of VT. Detection failure and/or delay has been described with the use of enhancement criteria in single chamber ICDs[10,11,12]. The single chamber enhanced detection criteria used to detect a tachyarrhythmia are the same in the Phylax AV. The SMART Detection™ algorithm is used to enhance the specificity of arrhythmia detection with addition of information derived from the atrial lead. The activated SMART Detection™ algorithm correctly classified all ventricular tachyarrhythmias. The use of the SMART Detection™ algorithm did not result in a loss of sensitivity in the detection of ventricular tachyarrhythmias.

Recently, additional atrial sensing resulted in improved specificity of arrhythmia detection with a potential significant reduction of inappropriate therapies due to SVT[8,9,13]. In our study, the SMART Detection™ algorithm withheld therapy in 21 cases out of 26. In these cases, atrial fibrillation or atrial flutter was present. Based on RR stability, therapy was also inhibited in these episodes with single chamber criteria. In several studies, it has been shown that the stability criterion in single

chamber ICDs can be used with a high specificity to differentiate atrial fibrillation from VT[5,6,14]. However, limitations of the stability criterion during supraventricular tachyarrhythmias with rapid and stable ventricular response have been reported[12]. In comparison to single chamber detection criteria, the use of dual chamber enhancement criteria might further improve the detection during rapid and stable ventricular rates in supraventricular tachyarrhythmias. The multiplicity criterion in the SMART Detection™ algorithm is used to detect stable supraventricular tachyarrhythmias with n:1 conduction. The criterion is based on the calculation of the mean atrial rate as a multiple of the mean ventricular rate. However, a variation in the calculated mean atrial rates can lead to inappropriate therapy in 2:1 conducted atrial flutter.

Despite the activation of the SMART Detection™ algorithm, supraventricular tachycardias with 1:1 conduction and a progressive prolonging AV interval can be misclassified as VT with retrograde 1:1 conduction. This problem is similar to the most common failure described for the PR Logic™ algorithm (Medtronic Inc., Minneapolis, USA)[15]. Inappropriate therapy for sinus tachycardia in our study was related to incorrect device programming. Normally, a programmed onset of 9% is able to prevent inappropriate detection of sinus tachycardia[16]. After reprogramming the onset, no episodes of sinus tachycardia were misclassified as VT.

Comparison of dual chamber algorithms

A comparison of the performance of this algorithm with other dual chamber algorithms is difficult, because the number of episodes, the number of patients and the programmed detection criteria differ between the published studies. Studies with dual chamber ICDs have reported positive predictive values for the diagnosis of atrial fibrillation and atrial flutter of 92% and 86% respectively, with an incidence of inappropriate therapy of 3.8%[7,17]. Other data indicate that while the sensitivity for ventricular arrhythmias is high (99 to 100%), the specificity for atrial arrhythmias remains rather poor (even as low as 70% in some cases)[18,19]. In a survey by a group comparing dual chamber with single chamber detection criteria, no major benefit was demonstrated with respect to dual chamber detection criteria[20]. The incidence for inappropriate therapy due to supraventricular arrhythmias is still in the range of

16%[4]. Recently, we demonstrated a trend towards less inappropriate interventions in a retrograde analysis of 123 patients[21].

Limitations of the study

The efficacy of the SMART Detection™ algorithm in comparison to single chamber enhanced detection criteria is unknown. A randomized study between enhanced single chamber detection criteria and the SMART Detection™ algorithm might answer the question. The overall incidence of documented supraventricular tachyarrhythmias is low. Information is stored in the memory log in chronological order. When the log is full, new episodes of tachyarrhythmias overwrite the older episodes in the memory. This means that the incidence of appropriate as well as inappropriate detections of tachyarrhythmias may have been underestimated.

Conclusions

In conclusion, the SMART Detection™ algorithm for tachyarrhythmias is safe for the detection of ventricular tachyarrhythmias. The high accurracy for AF is encouraging, as other dual chamber algorithms have a low performance in this field[11]. The incidence of inappropriate therapy due to atrial fibrillation is reduced.

References

1. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators: A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
2. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients coronary artery disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
3. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. PACE 1992;15:1667-1673.
4. Osswald S, Cron TA, Sterns L, Alt E, Stotts L, Coenen M. New ICD-technologies: First clinical experience with dual-chamber sensing for differentiation of supraventricular tachyarrhythmias. PACE 1998;21:292-295.
5. Swerdlow CD, Chen PS, Kass RM, Allard JR, Peter CT. Discrimination of ventricular tachycardia from sinus tachycardia and atrial fibrillation in a tiered-therapy cardioverter-defibrillator. J Am Coll Cardiol 1994; 23:1342-1355.
6. Brugada J. Is inappropriate therapy a resolved issue with current implantable cardioverter defibrillators? Am J Cardiol 1999;83:40D-44D.
7. Duru F, Bauersfeld U, Rahn-Schönbeck M, Candinas R. Morphology discriminator feature for enhanced ventricular tachycardia discrimination in implantable cardioverter defibrillators. PACE 2000;23:1364-1374.
8. Schuger CD, Jackson K, Steinman RT, Lehmann MH. Atrial sensing to augment ventricular tachycardia detection by the automatic implantable cardioverter defibrillator: A utility study. PACE 1988;11:1456-1464.
9. Lavergne T, Daubert JC, Chauvin M, et al. Preliminary clinical experience with the first dual chamber pacemaker defibrillator. PACE 1997;20:182-188.
10. Swerdlow CD, Ahern T, Chen PS et al. Underdetection of ventricular tachycardia by algorithms to enhance specificity in a tiered-therapy cardioverter-defibrillator. J Am Coll Cardiol 1994;24:416-424.
11. Weber M, Böcker D, Bänsch D et al. Efficacy and safety of the initial use of stability and onset criteria in implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 1999;10:145-153.

12. Nanthakumar K, Paquette M, Newman D et al. Inappropriate therapy from atrial fibrillation and sinus tachycardia in automated implantable cardioverter defibrillators. Am Heart J 2000 ;139 :797-803.
13. Sticherling C, Schaumann A, Klingenheben T, Hohnloser SH for the Ventak AV II DR investigators. First worldwide clinical experience with a new dual chamber implantable cardioverter defirbillator. Europace 1999;1:96-102.
14. Higgins SL, Lee RS, Kramer RL. Stability: An ICD detection criterion for discriminating atrial fibrillation from ventricular tachycardia. J Cardiovasc Electrophysiol 1995;6:1081-1088.
15. Swerdlow C, Sheth N, Olson WH et al. Clinical performance of a pattern based, dual-chamber algorithm for discrimination of ventricular from supraventricular arrhythmias (abstract). PACE 1998;21:4:800.
16. Neuzner J, Pitschner HF, Schlepper, M. Programmable VT detection enhancements in implantable cardioverter defibrillator therapy. PACE 1995;18:539-547.
17. Nair M, Saoudi N, Kroiss D, Letac B. Automatic arrhythmia identification using analysis of the atrioventricular association. Application to a new generation of implantable defibrillators. Participating centers of the automatic recognition of arrhythmia study group. Circulation 1997:95;967-973.
18. Dijkman B, Wellens HJJ. The VT:SVT discrimination algorithms in dual chamber ICDs-improved but still not perfect automatic arrhythmia detection (abstract). PACE 1999;22:853.
19. Wilkoff BL, Kühlkamp V, Gillberg JM, et al. Performance of a dual chamber detection algorithm (PR Logic^{TM}) based on the worldwide Gem DR clinical results (abstract). PACE 1999;22:720.
20. Kühlkamp V, Dörnberger V, Mewis C, Suchalla R, Bosch RF, Seipel L. Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. J Cardiovasc Electrophysiol 1999;10:905-915.
21. Kimman GJ, Theuns D, Klootwijk A, Tavernier R, Sutter J, Jordaens L. Comparison of events and survival in dual versus single chamber ICD's (abstract). PACE 1999;22:A73.

Chapter 7

Inappropriate Therapy in Implantable Cardioverter-Defibrillators: Review of Timing-based Detection Algorithms

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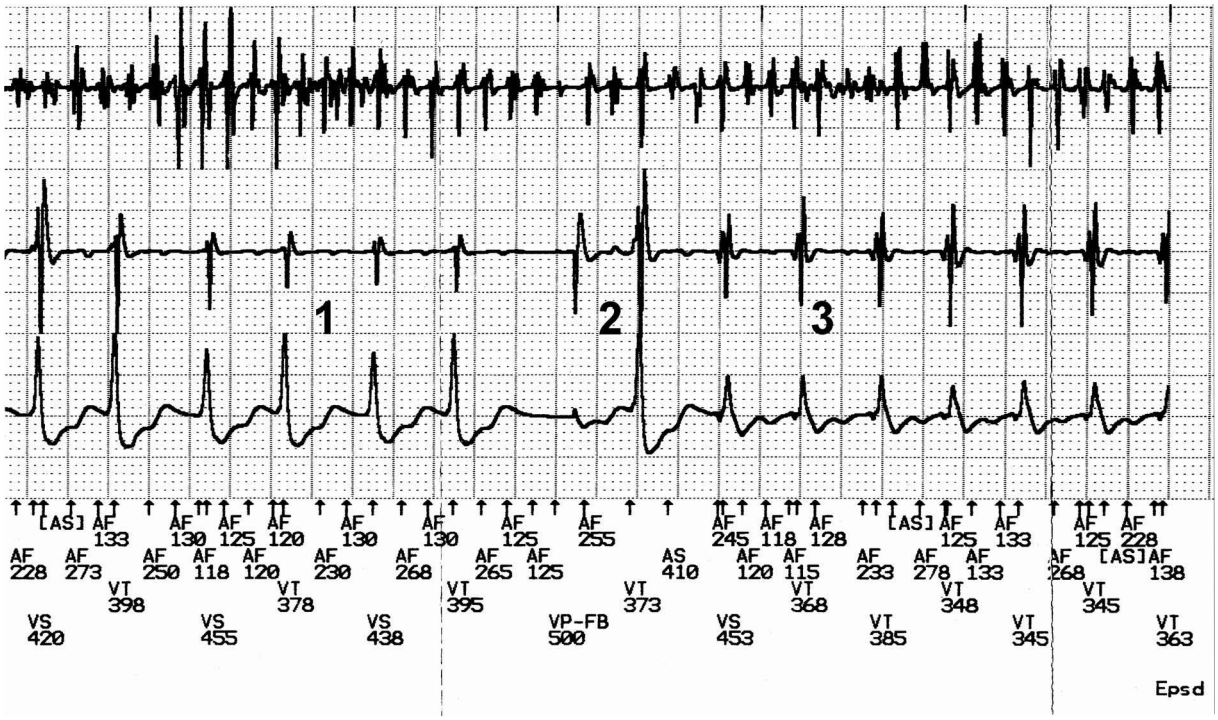
Submitted for publication: 2004.



Abstract

To avoid inappropriate therapy for atrial tachyarrhythmias, implantable cardioverter-defibrillators (ICDs) base distinction of atrial and ventricular tachyarrhythmias on timing-based detection criteria. The original single chamber detection criteria have been implemented as such in dual chamber devices and resynchronization devices. Atrial signals are reliably recognized with atrial leads and better algorithms based on atrial signals were developed. Unfortunately, the incidence of inappropriate therapy did not decrease over time with the development of detection criteria as was proven with comparative studies. Further improvement of arrhythmia detection specificity remains necessary.

Introduction

First used as secondary prevention after cardiac arrest, the indication of the implantable cardioverter-defibrillator (ICD) has expanded to prophylaxis for patients with high risk for sudden cardiac death (primary prevention).(1-3) Despite the fact that ICDs are very accurate and effective in the treatment of ventricular arrhythmias, a substantial proportion of ICD recipients receives inappropriate therapy. The major cause of inappropriate therapy is the prevalence of atrial tachyarrhythmias.(4) This is potentially dangerous as it might trigger ventricular tachyarrhythmias.(5) To avoid inappropriate therapy, arrhythmia detection enhancements were developed. The development of arrhythmia discrimination paralleled the development in diagnostic information storage. The current generation of ICDs offers an array of diagnostic storage capabilities, which improved not only the understanding of triggers precipitating arrhythmias, but also allowed a correct diagnosis of arrhythmias and verification of the appropriateness of delivered therapies.

In this report we will first review the history and the evolution of stored diagnostic information and arrhythmia detection enhancements. Next, we will present methods to minimize bias in the evaluation of arrhythmia detection algorithms in relation to inappropriate therapy. Further, we will provide an overview of the incidence of inappropriate therapy in relation to the applied arrhythmia detection enhancements.

Historical perspective of diagnostic information and arrhythmia detection

First- and second-generation devices

The first ICD implantation in a patient occurred on February 4, 1980 at the John Hopkins Hospital.(6) The first-generation devices were designed to recognize ventricular fibrillation by rate-only detection. Further, the devices were nonprogrammable, committed, and had no telemetry capabilities. Some models used a morphology detection algorithm, the probability density function (PDF). This algorithm lacked specificity, and soon in the development it was recognized that rate-only detection systems had advantages over PDF-based systems. In the first-generation devices, the definition of “appropriate” therapy relied on concomitant ECG monitoring. In general, the clinical history of the patient and the presence or absence of hemodynamically significant symptoms were taken into account. Only later, it became evident that some true ventricular arrhythmias were asymptomatic, and that

some atrial arrhythmias could cause severe symptoms.(7, 8) The second-generation ICDs had recording of RR intervals. This storage allowed analysis of the rate of the arrhythmia preceding and following ICD therapy. Differentiation of arrhythmias was based on the regularity of RR intervals. Irregular RR intervals suggested atrial fibrillation (AF), while regular RR intervals could indicate sinus tachycardia, atrial flutter, or atrial tachycardia as well as ventricular tachycardia. Interpretation of the appropriateness of therapy was a major limitation in first as well in second-generation devices.(9) As a consequence, clinical decision-making in patients treated with the first- and second-generation devices was associated with uncertainty.

Third-generation devices

From the third-generation, the ICD became a tiered-therapy device that provide bradycardia sensing and pacing in standard and post-shock situations, antitachycardia pacing (ATP) modalities, as well as low- and high-energy shock therapies.(10) The most significant advance in diagnostic information was the storage of intracardiac electrogram recordings. This diagnostic information included recording of RR intervals preceding and following the arrhythmia, and stored electrograms with real-time marker channels of arrhythmias triggering ICD therapy (Figure 1).

In order to prevent inappropriate therapy, enhanced detection criteria were developed to improve the specificity of arrhythmia detection.(11) The detection criteria are based on characteristics of arrhythmias. The criterion “stability” measures the degree of regularity of the ventricular response during the arrhythmia. Atrial fibrillation is characterized by an irregular response whereas monomorphic VT is typically more stable. The criterion “sudden onset” discriminates monomorphic VT from sinus tachycardia based on the increase of rate.

Dual chamber devices

In addition to sudden onset and stability, an improvement in arrhythmia discrimination was proposed by the addition of atrial information.(12) The imposition of the simple criterion “ventricular rate > atrial rate” would facilitate differentiation of ventricular from supraventricular tachyarrhythmias. This method has limitations in separation of 1:1 ventriculoatrial conducted tachycardias. Arrhythmia discrimination can be further improved by the analysis of the timing and relationship between atrial and ventricular

electrograms. Dual chamber discrimination algorithms comprise both single and dual chamber detection enhancements.

Atrioverters

Atrial tachyarrhythmias are common in patients with an ICD.(4) A specific device for atrial fibrillation, Metrix atrioverter system (Incontrol Inc., Redmond, WA, USA), was developed with a two-step detection algorithm.(13, 14) The first algorithm is used to discriminate between sinus and a non-sinus rhythm. The second algorithm, a baseline crossing test is invoked to detect atrial fibrillation characterized by random atrial activity unrelated to the cardiac cycle. The result of both algorithms was a high sensitivity (100%) for the detection of non-sinus rhythm with a specificity of 96% for atrial fibrillation.(13) However, concerns were raised whether or not a stand alone atrial defibrillator is safe enough or should have ventricular backup defibrillation in case of shock induced ventricular proarrhythmia. As such, a dual chamber device was developed that provides detection and treatment for atrial fibrillation, atrial tachycardia, and ventricular tachyarrhythmias.(15-17) In the majority of these devices, the detection of atrial arrhythmias is mainly based on rate. For a more accurate classification of atrial tachyarrhythmias, a more advanced atrial detection algorithm was developed.(18) This algorithm uses the maximum atrial rate, the standard deviation, and the dispersion of atrial rate to classify unstable and stable atrial arrhythmias. In case of ventricular arrhythmias, the same detection algorithms are applied.

Resynchronization devices

The latest generation of devices provides treatment for congestive heart failure, by means of biventricular pacing. This technique uses a lead in a tributary of the coronary sinus for left-ventricular pacing. In the earliest generation of resynchronization devices, unique cases of inappropriate therapy were observed.(19, 20) These cases were due to double-counting of ventricular activity, as ventricular sensing was obtained from the right ventricle as well as the left ventricle (Figure 2). This problem was solved as current generation of resynchronization devices have right ventricular-only sensing. For detection of ventricular arrhythmias, atrioverters and resynchronization devices use the same detection algorithms as applied in dual chamber ICDs of the same manufacturer.

Figure 1. *The ICD rhythm strip demonstrates the stored bipolar shock electrogram of a spontaneous tachyarrhythmia detected in the ventricular tachycardia zone. The electrogram during the tachyarrhythmia changed as compared to the electrogram of the baseline rhythm.*

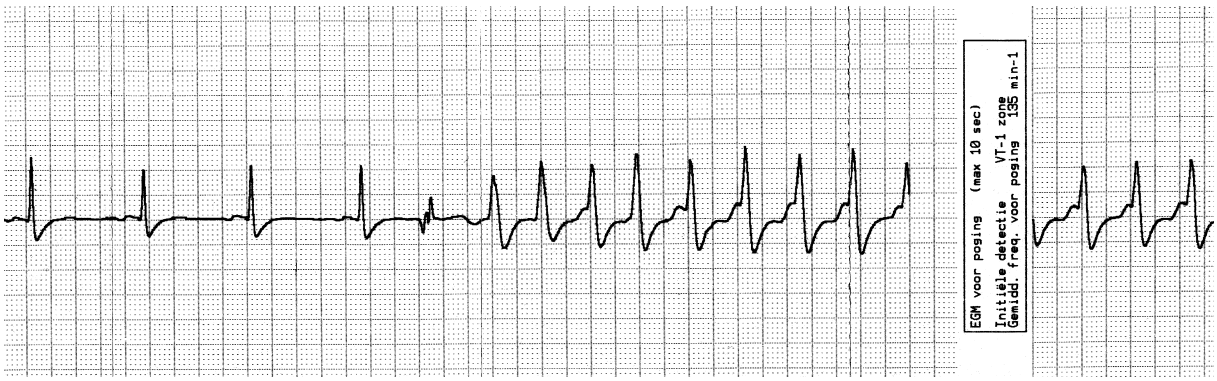
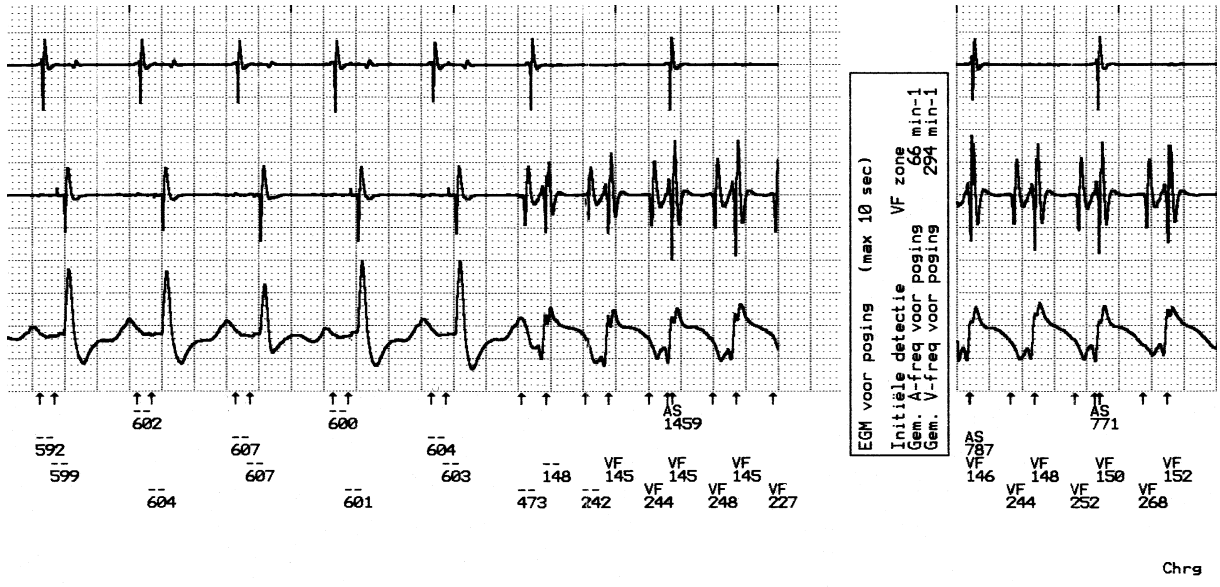


Figure 2*. Stored electrogram from a Guidant Contak CD demonstrating ventricular double counting. During biventricular pacing, a ventricular premature beat (VBP) initiated a ventricular tachycardia (VT). The simultaneous recording of rate-sensing bipoles and the electrogram of wide bipolar shocking leads demonstrated ventricular double counting. Markers: AS = atrial sensing; VF = ventricular fibrillation window (< 300 ms); Chrg: begin of charging; -- : no annotation of stored events before detection of tachycardia.*

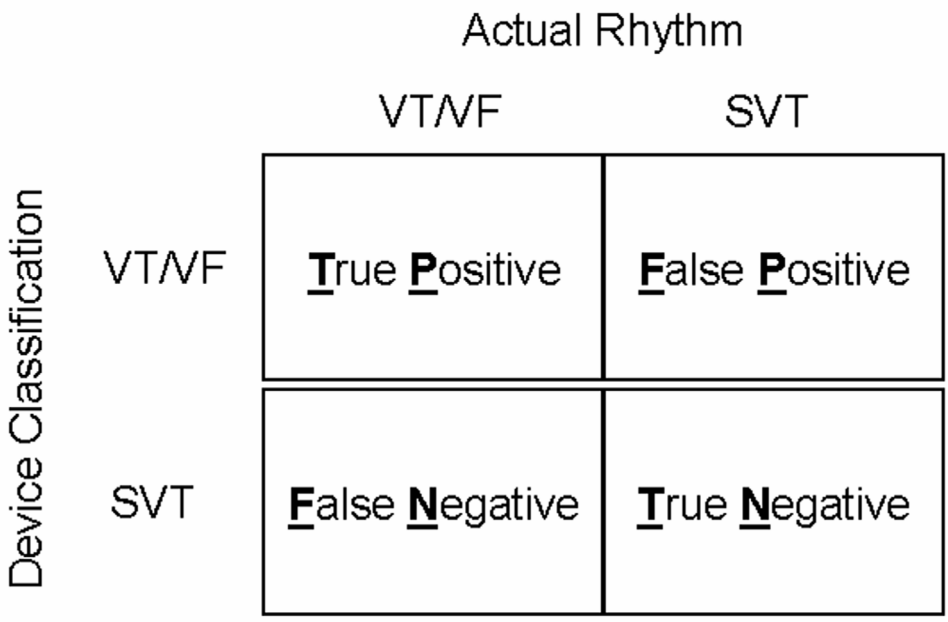


Methodological considerations

Definitions

For analysis or comparison of detection algorithms, independent measures are used to express the success of discrimination between ventricular tachyarrhythmias and atrial tachyarrhythmias. The following definitions are applied when analyzing the performance of algorithms: the ability of detection criteria to accurately detect ventricular arrhythmias (true positive; TP), accurately detect atrial arrhythmias without coexistent ventricular arrhythmias (true negative; TN), falsely detect atrial arrhythmias as ventricular (false-positive; FP), and falsely detect ventricular arrhythmias as atrial (false-negative; FN). The definitions are presented in Figure 3.

Figure 3. *Definitions of tachycardia detection*



The sensitivity of detection algorithms is the probability that a ventricular arrhythmia is detected when present [TP/(FN + TP)]. The specificity of detection algorithms is the probability that a ventricular arrhythmia was not detected given that a ventricular arrhythmia was not present [TN/(FP + TN)]. An absolute specificity cannot be calculated due to an underdetection of atrial arrhythmias. Some ICD models do not store episodes that satisfied rate criteria but were subquently rejected by the detection algorithms. To address this limitation, the positive predictive value of the detection algorithm is calculated [TP/(TP + FP)]. The positive predictive value measures the appropriateness of all delivered therapies, whereas specificity

measures the proportion of inappropriately detected atrial tachyarrhythmias. However, the positive predictive value is highly dependent on the ratio appropriate/inappropriate detected atrial tachyarrhythmias versus the appropriate detected ventricular tachyarrhythmias.
Another aspect is the interpretation of stored electrograms by the physician. The accuracy of electrogram interpretation is higher when an atrial electrogram is present.(21)

Pitfalls of performance analysis of detection algorithms
Some investigators used the concepts of “incremental specificity” and “incremental positive predictive value” to express the performance of dual chamber detection. The term “incremental” is used to indicate that specificity and positive predictive value are related to dual chamber algorithms that operate on top of single chamber rate-only detection. The pitfalls of this concept of incremental specificity have been discussed.(22)
A valid analysis of dual chamber algorithm performance requires control of multiple parameters. The parameters can be divided into ICD parameters and clinical parameters, which can influence the outcome of algorithm performance measurements. ICD detection algorithms are only applicable in the ventricular tachycardia detection zone. The programmed lower and upper limit of the tachycardia detection zone defines the range in which the algorithms are applied. This detection range may influence the type of atrial tachyarrhythmias presented to the algorithm (sinus tachycardia, atrial fibrillation, atrial flutter, or atrial tachycardia). Other important clinical aspects are the frequency and distribution of the different atrial tachyarrhythmias. For example, a low programmed tachycardia detection rate will present more episodes of sinus tachycardia to the algorithm.
The analysis can be performed on a per-episode or a per-patient basis. The accuracy of a per-episode analysis is higher and allows stratifications by types or rates of tachyarrhythmias, whereas per-patient analysis allows to assess reproducible errors, and the impact on the treated population. Therefore, as the contribution of large number of events by a few patients introduces bias in raw algorithm performance measures, statistical methods such as the generalized estimating equation (GEE) with an exhangeable correlation structure should be used.(23, 24) This reduces the bias considerably.

Table 1. *Inappropriate therapy due to atrial tachyarrhythmias in single chamber devices with enhanced detection criteria*

Author	Year	Manufacturer	Follow-up (months)	Patients (N)	*Episodes (N)*	Inappropriate Rx Patient Number (%)	Inappropriate Rx Episode Number (%)
Fromer et al.	1992	2	9.4	102		10 (10%)	
Bardy et al.	1993	2	11	84	471		47 (10%)
Nunain et al.	1995	1,2,3	15.3	154		32 (21%)	
Bardy et al.	1996	2	5.8	464		55 (12%)	
Schaumann et al.	1996	1	20	124		13 (10%)	
Fenelon et al.	1997	1	3.6	113	359		27 (8%)
Sticherling et al.	1998	2	3	162		9 (6%)	
Rosenqvist et al.	1998	2	4	778		116 (15%)	
Brugada et al.	1999	1	26	82	690		34 (5%)
Weber et al.	1999	1	-	87		11 (13%)	

1 = Guidant; 2 = Medtronic; 3 = Ventitrex

Inappropriate therapy and single chamber devices

The eighties

The primary goal of the ICD is to detect and treat life-threatening ventricular tachyarrhythmias. The detection of tachyarrhythmias is mainly based on the measurement of heart rate. With correct sensing, this ensures 100% sensitivity of tachyarrhythmias with rates above the programmed detection rate. However, the implemented rate-only detection in the first- and second-generation devices has a poor specificity in arrhythmia discrimination.(8) The reported incidence of inappropriate therapy during the first decade of ICD therapy ranged between 16% and 41%.(25-29) Fogoros et al. analysed the actuarial incidence of therapy in 65 patients.(7) During follow-up, the actuarial incidence of inappropriate therapy was 17 ± 5% and 21 ± 6%, at 1 and 4 years, respectively. With the first- and second-generation devices, this incidence may have been underestimated due to the lack of electrogram storage. Delivery of inappropriate therapy was only noted during fortuitous ECG monitoring.(8, 28) The fact that atrial tachyarrhythmias contributed to the incidence of inappropriate therapy was established. The reported incidence of inappropriate shocks for atrial fibrillation was approximately 50%.(7, 28) Inappropriate therapy for sinus tachycardia occurred in up to 9% of patients.(7, 25, 28) With tiered-therapy devices the inappropriate detection of atrial tachyarrhythmias became a greater problem.(30) This was due to the increased probability of rate overlap between the target ventricular tachyarrhythmias and atrial tachyarrhythmias, as lower detection zones could be programmed.

Detection enhancements

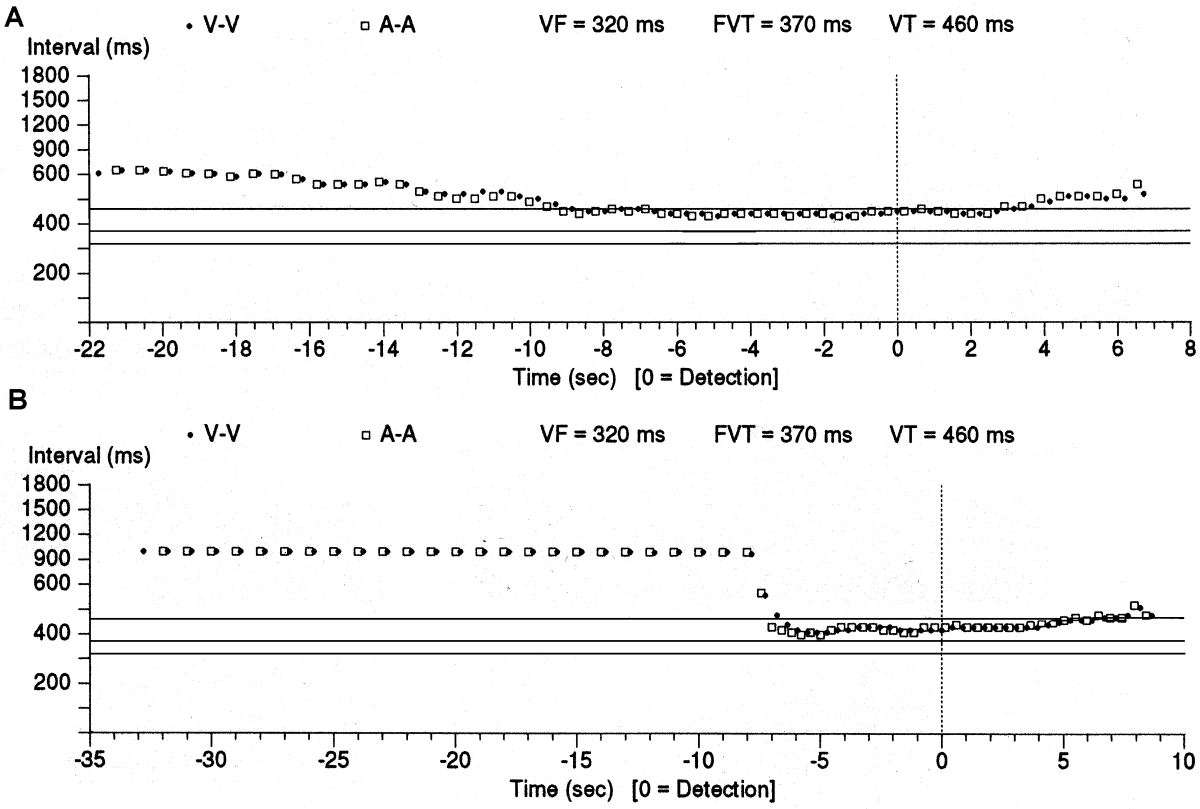
The detection enhancements “sudden onset” and “stability” have been implemented in the ventricular tachycardia zones of devices to reduce inappropriate detections. The proportion of patients experiencing inappropriate therapy with activated detection enhancements is presented in Table 1. The reported incidence on a per-patient basis ranged between 6% and 21%.(31-38) On a per-episode basis, the incidence ranged between 5% and 10%.(30, 39) Despite the reduction in inappropriate therapy, the applied detection enhancements have certain limitations.

The stability criterion was designed to discriminate ventricular tachycardia, characterised by stable intervals, from atrial fibrillation with irregular ventricular response. This criterion has proven to be reliable in the rejection of atrial fibrillation

with a mean ventricular < 170 min^{-1}.(38, 40, 41) However, the performance of the stability criterion during atrial fibrillation is dependent on the rate of ventricular response. The degree of irregularity of the ventricular response decreases at faster rates.(42, 43)

The onset criterion is designed to discriminate ventricular tachycardia from sinus tachycardia and is based on a sudden increase in rate.(Figure 4) The onset criterion has a high specificity for rejecting sinus tachycardia.(38-40) Despite this high specificity, the sudden onset criterion may prevent detection of ventricular tachycardias originating during atrial tachyarrhythmias and ventricular tachycardias starting with rates below the tachycardia detection rate. The risk for detection failures is increased with increasing values of sudden onset criterion.(44)

Figure 4. *Panel A, interval plot showing a tachyarrhythmia with a gradual onset. Panel B, interval plot showing a tachyarrhythmia with a sudden onset. (Medtronic, model GEM 7271 DR). □ A-A: AA intervals; • V-V: VV intervals: FVT = fast ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.*



Initially, both detection enhancements have been used infrequently because physicians were concerned about underdetection of ventricular tachycardias.(30, 40) Serious underdetection was observed in only a minor proportion of the episodes.(38-40) The addition of sustained rate duration in some devices prevents underdetection of ventricular tachycardias by onset criteria. However, the feature ensured 100% sensitivity for ventricular tachyarrhythmias at the price of decreased specificity for rejection of atrial tachyarrhythmias.(39) The major limitation of the onset and stability criterion is the inefficiency to reject sudden onset atrial tachyarrhythmias with stable atrioventricular (AV) conduction, e.g. atrial tachycardia and atrial flutter. Complex detection enhancements with the addition of atrial information might improve the specificity of arrhythmia discrimination.

Dual chamber devices

Dual chamber arrhythmia discrimination

An early argument for the addition of atrial sensing to improve tachycardia detection was proposed by Furman as early as in 1982.(45) The comparison between atrial and ventricular rates is a simple and effective arrhythmia discriminator.(12) In the majority of ventricular tachycardias, the ventricular rate is faster than the atrial rate. Limitations of this simple criterion are the underdetection of ventricular tachycardias with 1:1 retrograde AV conduction and ventricular tachyarrhythmias during atrial fibrillation. To address this limitation, the analysis of AV relationship was postulated as a feature of interest to discriminate sinus tachycardia from ventricular tachycardia.(46) Measurement of the AV relationship provides a reliable diagnostic tool of AV association. Further, timing relationships between atrial and ventricular electrograms can be used to identify atrial tachyarrhythmias with stable atrioventricular conduction.

All dual chamber algorithms comprise both single and dual chamber detection enhancements (Table 2). Dual chamber discrimination algorithms include comparison of atrial and ventricular rates and/or measures of the atrioventricular relationship. The algorithms in dual chamber devices can be roughly divided into 2 groups: 1). comparison of atrial and ventricular rates (rate branches), and 2). hierarchical analysis of the atrioventricular relationship.

Table 2. *Arrhythmia discrimination components in dual chamber algorithms*

	Biotronik	ELA Medical	Guidant	Medtronic	St Jude Medical
Single chamber detection					
Stability	+	+	+	+	+
Sudden onset	+	+	+		+
Sustained duration	+		+		+
Dual chamber detection					
Atrial vs ventricular rates	+		+		+
AV association	+	+		+	+
Timing relationship	+			+	
Chamber of origin		+			

AV = atrioventricular

Dual chamber algorithms based on rate branches

Comparison of atrial and ventricular rates is applied in 3 algorithms. The dual chamber algorithms in Biotronik (Berlin, Germany) and St. Jude Medical (Sylmar, CA, USA) initially divide tachyarrhythmias into three rate branches: ventricular rate > atrial rate, ventricular rate < atrial rate, and ventricular rate = atrial rate. In the latter 2 branches, applicable single and dual chamber arrhythmia discriminators are applied to classifiy the arrhythmia. In case of the ventricular rate = atrial rate branch, the onset criterion and analysis of the atrioventricular relationship are applied. The association or dissociation of the rhythms is monitored based on the stability criterion. If the ventricular rhythm is stable and the atrial rhythm is unstable, the tachyarrhythmia will be classified as ventricular. If both rhythms are stable, the stability of the atrioventricular relationship is analyzed to exclude atrioventricular dissociation.

In Guidant dual chamber devices (St. Paul, MN, USA), priority is given to the single chamber detection criteria onset and stability. An aggressively programming of single chamber detection criteria in these devices will decrease the sensitivity but increase the specificity of arrhythmia discrimination.(47, 48) The dual chamber detection criterion “ventricular rate > atrial rate” can be applied to prevent underdetection of ventricular tachyarrhythmias. The “Afib threshold” criterion can not prevent inappropriate classification of the arrhythmia as priority is given to the stability criterion.

Dual chamber algorithms based on analysis of the atrioventricular relationship

A hierarchical structure of single and dual chamber arrhythmia discriminators is applied in the algorithms PARAD, PARAD+ (ELA Medical, Le Plessis, France) and PR Logic (Medtronic Inc, Minneapolis, MN, USA). The PARAD algorithm first analyses the stability of the rhythm, then atrioventricular association, onset, and finally the chamber of origin.(49, 50) The chamber of origin is used to discriminate between ventricular tachyarrhythmias and atrial tachyarrhythmias with 1:1 AV relation by identification of atrial activity preceding ventricular activity or vice versa. In PARAD+, the additional criterion “long cycle search” can be activated to inhibit therapy for atrial fibrillation with fast ventricular response.

The PR Logic algorithm is based on the timing relationship of atrial activity with respect to ventricular activity.(51) For atrioventricular relationship analysis, each RR

interval is divided into 4 zones. Arrhythmia classification is based on PP and RR intervals, stability of PP and RR intervals, PR:RP relation, and PR dissociation. The findings receive a code, which is compared with templates in a library of arrhythmias. PP intervals and AV relation are used for identification of atrial tachyarrhythmias, and stability of RR intervals and AV dissociation are used to identify ventricular arrhythmias when atrial fibrillation is present. In both algorithms therapy is delivered unless a discriminator identifies an atrial tachyarrhythmia.

Dual chamber devices and inappropriate therapy

Performance of dual chamber algorithms

The reported incidence of inappropriate therapy with dual chamber devices ranges between 5 and 15%.(48, 49, 52-60) The majority of studies conducted with dual chamber devices were restricted to one manufacturer. These studies mainly focussed on the feasibility and safety of the dual chamber devices, and provided data of improved specificity of arrhythmia detection without compromising the sensitivity to ventricular tachyarrhythmias (Table 3). The specificity ranged between 66.7% and 93.3% with positive predictive values for ventricular tachyarrhythmias between 87.4% and 98.4%. These data support an actual benefit of dual chamber devices over single chamber devices. However, caution is necessary when interpreting these data. The comparison of reports is difficult due to differences in methodology, follow-up time, number of patients, number of episodes, type of atrial tachyarrhythmias, and the applied algorithm.

Studies comparing single chamber and dual chamber devices reported small or even non-existent advantages of dual chamber discrimination.(61-64) In an open-label nonrandomized study by Kuhlkamp et al., the number of inappropriate therapies for atrial fibrillation was not decreased with a dual chamber device in comparison to a single chamber device.(61) The authors attributed this higher incidence of inappropriate therapy to atrial sensing problems and the high cut-off value of the “Afib threshold” dual chamber detection criterion. These problems weakened the stability criterion in the dual chamber device. The “Afib threshold” criterion increased by 46% the number of inappropriate therapies as compared to the stability criterion. The study by Deisenhofer et al. confirmed a higher incidence of inappropriate therapy due to atrial sensing problems in dual chamber devices.(62)

In contrast, the recently published randomized, crossover study “1+1 Trial” by Bänsch et al. reported a significant benefit for dual chamber detection.(65) However, the combined end-point included all inappropriate therapies and ventricular tachyarrhythmias above the tachycardia detection interval or with a significant delay in therapy deliverance. The absolute numbers of inappropriate therapy were not significantly different between both study groups (74 single chamber group versus 62 dual chamber group).

Limitations of dual chamber algorithms

The functionality of dual chamber algorithms is influenced by the accurate determination of the atrial rate. This depends on the position of the atrial lead, the characteristics of the electrode tip, and the pulse-generator software. The presence of far-field R waves and atrial blanking should be recognized.(56, 61, 62, 66) Dual chamber ICDs use postventricular blanking periods after paced and sensed events to avoid oversensing of far field R waves. Atrial blanking after a ventricular sensed event may cause atrial undersensing, particularly during fast ventricular rates.(Figure 5) During fast conducted atrial tachyarrhythmias, the total fraction of blanked atrial activity is increased, again causing atrial undersensing. This may result in inappropriate detection of atrial fibrillation or flutter.(61) On the other hand, without atrial blanking periods, atrial oversensing of far field R waves may occur, resulting in overestimation of the atrial rate during tachyarrhythmias with 1:1 atrioventricular relationship. This can cause either inappropriate classification of atrial tachyarrhythmia as ventricular tachyarrhythmia or inappropriate rejection of ventricular tachyarrhythmia.(56) Atrial sensing errors occur in up to 66% of episodes.(66)

Despite the advanced detection algorithms in dual chamber devices, inappropriate classification of atrial tachyarrhythmias is still a problem, especially for atrial arrhythmias with stable atrioventricular conduction (e.g. atrial flutter and atrial tachycardia).(48, 64, 65)(Figure 6) Neither sinus tachycardia nor atrial fibrillation is a major problem for single as well as dual chamber detection algorithms.(64)

Table 3. *Values of sensitivity, specificity, and positive predicitive value of arrhythmia discrimination in dual chamber devices*

Author	Year	Manufacturer	Patients (N)	Follow-up (months)	Sensitivity (%)	Specificity (%)	PPV (%)
Kaplan *et al*.	2001	Biotronik	-	-	99.4	93.3	98.4
Theuns *et al*.	2001	Biotronik	26	8	100	80.8	93.2
Sinha *et al*.	2004	Biotronik	209	10.0	100	89.0	94.5
Sadoul *et al*.	2002	ELA Medical	95	15	99.3	89.2	91.4
Mletzko *et al*.	2003	ELA Medical	90	10.1	100	90.6	88
Sticherling *et al*.	2001	Guidant	52	3	100	-	-
Kouakam *et al*.	2004	Guidant	51	12	98.8	89.4	93.3
Wilkoff *et al*.	2001	Medtronic	933	3.9	100	66.7	87.8
Kühlkamp *et al*.	2002	Medtronic	300	1.7	100	72.4	88.7
Bailin *et al*.	2003	St Jude Medical	107	2.0	100	84.4	87.4

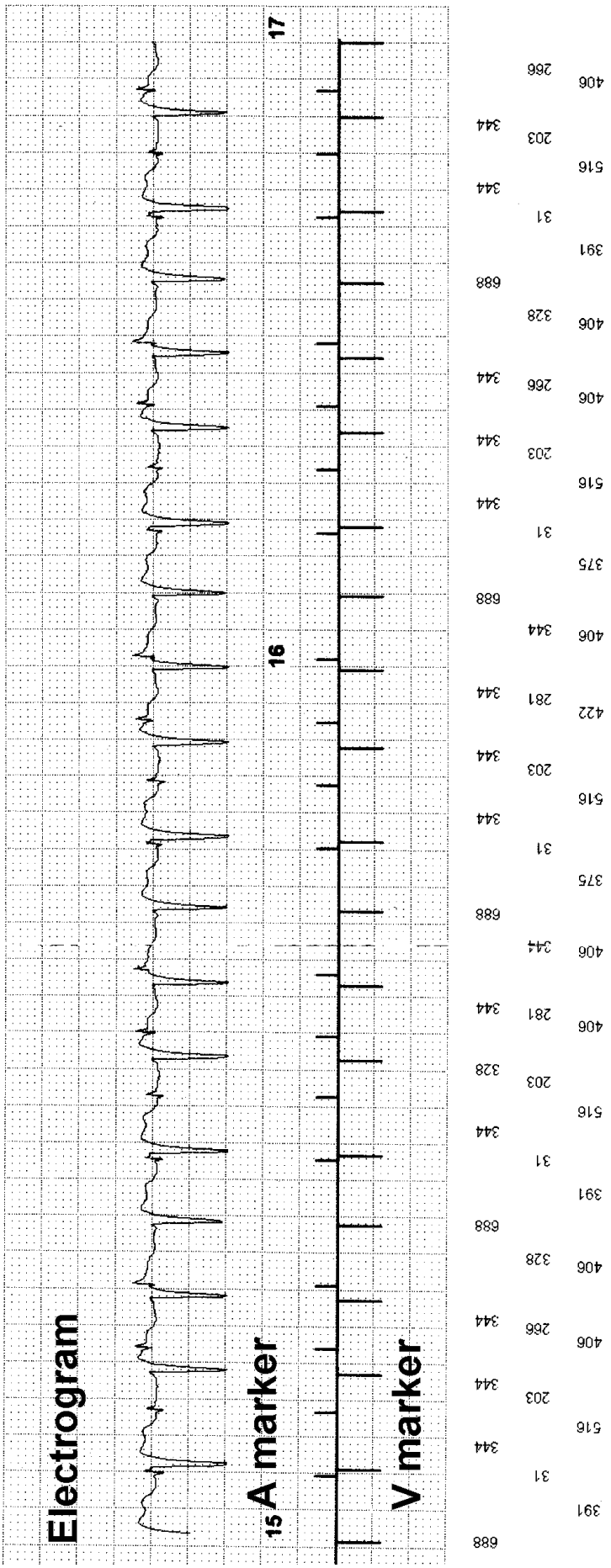
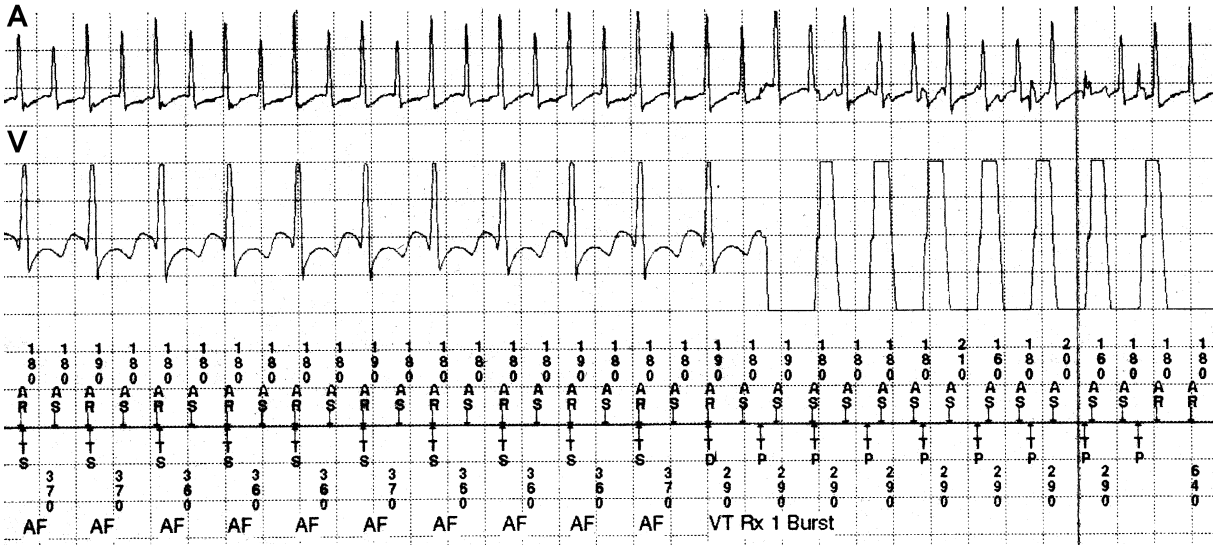


Figure 5. *Stored bipolar wide-band electrogram showing atrial tachycardia with Wenckebach. Due to VA-crossblanking some atrial events were not sensed, and the diagnosis of ventricular tachycardia was made by the device (ELA, model Defender IV).*

Figure 6. *Stored bipolar electrogram showing atrial flutter with 2:1 atrioventricular conduction. The device classified the arrhythmia as ventricular tachycardia, resulting in inappropriate therapy (Medtronic, model InSync 7272). A = atrial electrogram, V = ventricular electrogram. Markers: AF – atrial fibrillation; AR = atrial refractory sensing; AS = atrial sensing; TD = tachycardia detected; TP = tachycardia pacing; TS = ventricular tachycardia window (< 400 ms).*



Conclusion

The primary goal of the ICD is to detect and subsequently terminate life-threatening ventricular tachyarrhythmias. Despite the effectiveness in the treatment of ventricular tachyarrhythmias, inappropriate therapy due to atrial arrhythmias is still a relatively common problem in ICD patients. With the increasing indications for ICD implantation, device selection remains a matter of debate. The rules for device selection for patients with a primary prevention indication can be different from those applied for patients with a secondary prevention indication. The recently published DAVID trial demonstrated deleterious effects of DDD pacing with a conventional right ventricular lead in patients without a bradycardia pacing indication.(67)

To reduce inappropriate therapy, detection algorithms other than timing-based algorithms have evolved. For further improvement of arrhythmia discrimination, the current generation of devices applies morphology discrimination algorithms in conjunction with timing-based algorithms. Nevertheless, to avoid inappropriate therapy, it is particularly important to program carefully the enhanced detection criteria of the device, irrespective of the indication.

References

1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
2. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmiasN Engl J Med 1997;337:1576-1583.
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
4. Schmitt C, Montero M, Melichercik J. Significance of supraventricular tachyarrhythmias in patients with implanted pacing cardioverter defibrillators. Pacing Clin Electrophysiol 1994;17:295-302.
5. Birgersdotter-Green U, Rosenqvist M, Lindemans FW, Ryden L, Radegran K. Holter documented sudden death in a patient with an implanted defibrillator. Pacing Clin Electrophysiol 1992;15:1008-1014.
6. Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322-324.
7. Fogoros RN, Elson JJ, Bonnet CA. Actuarial incidence and pattern of occurrence of shocks following implantation of the automatic implantable cardioverter defibrillator. Pacing Clin Electrophysiol 1989;12:1465-1473.
8. Maloney J, Masterson M, Khoury D, Trohman R, Wilkoff B, Simmons T, Morant V, Castle L. Clinical performance of the implantable cardioverter defibrillator: electrocardiographic documentation of 101 spontaneous discharges. Pacing Clin Electrophysiol 1991;14:280-285.
9. Marchlinski FE, Buxton AE, Flores BF. The automatic implantable cardioverter defibrillator: Followup and complications. In: El-Sherif N, Samet P, editors. Cardiac pacing and electrophysiology. Orlando, FL: Grune and Stratton; 1990. p. 743-758.
10. Bardy GH, Troutman C, Poole JE, Kudenchuk PJ, Dolack GL, Johnson G, Hofer B. Clinical experience with a tiered-therapy multiprogrammable antiarrhythmia device. Circulation 1992;85:1689-1698.

11. Olson WH, Bardy GH, Mehra R, Keimel JG, Almquist C, Biallas RM. Onset and stability for ventricular tachyarrhythmia detection in an implantable pacemaker, cardioverter and defibrillator. Comput Cardiol 1986:167-170.
12. Schuger CD, Jackson K, Steinman RT, Lehmann MH. Atrial sensing to augment ventricular tachycardia detection by the automatic implantable cardioverter defibrillator: a utility study. Pacing Clin Electrophysiol 1988;11:1456-1464.
13. Wellens HJ, Lau CP, Luderitz B, Akhtar M, Waldo AL, Camm AJ, Timmermans C, Tse HF, Jung W, Jordaens L, Ayers G. Atrioverter: an implantable device for the treatment of atrial fibrillation. Circulation 1998;98:1651-1656.
14. Daoud EG, Timmermans C, Fellows C, Hoyt R, Lemery R, Dawson K, Ayers G, Investigators ftM. Initial clinical experience with ambulatory use of an implantable atrial defibrillator for conversion of atrial fibrillation. Circulation 2000;102:1407-1413.
15. Swerdlow CD, Schsls W, Dijkman B, Jung W, Sheth NV, Olson WH, Gunderson BD. Detection of atrial fibrillation and flutter by a dual-chamber implantable cardioverter-defibrillator. For the Worldwide Jewel AF Investigators. Circulation 2000;101:878-885.
16. Dijkman B, Wellens HJ. Diagnosis and therapy of atrial tachyarrhythmias in the dual chamber implantable cardioverter defibrillator. J Cardiovasc Electrophysiol 2000;11:1196-1205.
17. Schoels W, Swerdlow CD, Jung W, Stein KM, Seidl K, Haffajee CJ. Worldwide clinical experience with a new dual-chamber implantable cardioverter defibrillator system. J Cardiovasc Electrophysiol 2001;12:521-528.
18. Morris MM, KenKnight BH, Lang DJ. Detection of atrial arrhythmia for cardiac rhythm management by implantable devices. J Electrocardiol 2000;33 Suppl:133-139.
19. Garcia-Moran E, Mont L, Brugada J. Inappropriate tachycardia detection by a biventricular implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2002;25:123-124.
20. Schreieck J, Zrenner B, Kolb C, Ndrepepa G, Schmitt C. Inappropriate shock delivery due to ventricular double detection with a biventricular pacing implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2001;24:1154-1157.
21. Kim MH, Bruckman D, Sticherling C, Oral H, Pelosi F, Knight BP, Morady F, Strickberger SA. Diagnostic value of single versus dual chamber electrograms recorded from an implantable defibrillator. J Interv Card Electrophysiol 2003;9:49-53.
22. Malik M. Pitfalls of the concept of incremental specificity used in comparisons of dual chamber VT/VF detection algorithms. Pacing Clin Electrophysiol 2000;23:1166-1170.
23. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13-22.

24. Zeger S, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics 1988;44:1049-1060.
25. Kelly PA, Cannom DS, Garan H, Mirabal GS, Harthorne JW, Hurvitz RJ, Vlahakes GJ, Jacobs ML, Ilvento JP, Buckley MJ, et al. The automatic implantable cardioverter-defibrillator: efficacy, complications and survival in patients with malignant ventricular arrhythmias. J Am Coll Cardiol 1988;11:1278-1286.
26. Gabry MD, Brodman R, Johnston D, Frame R, Kim SG, Waspe LE, Fisher JD, Furman S. Automatic implantable cardioverter-defibrillator: patient survival, battery longevity and shock delivery analysis. J Am Coll Cardiol 1987;9:1349-356.
27. Winkle RA, Mead RH, Ruder MA, Gaudiani VA, Smith NA, Buch WS, Schmidt P, Shipman T. Long-term outcome with the automatic implantable cardioverter-defibrillator. J Am Coll Cardiol 1989;13:1353-1361.
28. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1992;15:1667-1673.
29. Neuzner J. Clinical experience with a new cardioverter defibrillator capable of biphasic waveform pulse and enhanced data storage: results of a prospective multicenter study. European Ventak P2 Investigator Group. Pacing Clin Electrophysiol 1994;17:1243-1255..
30. Bardy GH, Hofer B, Johnson G, Kudenchuk PJ, Poole JE, Dolack GL, Gleva M, Mitchell R, Kelso D. Implantable transvenous cardioverter-defibrillators. Circulation 1993;87:1152-1168.
31. Fromer M, Brachmann J, Block M, Siebels J, Hoffmann E, Almendral J, Ohm OJ, den Dulk K, Coumel P, Camm AJ, et al. Efficacy of automatic multimodal device therapy for ventricular tachyarrhythmias as delivered by a new implantable pacing cardioverter-defibrillator. Results of a European multicenter study of 102 implants. Circulation 1992;86:363-374.
32. Nunain SO, Roelke M, Trouton T, Osswald S, Kim YH, Sosa-Suarez G, Brooks DR, McGovern B, Guy M, Torchiana DF, et al. Limitations and late complications of third-generation automatic cardioverter-defibrillators. Circulation 1995;91:2204-2213.
33. Bardy GH, Yee R, Jung W. Multicenter experience with a pectoral unipolar implantable cardioverter-defibrillator. Active Can Investigators. J Am Coll Cardiol 1996;28:400-410.
34. Schaumann A, von zur Muhlen F, Gonska BD, Kreuzer H. Enhanced detection criteria in implantable cardioverter-defibrillators to avoid inappropriate therapy. Am J Cardiol 1996;78:42-50.
35. Fenelon G, Huvelle E, Brugada P. Initial clinical experience with a new small sized third-generation implantable cardioverter defibrillator: results of a multicenter study.

European Ventak Mini Investigator Group. Pacing Clin Electrophysiol 1997;20:2967-2974.

36. Rosenqvist M, Beyer T, Block M, den Dulk K, Minten J, Lindemans F. Adverse events with transvenous implantable cardioverter- defibrillators: a prospective multicenter study. European 7219 Jewel ICD investigators. Circulation 1998;98:663-670.
37. Sticherling C, Klingenheben T, Cameron D, Hohnloser SH. Worldwide clinical experience with a down-sized active can implantable cardioverter defibrillator in 162 consecutive patients. Worldwide 7221 ICD Investigators. Pacing Clin Electrophysiol 1998;21:1778-1783.
38. Weber M, Bocker D, Bansch D, Brunn J, Castrucci M, Gradaus R, Breithardt G, Block M. Efficacy and safety of the initial use of stability and onset criteria in implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 1999;10:145-153.
39. Brugada J. Is inappropriate therapy a resolved issue with current implantable cardioverter defibrillators? Am J Cardiol 1999;83:40D-44D.
40. Swerdlow CD, Chen PS, Kass RM, Allard JR, Peter CT. Discrimination of ventricular tachycardia from sinus tachycardia and atrial fibrillation in a tiered-therapy cardioverter-defibrillator. J Am Coll Cardiol 1994;23:1342-355.
41. Higgins SL, Lee RS, Kramer RL. Stability: an ICD detection criterion for discriminating atrial fibrillation from ventricular tachycardia. J Cardiovasc Electrophysiol 1995;6:1081-1088.
42. Kuhlkamp V, Mewis C, Suchalla R, Bosch RF, Doernberger V, Seipel L. Rate dependence of R-R stability during atrial fibrillation and ventricular tachyarrhythmias. Circulation 1998;98:I-783.
43. Kettering K, Dornberger V, Lang R, Vonthein R, Suchalla R, Bosch RF, Mewis C, Eigenberger B, Kuhlkamp V. Enhanced detection criteria in implantable cardioverter defibrillators: Sensitivity and specificity of the stability algorithm at different heart rates. Pacing Clin Electrophysiol 2001;24:1325-1333.
44. Neuzner J, Pitschner HF, Schlepper M. Programmable VT detection enhancements in implantable cardioverter defibrillator therapy. Pacing Clin Electrophysiol 1995;18:539-547.
45. Furman S, Fisher JK, Panizzo F. Necessity of signal processing in tachycardia detection. In: Barold SS, Mugica J, editors. The third decade of cardiac pacing: Advances in technology and clinical applications. Mount Kisco, NY: Futura; 1982. p. 265-274.
46. LeCarpentier GL, Baga JJ, Yang H, Steinman RT, Meissner MD, Lehmann MH. Differentiation of sinus tachycardia from ventricular tachycardia with 1:1 ventriculoatrial conduction in dual chamber implantable cardioverter defribillators: Feasibility of a

criterion based on the atrioventricular interval. Pacing Clin Electrophysiol 1994:1818-1831.

47. Dorian P, Newman D, Thibault B, Philippon F, Kimber S. A randomized clinical trial of a standardized protocol for the prevention of inappropriate therapy using a dual chamber defibrillator. (Abstract). Circulation 1999;100:I-786.
48. Kouakam C, Kacet S, Hazard JR, Ferraci A, Mansour H, Defaye P, Davy JM, Lambiez M. Performance of a dual-chamber implantable defibrillator algorithm for discrimination of ventricular from supraventricular tachycardia. Europace 2004;6:32-42.
49. Lavergne T, Daubert JC, Chauvin M, Dolla E, Kacet S, Leenhardt A, Mabo P, Ritter P, Sadoul N, Saoudi N, Henry C, Nitzsche R, Ripart A, Murgatroyd F. Preliminary clinical experience with the first dual chamber pacemaker defibrillator. Pacing Clin Electrophysiol 1997;20:182-188.
50. Nair M, Saoudi N, Kroiss D, Letac B. Automatic arrhythmia identification using analysis of the atrioventricular association. Application to a new generation of implantable defibrillators. Participating Centers of the Automatic Recognition of Arrhythmia Study Group. Circulation 1997;95:967-973.
51. Gillberg JM, Olson WH. Dual-chamber sensing and detection for implantable cardioverter-defibrillators. In: Singer I, editor. Interventional electrophysiology 2nd edition. Philadelphia: Lippincott, Williams & Wilkins; 2001. p. 523-569.
52. Sticherling C, Schaumann A, Klingenheben T, Hohnloser SH. First worldwide clinical experience with a new dual chamber implantable cardioverter defibrillator: advantages and complications. Europace 1999;1:96-102.
53. Dijkman B, Wellens HJ. Dual chamber arrhythmia detection in the implantable cardioverter defibrillator. J Cardiovasc Electrophysiol 2000;11:1105-1115.
54. Theuns D, Klootwijk AP, Kimman GP, Szili-Torok T, Roelandt JR, Jordaens L. Initial clinical experience with a new arrhythmia detection algorithm in dual chamber implantable cardioverter defibrillators. Europace 2001;3:181-186.
55. Kaplan A, Skodacek K, Snell J. Efficacy of a new discrimination algorithm: Results from a multicenter, dual-chamber ICD clinical trial. Prog Biomed Research 2001;4:379-385.
56. Wilkoff BL, Kuhlkamp V, Volosin K, Ellenbogen K, Waldecker B, Kacet S, Gillberg JM, DeSouza CM. Critical analysis of dual-chamber implantable cardioverter-defibrillator arrhythmia detection : results and technical considerations. Circulation 2001;103:381-386.
57. Kuhlkamp V, Wilkoff BL, Brown AB, Volosin KJ, Hugl BJ, Stafford W, Cameron DA. Experience with a dual chamber implantable defibrillator. Pacing Clin Electrophysiol 2002;25:1041-1048.

58. Bailin SJ, Niebauer M, Tomassoni G, Leman R. Clinical investigation of a new dual-chamber implantable cardioverter defibrillator with improved rhythm discrimination capabilities. J Cardiovasc Electrophysiol 2003;14:144-149.
59. Sadoul N, Jung W, Jordaens L, Leenhardt A, Santini M, Wolpert C, Aliot E. Diagnostic performance of a dual-chamber cardioverter defibrillator programmed with nominal settings: a European prospective study. J Cardiovasc Electrophysiol 2002;13:25-32.
60. Mletzko R, Aliot E, Seidl K, Lavergne T, Mabo P, Hohnloser S, Bocker D, Schoels W, Sadoul N. Safety and efficacy of a dual chamber implantable cardioverter defibrillator capable of slow ventricular tachycardia discrimination: a randomized study. Pacing Clin Electrophysiol 2003;26:2275-2282.
61. Kuhlkamp V, Dornberger V, Mewis C, Suchalla R, Bosch RF, Seipel L. Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. J Cardiovasc Electrophysiol 1999;10:905-915.
62. Deisenhofer I, Kolb C, Ndrepepa G, Schreieck J, Karch M, Schmieder S, Zrenner B, Schmitt C. Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillators in reducing inappropriate therapy? A randomized, prospective study. J Cardiovasc Electrophysiol 2001;12:134-142.
63. Platia EV, Herre JM, Klein RC, Maasen K, Hayes JJ, Oren JW, Hallstrom AP. Inappropriate therapies in the dual chamber and VVI implantable defibrillator (DAVID) trial (abstract). Circulation 2003;108:364.
64. Theuns DAMJ, Klootwijk APJ, Goedhart DM, Jordaens LJ. Prevention of inappropriate therapy in implantable cardioverter-defibrillators: Results of a prospective, randomized study of tachyarrhythmia detection algorithms. J Am Coll Cardiol 2004;(In press).
65. Bansch D, Steffgen F, Gronefeld G, Wolpert C, Bocker D, Mletzko R, Schoels W, Seidl K, Piel M, Ouyang F, Hohnloser SH, Kuck KH. The 1+1 trial. A prospective trial of a dual- versus a single-chamber implantable defibrillator in patients with slow ventricular tachycardias. Circulation 2004;110:1022-1029.
66. Israel CW, Gronefeld G, Iscolo N, Stoppler C, Hohnloser SH. Discrimination between ventricular and supraventricular tachycardia by dual chamber cardioverter defibrillators: importance of the atrial sensing function. Pacing Clin Electrophysiol 2001;24:183-190.
67. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115-3123.

Chapter 8

Clinical Variables Predicting Inappropriate Use of Implantable Cardioverter-Defibrillator in Patients with Coronary Artery Disease or Non-ischemic Dilated Cardiomyopathy

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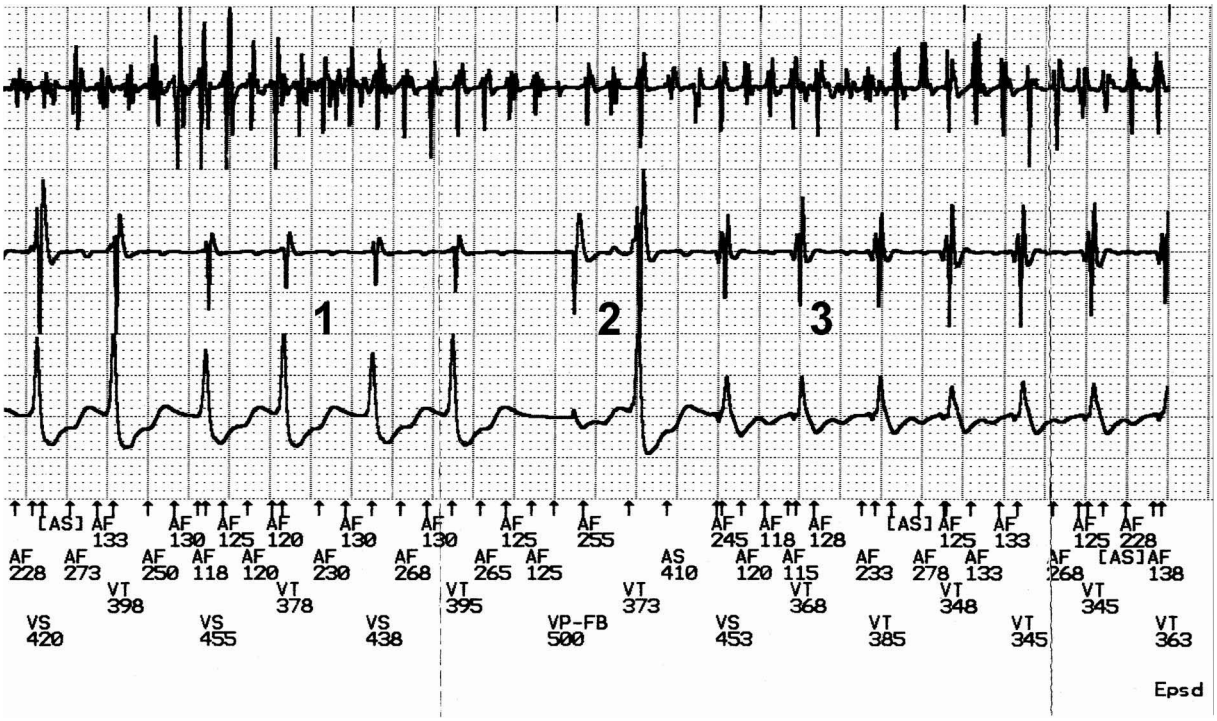
American Journal of Cardiology 2005;95:271-274



Inappropriate therapy is a common clinical problem in recipients of implantable cardioverter-defibrillators (ICDs). The present study evaluated whether clinical characteristics could predict inappropriate ICD therapy due to atrial tachyarrhythmias in a series of 260 patients.

The implantable cardioverter-defibrillator (ICD) has become the standard therapy for life-threatening ventricular tachyarrhythmias.[1-3] Despite the accuracy and effectiveness in the diagnosis and treatment of ventricular tachyarrhythmias, a substantial proportion of patients with ICDs experience inappropriate interventions. The reported incidence ranges from 8% to 40%.[4-7] Several studies have investigated clinical risk predictors for ventricular arrhythmia recurrence.[8-10] In contrast, clinical risk predictors for inappropriate ICD use have not been investigated. This study examined the variables that may predict which patients are more likely to receive inappropriate therapy.

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The study population consisted of 326 consecutive patients who underwent first transvenous implantation at the Erasmus Medical Center (Rotterdam, The Netherlands). Of these, 57 patients were excluded because of participation in a prospective, randomized study of single- and dual-chamber detection algorithms. Another 9 were excluded because of the presence of hyperthrophic cardiomyopathy. Thus, 260 patients were eligible for analysis. The patients were assigned to ICD therapy because of a history of cardiac arrest, spontaneous sustained ventricular tachycardia (VT), or nonsustained VT with subsequent inducible sustained VT. Data in the ICD registry are updated prospectively after each clinic visit.

The prospectively collected clinical and functional variables for each patient include age, gender, the presence of coronary artery disease (including myocardial infarction and cardiomyopathy), the left ventricular ejection fraction (LVEF) as determined by nuclear isotopes, index arrhythmia, history of atrial tachyarrhythmias documented in the clinical file, and pharmacologic treatment.

The implanted devices were manufactured by Biotronik (Phylax AV, Tachos DR, and Belos VR-T; Biotronik GmbH & Company, Berlin, Germany), ELA Medical (Defender IV, and Alto DR; ELA Medical, Paris, France), Guidant (Mini IV, Contak CD, Renewal

I, and Renewal II; Guidant Corporation, St Paul, Minnesota), and Medtronic (7227, 7250, 7271, and 7272; Medtronic, Inc, Minneapolis, Minnesota). The tachycardia detection rate was programmed according to the clinical presentation of each patient. For all patients the detection enhancements were activated immediately after ICD implantation. In single- and dual-chamber devices, the stability criterion was programmed at 40 to 50 ms, and the onset criterion was programmed at 15% to 20%. In all dual-chamber devices, the respective dual-chamber detection algorithms were activated.

Follow-up began at ICD implantation. At every follow-up visit (at 3-month intervals) or every visit prompted by ICD therapy, all stored data of tachyarrhythmia episodes were collected. Two independent researchers reviewed the stored electrocardiograms. In case of disagreement between the 2 reviewers about the stored electrocardiograms, a third reviewer was consulted and made a decision. For each episode, the date, type, morphology (monomorphic or polymorphic), and mean cycle length (CL) of the tachyarrhythmia and the type and outcome of delivered ICD therapy were recorded. A ventricular tachyarrhythmia was defined as an event with a sudden increase in rate combined with a change in electrocardiographic morphology from the baseline rhythm. If an atrial electrogram was present, the presence of atrioventricular dissociation was used to classify a ventricular tachyarrhythmia. Therapy delivered for atrial arrhythmias (including atrial fibrillation, atrial flutter, atrial tachycardia, and sinus tachycardia) was defined as inappropriate.

Continuous variables were evaluated using Student's *t* test or analysis of variance. The chi-square test was used for the analysis of categorical variables. The actuarial event-free rates from ventricular and atrial tachyarrhythmias triggering ICD therapy were calculated according to the Kaplan-Meier method. Differences between pairs of actuarial curves were tested by the log-rank test. Relative risks expressed as hazard ratios with 95% confidence intervals (CIs) were based on a Cox proportional-hazards model. Covariates previously identified to be independently associated with the occurrence of inappropriate ICD therapy were used in the multivariate model. A 2-tailed p value < 0.05 was considered significant.

The clinical characteristics are listed in Table 1. Coronary artery disease was present in 70% of the patients, nonischemic cardiomyopathy (excluding hyperthrophic

cardiomyopathy) in 30%, with dilation in 21%. Twenty-four percent received single-chamber devices, 53% dual-chamber devices, and 23% dual-chamber devices with cardiac resynchronization capability. The programmed mean detection CL of the VT zone was 377 ± 52 ms.

Table 1. *Patients' clinical characteristics (n=260)*

Characteristics	Value
Men	216 (83%)
Age (yrs)	60 ± 13
LVEF (%)	31 ± 14
Underlying cardiac disease	
Coronary artery disease	184 (71%)
Dilated cardiomyopathy	61 (24%)
History of atrial tachyarrhythmias	79 (29%)
Index arrhythmia	
Ventricular fibrillation	78 (30%)
VT	125 (48%)
Nonsustained VT	57 (22%)
Pharmacologic treatment at discharge	
Amiodarone	97(37%)
Betablockers	120 (46%)
Digoxin	57 (23%)
ACE inhibitor	189 (73%)
Diuretic	158 (61%)
Lipid-lowering drug	129 (50%)

ACE = angiotensin-converting enzyme

During a mean follow-up of 22 ± 16 months (range 1 to 60 months), 107 patients (41%) experienced ≥ 1 episode of sustained ventricular tachyarrhythmia, triggering ICD therapy. The actuarial event-free rates for ventricular tachyarrhythmias were 66.0%, 55.8%, and 45.0% at 1, 2, and 4 years, respectively. The mean CL of monomorphic VT was 333 ± 62 ms, for polymorphic VT or ventricular fibrillation, it was 223 ± 26 ms.

A total of 37 patients (14%) experienced inappropriate ICD therapy due to atrial tachyarrhythmias. The actuarial event-free rates for inappropriate therapy were 87.0%, 83.6, and 80.8%, at 1, 2 and 4 years, respectively (Figure 1). Nineteen patients experienced inappropriate therapy for atrial fibrillation at least once, and 18 patients received inappropriate therapy for sinus or atrial tachycardia. There was no significant difference between actuarial event-free rates for inappropriate therapy triggered by atrial fibrillation (94.4% and 88.8%) or atrial or sinus tachycardia (92.7%

and 91.3%), at 1 and 4 years, respectively. The mean ventricular CL during atrial fibrillation was 319 ± 44 ms (range 260 to 400 ms), for atrial or sinus tachycardia, the mean ventricular CL was 374 ± 48 ms (range 300 to 480 ms).

Figure 1. *Actuarial event rates for inappropriate device therapy*

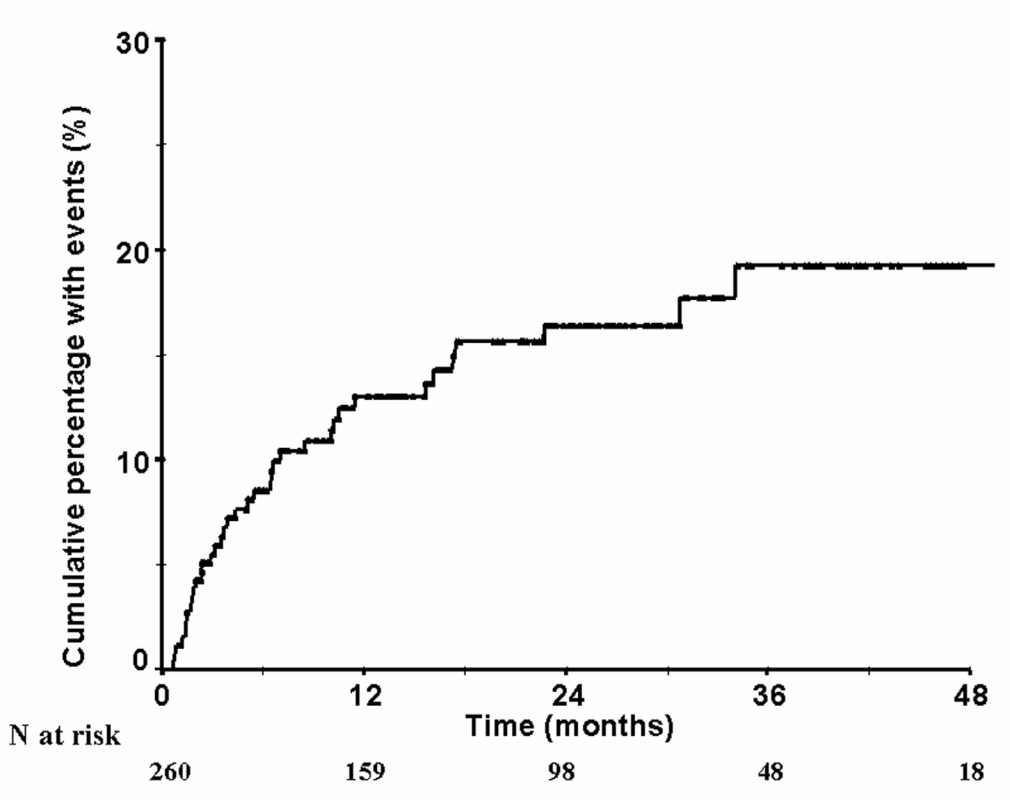
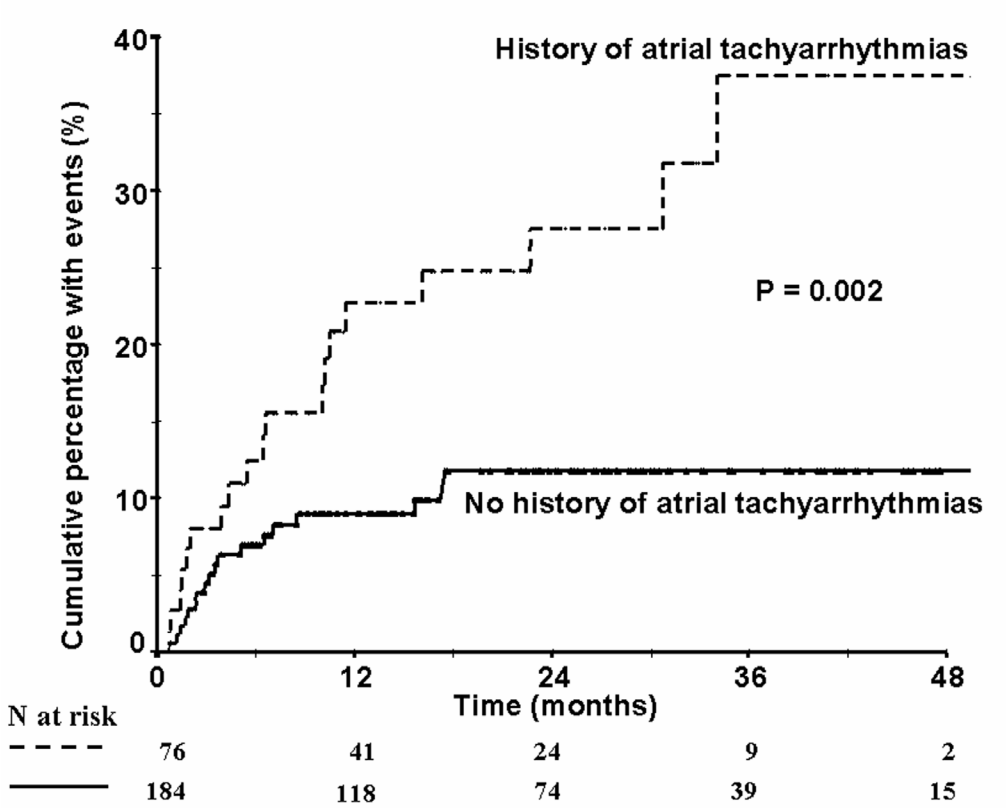


Table 2. *Comparison of patients with and without inappropriate device therapy*

Characteristic	Inappropriate ICD therapy (n = 37)	No inappropriate ICD therapy (n = 223)	p Value
Men	30 (81%)	186 (83%)	NS
Age (yrs)	61 ± 12	60 ± 13	NS
LVEF (%)	31 ± 14	31 ± 14	NS
Underlying cardiac disease			
Coronary artery disease	25 (68%)	159 (71%)	NS
Dilated cardiomyopathy	9 (24%)	52 (23%)	NS
History of atrial tachyarrhythmias	19 (51%)	57 (26%)	0.003
Index arrhythmia			
Ventricular fibrillation	12 (32%)	66 (30%)	NS
VT	19 (52%)	106 (47%)	NS
Nonsustained VT	6 (16%)	51 (23%)	NS
Pharmacologic treatment			
Amiodarone	12 (32%)	85 (38%)	NS
Betablockade	19 (51%)	101 (45%)	NS
Digoxin	11 (30%)	46 (21%)	NS
ACE inhibitor	30 (82%)	159 (74%)	NS
Diuretic	23 (62%)	135 (63%)	NS
Lipid-lowering drug	17 (46%)	112 (52%)	NS

Abbreviation as in Table 1

Figure 2. *Actuarial event rates for inappropriate device therapy for patients with and without a history of atrial tachyarrhythmias*



Clinical variables for patients with and without inappropriate device therapy are presnted in Table 2. Age, gender, LVEF, underlying cardiac disease, and pharmacologic treatment did not differ between those with and without inappropriate device therapy. The incidence of inappropriate device therapy was higher after a history of atrial tachyarrhythmias ($p = 0.003$). Additionally, inappropriate ICD therapy was noted more frequently in patients who received appropriate device therapy ($p = 0.001$).

To evaluate clinical predictors of inappropriate device therapy, variables were entered in a Cox proportional-hazards model (age, pharmacologic treatment, type of ICD, LVEF, CAD, cardiomyopathy, history of atrial tachyarrhythmias, and recurrent VT). This analysis revealed a history of atrial tachyarrhythmias and recurrent VT with CL $\geq$ 350 ms triggering device therapy as independent clinical predictors of inappropriate ICD therapy. The relative risk was 2.4 (95% CI 1.2 to 4.8, $p = 0.01$) for history of atrial tachyarrhythmias. This was supported by lower actuarial event-free rates for inappropriate device therapy for patients with a history of atrial tachyarrhythmias compared with patients without such a history (62.5% vs 88.2% at 4 years, $p = 0.002$; Figure 2).

The relative risk increased to 3.1 if patients had recurrent VT with CL $\geq$ 350 ms triggering device therapy (95% CI 1.5 to 6.3, $p = 0.002$). To address the question whether long interval programming explained this greater risk, we analyzed a detection interval of $\geq$ 350 ms as a tachycardia criterion. In multivariate analysis, this detection interval was not identified as an independent predictor for inappropriate therapy, with a relative risk of 2.2 (95% CI 0.6 to 7.5, $p = 0.21$). Although not significant, the programmed detection cycle length of the VT zone tended to be shorter in patients with inappropriate therapy compared with those without inappropriate therapy (386 ± 46 ms vs 371 ± 44 ms, $p = 0.06$). Proportionally, patients with dual-chamber devices experienced more inappropriate therapy compared with those with single-chamber devices (6% vs 17%, $p < 0.05$).

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The present study evaluated whether clinical characteristics could predict inappropriate ICD therapy due to atrial tachyarrhythmias. The observations noted in

this study are: (1) a history of atrial tachyarrhythmias is an independent predictor of inappropriate therapy and (2) recurrent VT with CL ≥ 350 ms triggering device therapy is associated with an increased risk for first inappropriate therapy.

In this study, the incidence of inappropriate ICD therapy was 14%. Most patients experienced an inappropriate ICD intervention in the first year after device implantation, regardless of primary and secondary prevention. These findings agree with studies reporting on inappropriate ICD therapy.[11,12] In the Antiarrhythmics Versus Implantable Defibrillators Trial, atrial tachyarrhythmias were responsible for inappropriate therapy in 22% of patients and 16% of all treated episodes.[12]

It is no surprise that patients with a history of atrial tachyarrhythmias are at risk for inappropriate intervention for atrial tachyarrhythmias. Given the epidemiology of atrial fibrillation, atrial tachyarrhythmias are common in ICD recipients, of whom most have structural heart disease.[13] More recently, it has been reported that a history of paroxysmal atrial fibrillation predicted a higher recurrence rate of atrial tachyarrhythmias.[14]

More notable is the association of recurrent VT with CL ≥ 350 ms with an increased risk for inappropriate therapy. The association between ventricular tachyarrhythmias and paroxysmal atrial tachyarrhythmias in ICD recipients has been established in previous studies.[15-17] Slow ventricular tachyarrhythmias were associated with left ventricular dysfunction (LVEF < 40%) and Class III antiarrhythmic drug therapy.[18] Another aspect to be addressed is the programmed detection interval. In case of slow ventricular tachyarrhythmias, an overlap with the ventricular rate of atrial tachyarrhythmias is present. The programmed detection interval was not identified in multivariate analysis as an independent predictor.

Whether device selection should depend on the knowledge of a history of atrial tachyarrhythmias is an open question, as inappropriate therapy occurs equally in patients with single- and dual-chamber devices. The addition of an atrial lead might improve the specificity of arrhythmia discrimination but introduces potential surgical and technical problems. This should be balanced against the potential minor advantages, such as the presence of slow ventricular tachyarrhythmias.

References

1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. NEJM 1996;335:1933-1940.
2. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. NEJM 1997;337:1576-1583.
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. NEJM 2002;346:877-883.
4. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1992;15:1667-1673.
5. Nunain SO, Roelke M, Trouton T, Osswald S, Kim YH, Sosa-Suarez G, Brooks DR, McGovern B, Guy M, Torchiana DF, Vlahakes GJ, Garan H, Ruskin JN. Limitations and late complications of third-generation automatic cardioverter-defibrillators. Circulation 1995;91:2204-2213.
6. Kuhlkamp V, Dornberger V, Mewis C, Suchalla R, Bosch RF, Seipel L. Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. J Cardiovasc Electrophysiol 1999;10:905-915.
7. Sticherling C, Schaumann A, Klingenheben T, Hohnloser SH. First worldwide clinical experience with a new dual chamber implantable cardioverter defibrillator: advantages and complications. Europace 1999;1:96-102.
8. Costeas XF, Link MS, Foote CB, Homoud MK, Wang PJ, Estes NA. Predictors of ventricular tachycardia recurrence in 100 patients receiving tiered therapy defibrillators. Clin Cardiol 2000;23:852-856.
9. Raitt MH, Klein RC, Wyse DG, Wilkoff BL, Beckman K, Epstein AE, Coromilas J, Friedman PL, Martins J, Ledingham RB, Greene HL. Comparison of arrhythmia recurrence in patients presenting with ventricular fibrillation versus ventricular tachycardia in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Am J Cardiol 2003;91:812-816.
10. Raitt MH, Dolack GL, Kudenchuk PJ, Poole JE, Bardy GH. Ventricular arrhythmias detected after transvenous defibrillator implantation in patients with a clinical history of only ventricular fibrillation. Implications for use of implantable defibrillator. Circulation 1995;91:1996-2001.

11. Gradaus R, Block M, Brachmann J, Breithardt G, Huber HG, Jung W, Kranig W, Mletzko RU, Schoels W, Seidl K, Senges J, Siebels J, Steinbeck G, Stellbrink C, Andresen D. Mortality, morbidity, and complications in 3344 patients with implantable cardioverter defibrillators: results from the German ICD Registry EURID. Pacing Clin Electrophysiol 2003;26:1511-1518.
12. Klein RC, Raitt MH, Wilkoff BL, Beckman KJ, Coromilas J, Wyse DG, Friedman PL, Martins JB, Epstein AE, Hallstrom AP, Ledingham RB, Belco KM, Greene HL. Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. J Cardiovasc Electrophysiol 2003;14:940-948.
13. Schmitt C, Montero M, Melichercik J. Significance of supraventricular tachyarrhythmias in patients with implanted pacing cardioverter defibrillators. Pacing Clin Electrophysiol 1994;17:295-302.
14. Wolpert C, Jung W, Spehl S, Schimpf R, Omran H, Schumacher B, Esmailzadeh B, Tenzer D, Mehra R, Luderitz B. Incidence and rate characteristics of atrial tachyarrhythmias in patients with a dual chamber defibrillator. Pacing Clin Electrophysiol 2003;26:1691-1698.
15. Tavernier RH, Kimman GP, Theuns DAMJ, Klootwijk AP, Kazmierczak J, Jordaens LJLM. Comparison of events and survival in dual- versus single chamber ICDs. Neth Heart J 1999;6:604-608.
16. Gronefeld GC, Mauss O, Li YG, Klingenheben T, Hohnloser SH. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. J Cardiovasc Electrophysiol 2000;11:1208-1214.
17. Stein KM, Euler DE, Mehra R, Seidl K, Slotwiner DJ, Mittal S, Markowitz SM, Lerman BB. Do atrial tachyarrhythmias beget ventricular tachyarrhythmias in defibrillator recipients? J Am Coll Cardiol 2002;40:335-340.
18. Bansch D, Castrucci M, Bocker D, Breithardt G, Block M. Ventricular tachycardias above the initially programmed tachycardia detection interval in patients with implantable cardioverter-defibrillators. Incidence, prediction and significance. J Am Coll Cardiol 2000;36:557-565.

Chapter 9

Prevention of Inappropriate Therapy in Implantable Cardioverter-Defibrillators: Results of a Prospective, Randomized Study of Tachyarrhythmia Detection Algorithms

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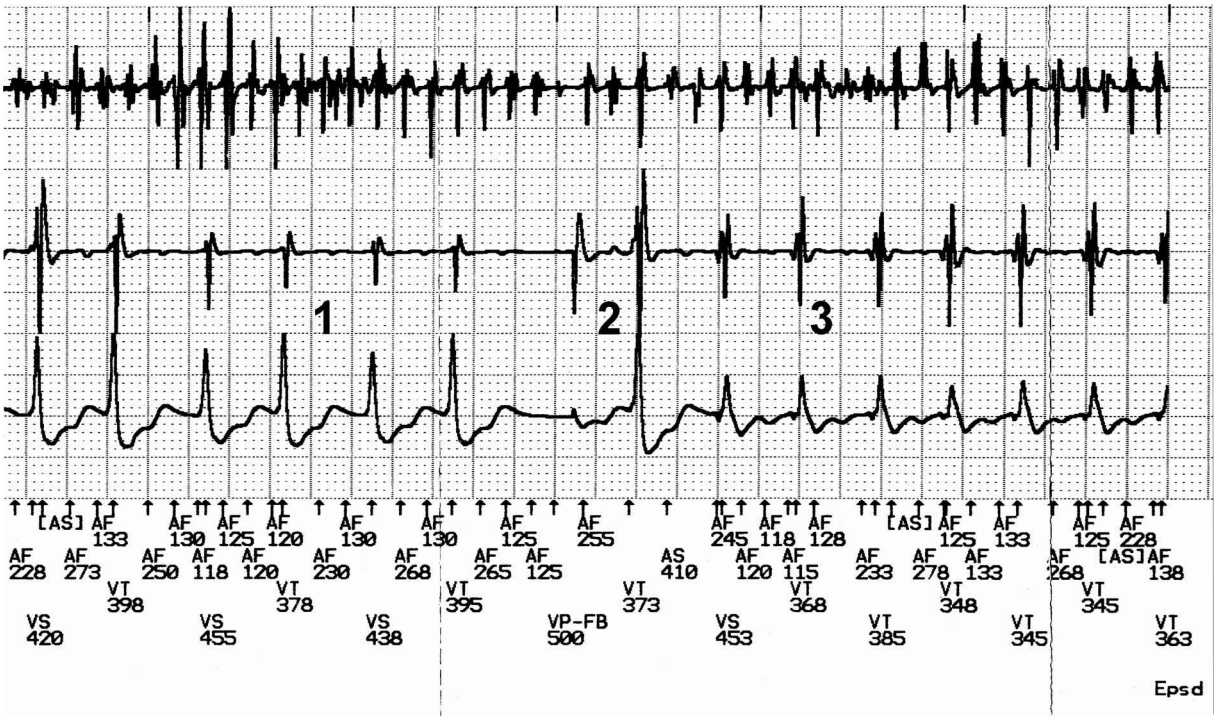
Published: Journal of American College of Cardiology 2004;44:2362-2367.



Abstract

Objectives: *The purpose of this randomized study was to investigate the performance of single- and dual-chamber tachyarrhythmia detection algorithms.*

Background: *A proposed benefit of dual-chamber implantable cardioverter-defibrillators (ICDs) is improved specificity of tachyarrhythmia detection.*

Methods: *All ICD candidates received a dual-chamber ICD and were randomized to programmed single- or dual-chamber detection. Of 60 patients (47 male, 58 ± 14 years, LVEF 30%), 29 had single-chamber and 31 dual-chamber settings. The detection results were corrected for multiple episodes within a patient with the generalized estimating equations (GEE) method.*

Results : *A total of 653 spontaneous arrhythmia episodes (39 patients) were classified by the investigators; 391 episodes were ventricular tachyarrhythmia (32 patients). All episodes of ventricular tachyarrhythmias were appropriately detected in both settings. In 25 patients, 262 episodes of atrial tachyarrhythmias were recorded. Detection was inappropriate for 109 atrial tachyarrhythmia episodes (42%, 18 patients). Rejection of atrial tachyarrhythmias was not significantly different between both groups (P=0.55). Episodes of atrial flutter/tachycardia were significantly more misclassified (P = 0.001). Overall, no significant difference in tachyarrhythmia detection (atrial and ventricular) between both settings was demonstrated (P=0.77).*

Conclusion: *The applied detection criteria in dual-chamber devices do not offer benefits in the rejection of atrial tachyarrhythmias. Discrimination of atrial tachyarrhythmias with stable atrioventricular relationship remains a challenge.*

Abbreviations and Acronyms

AF	= atrial fibrillation
AFL	= atrial flutter
AT	= atrial tachycardia
DC group	= dual-chamber supraventricular detection algorithm group
GEE	= generalized estimating equation
ICD	= Implantable Cardioverter-Defibrillator
SC group	= single-chamber supraventricular detection algorithm group
ST	= sinus tachycardia

Introduction

Despite the proven benefit from advancing implantable cardioverter-defibrillator (ICD) technology, a substantial proportion of ICD recipients experience inappropriate ICD therapy due to atrial tachyarrhythmias (1-5). In patients with a single-chamber device, inappropriate classification of atrial tachyarrhythmias occurs in approximately 20% to 30% of the patients (1,6,7). The development of dual-chamber devices provides the opportunity to improve the accuracy of tachyarrhythmia detection by the addition of atrial information (8,9). The superiority of detection algorithms in dual-chamber ICDs has not been proven so far. Prospective, randomized studies evaluating the efficacy of dual-chamber detection algorithms are lacking. The advantages of dual-chamber ICDs for accurate discrimination are small or even nonexistent (10,11). Even more, dual-chamber pacing offers no clinical advantage over ventricular backup pacing in ICD patients with no indication for cardiac pacing (12).

We designed a prospective, randomized study to compare the performance of tachyarrhythmia detection algorithms in single-chamber and dual-chamber ICDs.

Methods

Study design

The Prevention of Inappropriate (PINAPP) Therapy Study was a single-center, prospective, randomized study of patients comparing single- and dual-chamber discrimination criteria. All patients had a standard indication for ICD implantation for the treatment of ventricular tachyarrhythmias but without an indication for antibradycardia pacing. Patients with permanent atrial fibrillation (AF) or an indication for resynchronization therapy were excluded from the trial. The clinical characteristics of the patients are summarized in Table 1.

The local ethical committee approved the study. Written informed consent was obtained from all patients prior to enrollment in the study. All patients received a dual-chamber device. The patients were randomly assigned to have the device programmed to single-chamber supraventricular detection algorithms (SC group) or to the enhanced dual-chamber supraventricular detection algorithms (DC group). Random assignment was obtained by telephone to an independent service (Cardialysis, Rotterdam, the Netherlands).

Table 1. *Patient's clinical characteristics*

Patient Characteristics (n=60)			
	SC group (n=29)	**DC group (n=31)**	**p Value**
Gender (M/F)	24/5	23/8	NS
Age (years)	57 ± 17	61± 10	NS
LVEF (%)	29 ± 11	31 ± 10	NS
History of atrial arrhythmias (n)	8	7	NS
Underlying cardiac disease (n)			
CAD	21	26	NS
CMP (dilated)	6	3	NS
CMP (hyperthropic)	2	2	NS
Presenting arrhythmia (n)			
VF	7	9	NS
SMVT	17	15	NS
NSVT + inducible VT/VF	5	7	NS
Pharmacological treatment (n)			
Amiodarone	11	8	NS
β-blockers	17	17	NS
Digoxin	6	4	NS
No antiarrhythmic drug	7	7	NS
ACE inhibitor	21	26	NS
Diuretic	15	17	NS
Lipid-lowering drug	17	23	NS

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CMP = cardiomyopathy; DC group = dual-chamber supraventricular detection algorithm group; LVEF = left ventricular ejection fraction; NS = nonsignificant; NSVT = non-sustained ventricular tachycardia; SC group = single-chamber supraventricular detection algorithm group; SMVT = sustained monomorphic ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia

Device description

The devices implanted in this study were, in equal numbers and randomized order, the Prizm DR (Guidant, St. Paul, Minnesota) and the Tachos DR (Biotronik, Berlin, Germany). The pulse generator and endocardial leads were inserted through a single left pectoral incision. The endocardial lead used for the high right atrium was a bipolar active-fixation lead with an interelectrode spacing of 8.9 mm (model 5076, Medtronic Inc, Minneapolis, Minnesota). Far-field R-wave sensing in the atrial electrogram was to be excluded. If present, the atrial lead was relocated until appropriate sensing could be achieved.

Discrimination of tachyarrhythmias

In both the SC group and DC group, the onset and stability criterion are provided to inhibit therapy in case of an atrial arrhythmia. In addition, dual chamber devices have "enhanced discrimination" criteria to differentiate atrial from ventricular arrhythmias. In the Prizm DR, enhanced criteria are: 1) the "ventricular rate > atrial rate" criterion, and 2) the "AF rate threshold" criterion. When the ventricular rate > atrial rate (V > A) is programmed, onset and stability are ignored, and therapy will be delivered. The AF rate threshold (Afib threshold) criterion is programmed in conjunction with stability. The aim of this feature is to suppress inappropriate therapy for fast ventricular rates secondary to AF or atrial flutter (AFL). If the ventricular rhythm is classified unstable and the atrial rate is higher than the programmed Afib threshold, therapy is withheld (13).

The Tachos DR employs the SMART algorithm (Biotronik) as enhanced discrimination. This algorithm is based on continuous analysis of the average atrial and ventricular rate and their atrioventricular relationship which results in 3 rate-branches (VV < AA, VV > AA, and VV = AA). The features of this algorithm have been described in detail (14).

Table 2. *Programming of detection algorithms in the SC group and DC group*

	SC group		DC group	
	Biotronik	**Guidant**	**Biotronik**	**Guidant**
Onset (%)	15	16	15	16
Stability (ms)	40	40	40	40
SMART	OFF	NA	ON	NA
V>A	NA	OFF	NA	ON
Afib threshold	NA	OFF	NA	200/min

AF = atrial fibrillation; NA not applicable; V > A = ventricular rate > atrial rate; Other abbreviations as in Table 1.

Programmation of the devices

Throughout the study, the devices were programmed similarly as far as possible to facilitate comparison between both groups (Table 2). For all patients, the tachyarrhythmia detection algorithms were activated immediately after implantation. The SC group was programmed to supraventricular tachycardia discrimination on the basis of ventricular rate combined with onset (15 to 16%) and stability (40 ms). For the DC group, tachyarrhythmia discrimination was programmed to onset (15 to 16%) and stability (40 ms), and all applicable enhanced algorithms were activated. Safety

timers were not activated in both groups. The tachycardia detection zones were programmed to recognize fibrillation and either one or two tachycardia zones. The bradycardia support was programmed to VVI with a lower rate of 40/min for the SC group. The DC group was set to the DDI mode with a lower rate of 40/min. The storage of intracardiac electrograms was programmed to collect both atrial and ventricular bipolar electrograms and markers for all patients.

End points

The primary end point in the study was the deliverance of inappropriate therapy for atrial arrhythmias. Secondary end points were appropriate and inappropriate arrhythmia classification. All spontaneous episodes detected either as ventricular tachyarrhythmia or as atrial tachyarrhythmia with stored electrograms were retrieved from the device's memory. Two independent experienced physicians analyzed the stored episodes to assess the type of the clinical arrhythmia and the appropriateness of device classification. In case of doubt, a third physician was consulted to provide the decision. The stored arrhythmias were classified as: 1) ventricular arrhythmia, or 2) atrial arrhythmia without a co-existent ventricular arrhythmia. The atrial arrhythmias were further classified as AF, AFl, atrial tachycardia (AT), and sinus tachycardia (ST). Atrial fibrillation was assumed to occur if the atrial electrogram showed a changing morphology. The diagnosis of AFL was based on regular AA intervals and no changes in morphology of the atrial electrogram. The prerequisite of ST and AT was an atrial electrogram preceding the ventricular electrogram. Sinus tachycardia was diagnosed if the ventricular rhythm showed a gradual increase in heart rate with an unchanged morphology of the atrial and ventricular electrogram. In contrast, the diagnosis of AT was based on a sudden increase of the ventricular rate and a change in morphology of the atrial electrogram.

Statistical analysis

Based on the assumption of a 30% reduction in the incidence of inappropriate therapy with dual-chamber devices, 27 patients were required in each arm, for a power of 80% and a probability value of 0.05.

Continuous variables were expressed as mean values ± SD. Chi-square testing was used for analysis of categorical variables, and Student *t* test was used for analysis of continuous variables. A p value < 0.05 was considered statistically significant.

The set of tachyarrhythmia episodes cannot be considered as independent because patients contribute one or more tachyarrhythmia episodes to the dataset. To correct for these factors, statistical analysis was performed by using the generalized estimating equations (GEE) statistical method with an exchangeable correlation structure to correct the varying number of episodes that were obtained from each patient (15,16). Only episodes with a stored electrogram and the physician's classification were included in the analysis. Statistical analysis was performed with SPSS for Windows (release 10.1, SPSS Inc., Chicago, Illinois) and SAS for Windows (release 8.2, SAS Institute, Cary, North Carolina).

Calculations were based on the possibility to accurately detect ventricular arrhythmias (true positive [TP]), accurately detect atrial arrhythmias (true negative [TN]), falsely detect atrial arrhythmias as ventricular (false positive [FP]), and falsely detect ventricular arrhythmias as atrial (false negative [FN]). The sensitivity of detection algorithms is the probability that a ventricular arrhythmia is detected when present: [TP/(FN + TP)]. The specificity of detection algorithms is the ability to reject atrial tachyarrhythmias. An absolute specificity cannot be calculated. The specificity is dependent on the prevalence of atrial tachyarrhythmias and the programmed detection interval of the device. Therefore, we calculated the positive predictive value of the detection algorithm, as follows: [TP /(TP + FP)].

Results

Patient population

Sixty patients were included in the study. Twenty-nine patients were randomly assigned to the SC group and 31 to the DC group. Fifteen patients in the SC group were randomized to Biotronik and 14 patients to Guidant. In the DC group, 14 patients were randomized to Biotronik and 17 patients to Guidant. Baseline clinical

characteristics did not differ between the two groups (Table 1). At the time of implantation, all patients had sinus rhythm. A history of atrial tachyarrhythmias was documented in 15 patients (25%), paroxysmal AF in 11 patients (18%), paroxysmal AFL in 2 patients (3%). Pharmacological treatment at discharge was not significantly different between both groups. Antiarrhythmic drug therapy was amiodarone in 19 patients (32%), beta-blockade in 34 patients (57%), and 10 patients (17%) received digoxin.

Five patients (8%) had 2 tachycardia zones activated. In four of these patients, the programmed detection criteria were applicable to both tachycardia zones. The programmed fibrillation and tachycardia zones were 290 ± 14 ms and 387 ± 34 ms, respectively. The programmed tachycardia detection interval was not significantly different between the two groups (SC group, 379 ± 31 ms versus DC group, 389 ± 35 ms).

Spontaneous tachyarrhythmias

The mean follow-up was 12 months, with a cumulative follow-up of 717 months. During this follow-up, 653 tachyarrhythmia episodes with stored electrogram occurred in 39 patients (range 1 to 89 episodes per patient). Figure 1 presents a tree diagram that outlines the results of arrhythmia detection for each of the 653 stored tachyarrhythmia episodes. Based on the physician classification, there were a total of 391 episodes of true ventricular tachyarrhythmias in 32 patients (mean ventricular rate 358 ± 77 ms). In 25 patients, 262 episodes of true atrial tachyarrhythmias (mean ventricular rate 368 ± 32 ms) occurred. In Figure 2, the number of episodes for the two study groups is presented. In the SC group, 166 episodes of ventricular tachyarrhythmias were recorded in 16 patients (range 1 to 57 episodes per patient); in the DC group, 225 episodes in 16 patients (range 1 to 89 episodes per patient). All ventricular tachyarrhythmias were appropriately detected in both groups. The sensitivity for ventricular tachyarrhythmias in both groups was 100%.

Figure 1. *Tree diagram showing the results for 653 stored spontaneous tachyarrhythmia episodes. DC group = dual-chamber supraventricular detection algorithm group; EGM = electrogram; pts = patients; SC group = single-chamber supraventricular detection algorithm group; SVT = supraventricular tachyarrhythmias; VT = ventricular tachycardia.*

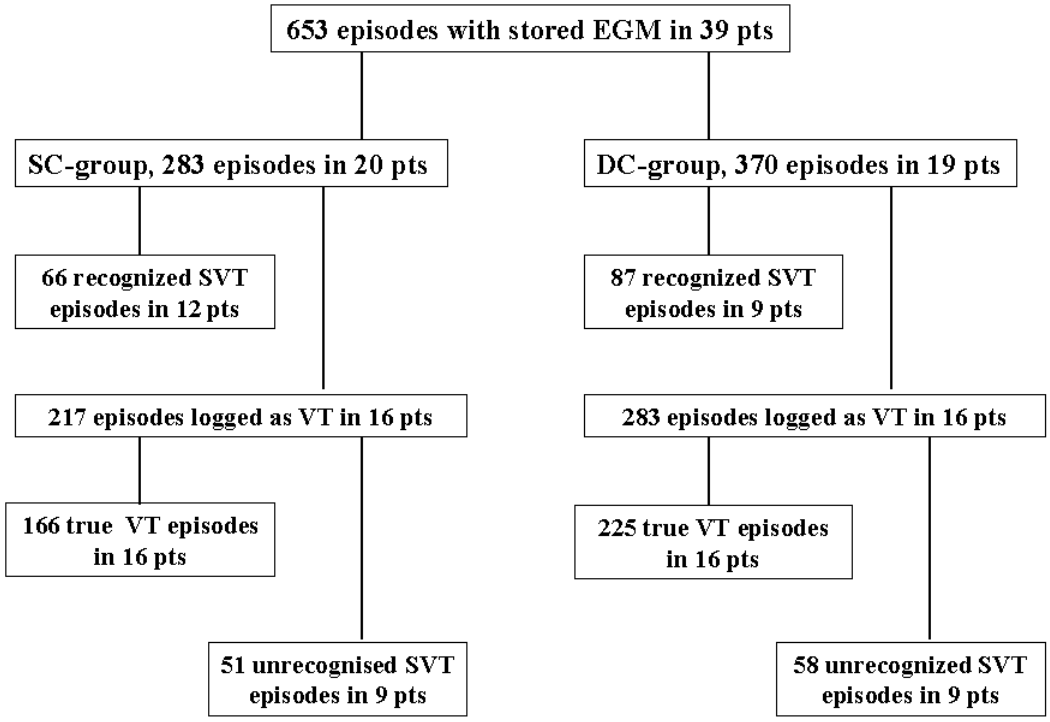
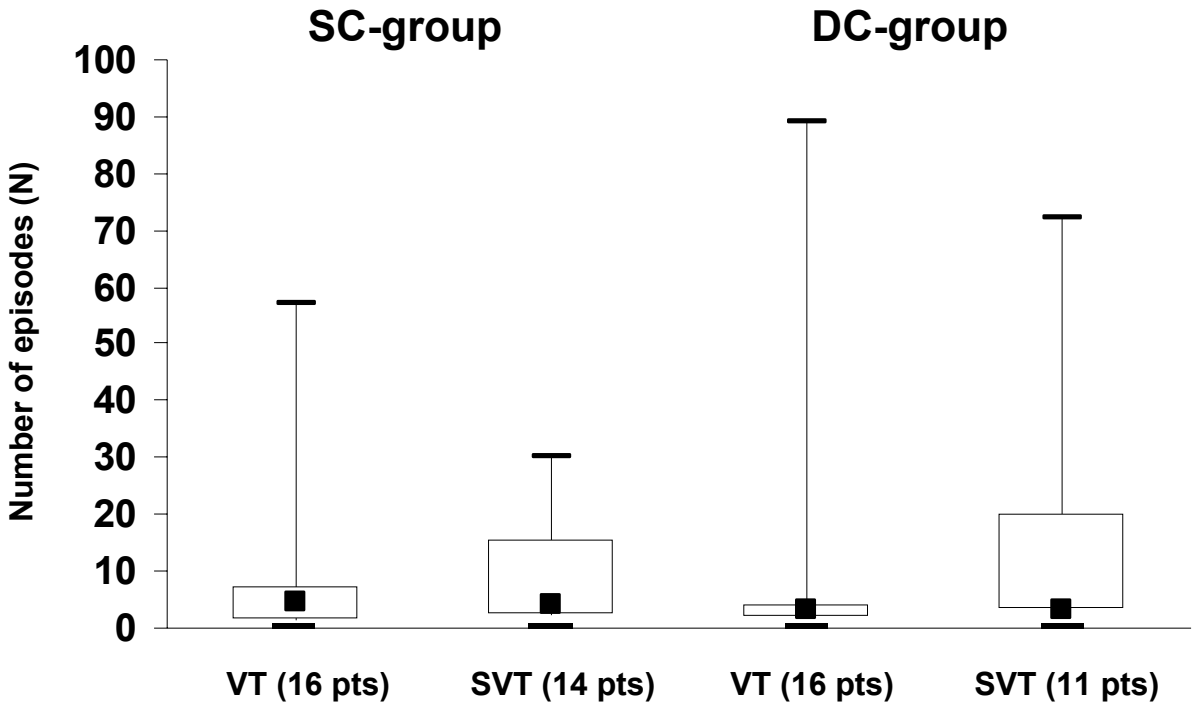


Figure 2. *Number of spontaneous episodes per patient for the two study groups. The error bars extend down to the minimum value and up to the maximum value. The box extends from the 25th percentile to the 75th percentile, with a black box at the median (50th percentile).Abbreviations as in Figure 1.*



Of the 262 atrial tachyarrhythmia episodes in the ventricular tachyarrhythmia detection window, 153 (58%) were detected as atrial tachyarrhythmia and not as ventricular tachyarrhythmia (20 patients). Inappropriate detection was observed in 109 atrial tachyarrhythmia episodes (18 patients). The mean ventricular rate of misclassified atrial tachyarrhythmias was significantly shorter as compared to rejected atrial tachyarrhythmias (354 ± 30 ms vs. 378 ± 30 ms; $p < 0.001$). The number of misclassified episodes was not significantly different between both groups (51 in the SC group versus 58 in the DC group). Analysis performed with the GEE method demonstrated no significant difference in the rejection of spontaneous atrial tachyarrhythmias between single- and dual-chamber devices ($p = 0.56$). The detection of ventricular tachyarrhythmias and the rejection of atrial tachyarrhythmias was not significantly different between both groups ($p = 0.77$). The specificity and positive predictive value of arrhythmia discrimination were 56% and 76% in SC group, versus 60% and 79% in DC group, respectively.

During 60 atrial tachyarrhythmia episodes (13 patients), inappropriate device therapy was delivered. The number of inappropriately treated episodes was not significantly different between the two groups (28 in the SC group vs. 32 in the DC group).

Subanalysis of atrial tachyarrhytmias

The misclassified atrial tachyarrhythmias are presented in Table 3. Subanalysis of the type of atrial arrhythmia and the appropriateness of classification was perfomed with the GEE method. Analysis demonstrated a significantly higher misclassification in case of AFL/AT compared with ST and AF ($p = 0.001$). The misclassified episodes of AT/AFL had a sudden onset > 16% and a regular ventricular response (stability < 40 ms). Episodes of ST were misclassified due to the presence of ventricular premature beats, which resulted in false sudden onset calculations or false V > A detection in dual-chamber devices.

Table 3. *Inappropriate classification of spontaneous atrial tachyarrhythmias for both groups*

		Misclassified episodes		
Arrhythmia	**(n)**	**SC group (%)**	**DC group (%)**	**p Value**
Atrial fibrillation	89	38 (2 patients)	26 (4 patients)	NS
Atrial flutter	30	47 (1 patient)	50 (1 patient)	NS
Atrial tachycardia	63	97 (6 patients)	96 (5 patients)	NS
Sinus tachycardia	80	5 (1 patient)	18 (2 patients)	NS

DC-group = dual chamber group; NS = non siginificant; SC-group = single chamber group

Discussion

The present prospective, randomized study evaluated the performance of tachyarrhythmia detection algorithms in single-chamber and dual-chamber ICDs. Although identical programmed stability and onset values, the number of inappropriate classifications with dual-chamber detection was not significantly reduced as compared to single-chamber detection.

Inappropriate ICD therapy for atrial tachyarrhythmias is the most common adverse event in ICD recipients with single chamber devices (17). With the development of dual-chamber cardioverter-defibrillators, it was anticipated that these devices could improve arrhythmia detection by providing additional information about the underlying atrial rhythm. In previous studies, enhanced detection algorithms in dual-chamber devices based on the atrioventricular relationship could accurately discriminate atrial from ventricular tachyarrhythmias (8,9). However, most of the studies were restricted to one manufacturer and mainly focused on the technical performance of the implanted device (8,14,18-20). Prospective, randomized studies to evaluate the efficacy of enhanced detection algorithms to decrease the incidence of inappropriate therapies are lacking in a well-defined population.

Accuracy of tachyarrhythmia detection

The primary goal of the ICD is to detect and subsequently terminate life-threatening ventricular tachyarrhythmias. When evaluating tachyarrhythmia detection criteria in our study, the sensitivity for detection of ventricular tachyarrhythmias was 100% for both study groups. Single-chamber and dual-chamber ICDs were equally safe and effective in treating ventricular tachyarrhythmias. This is in agreement with other device trials (8,10,11,14,18,19).

The secondary goal of the ICD is to deliver therapy only when required. Thus, accurate discrimination between atrial and ventricular tachyarrhythmias is an important clinical issue. The overall incidence of inaccurately detected tachyarrhythmias by the device was 16.7%. This finding is in agreement with studies reporting on inappropriate ICD therapy (21,22). We found no significant difference in the number of misclassified episodes between both groups (51 episodes, SC group vs. 58 episodes, DC group). The results in our study demonstrated that enhanced detection criteria in single-chamber and dual-chamber ICDs are equally effective in the rejection of atrial tachyarrhythmias. This finding is confirmed by previous comparisons of enhanced detection criteria between single- and dual-chamber ICDs (10,11). They reported no reduction or even an excess of inappropriate ICD therapies in dual-chamber devices. The failure of detection enhancements in dual-chamber devices to withhold therapy for atrial tachyarrhythmias was attributed by the authors to atrial sensing problems. Inappropriate classification of atrial tachyarrhythmias due to atrial sensing problems was also reported in other studies (19,23).

Limitations of the applied enhanced detection criteria

The strength and weakness of enhanced detection criteria are dependent on the frequency and distribution of atrial tachyarrhythmias. The complete picture of the performance of detection criteria is provided not only by statistical measures. The picture is complemented with observations during misclassified atrial tachyarrhythmias. The observed weaknesses of the applied detection criteria to discriminate between atrial and ventricular tachyarrhythmias were the presence of: 1) atrial tachyarrhythmias with stable N:1 atrioventricular conduction, and 2) ST with the presence of ventricular premature beats.

Atrial tachyarrhythmias with stable atrioventricular conduction

In both settings, detection was inappropriate in the majority of atrial tachyarrhythmias with a fixed N:1 atrioventricular conduction (AT and AFL). In single-chamber setting, the sudden onset (onset $>$ 16%) and the stable ventricular response (stability $<$ 40 ms) fulfilled ventricular tachyarrhythmia detection. Given the priority of single-chamber detection criteria, the additional dual-chamber detection enhancement “Afib threshold” cannot decrease the incidence of inappropriate detections for atrial tachyarrhythmias with stable N:1 atrioventricular conduction. A recent study

confirmed the high incidence of inappropriate classification of ATs with stable 1:1 atrioventricular conduction (24).

Dual-chamber algorithms analyzing the atrioventricular conduction have the possibility to detect stable atrial tachyarrhythmias with N:1 atrioventricular conduction. Despite the use of the dual-chamber algorithm SMART, a variation in the calculated mean atrial rates led to inappropriate therapy in 2:1 conducted atrial flutter. A progressively prolonging atrioventricular conduction interval can be misclassified as ventricular tachycardia with retrograde conduction. This problem has been reported as the most common failure of the PR Logic algorithm (Medtronic Inc.) (19,25).

ST

In case of ventricular premature beats during ST, the dual-chamber detection enhancement “V > A” can act as an accelerator of inappropriate detection. During a ventricular premature beat, the normal atrial activation might be not sensed due to the atrial blanking period after a sensed ventricular event, which fulfills the detection enhancement “V > A”. Another problem associated with premature ventricular beats is the inappropriate calculation of a sudden onset. This problem has also been reported in previous studies (26,27).

Comparison with other studies

A comparison of the performance of the applied detection criteria with other studies is difficult because the applied detection criteria, the number of episodes, the number of patients, and the methodology differ between the published studies. In an open-label non-randomized study comparing single- and dual-chamber devices, the incidence of inappropriate therapies during AF was significantly higher in dual-chamber devices compared to single-chamber devices (41% vs. 24%) (10). In a recent prospective, randomized study between single- and dual-chamber devices, no differences in performance of detection criteria were observed (11). However, the results must be interpreted with caution, because all inappropriate therapies, including those in the ventricular fibrillation zone and those not related to atrial tachyarrhythmias, were considered in the study by Deisenhofer et al. (11).

Studies with dual-chamber ICDs have reported high sensitivity and specificity values for the applied dual-chamber algorithm. In a recent study with the PARAD algorithm

(ELA Medical, Le Plessis Robinson, France), a specificity of 89.2% on a per episode basis and 91.6% on a per patient basis were reported (20). Despite the high overall specificity, the performance during atrial fibrillation was poor (47.2% of 53 episodes were inappropriately detected). Studies evaluating the PR Logic algorithm reported lower specificity values of 66.6% or 72% on a per episode basis (19,25). For Guidant devices, the performance of “Afib threshold” and “V > A“ in conjunction with a more aggressively programmed onset (9%) and stability (24 ms) was recently reported with a specificity of 89% (24).

Limitations of the study

We used devices from only 2 manufacturers to assess the accuracy of atrial tachyarrhythmia detection in single- and dual-chamber ICDs. The results of our study must therefore be interpreted with caution. The findings of the study do not reflect the status of current detection algorithms in general. Current devices can apply morphology discrimination in conjunction with timing-based detection algorithms. The present study evaluated only timing-based detection algorithms. The predefined programming of the onset (16%) and stability criterion (40 ms) in the Guidant dual chamber devices reduced the potential advantage of the enhancement criteria (“V > A” and “Afib threshold”) (24). A more aggressive onset and stability will first cause a loss in sensitivity but an increase in specificity.

“V > A” will compensate the loss in sensitivity. As our study demonstrated that not ST nor AF but AT and AFL with a fixed N:1 conduction were the problem, it is very unlikely that lower stability values would have changed the results. Another possible limitation is the number of patients. However, 653 episodes of tachyarrhythmias were analyzed. The programmed detection rate affects both the distribution of the type of atrial tachyarrhythmias as well as the relative number of atrial tachyarrhythmias presenting to the detection algorithms. In our study, the programmed detection rate was similar for both groups.

Conclusion

In this study, using stored atrial electrograms from dual-chamber devices, the applied detection criteria in single- and dual-chamber setting were equally effective for detection of ventricular tachyarrhythmias and the rejection of atrial tachyarrhythmias. This was true for this study group without a bradycardia indication. Both subgroups were comparable in terms of underlying heart disease, indication for implantation, antiarrhythmic drug therapy, and follow-up period. This has important repercussion on health care in general as in recent ICD trials hospital readmissions due to new or worsened heart failure increased (5,12). This higher incidence was related to dual chamber bradycardia pacing in patients without a bradycardia pacing indication. With the increasing indications for ICD implantation, a matter of debate is the device selection. The rules for device selection for patients with a primary prevention indication can be different from those applied for patients with a secondary prevention indication. Nevertheless, to avoid inappropriate therapy, it is particularly important to program carefully the enhanced detection criteria of the device, irrespective of the indication. Further work should be done to improve arrhythmia discrimination, in particular for atrial tachyarrhythmias with stable atrioventricular conduction, which was most often misclassified.

References

1. O'Nunain S, Roelke M, Trouton T*, et al.* Limitations and late complications of third-generation automatic cardioverter-defibrillators. Circulation 1995;91:2204-13.
2. Moss AJ, Hall WJ, Cannom DS*, et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.
3. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-83.
4. Buxton AE, Lee KL, DiCarlo L*, et al.* Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 2000;342:1937-45.
5. Moss AJ, Zareba W, Hall WJ*, et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
6. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 1992;15:1667-73.
7. Schmitt C, Montero M, Melichercik J. Significance of supraventricular tachyarrhythmias in patients with implanted pacing cardioverter defibrillators. Pacing Clin Electrophysiol 1994;17:295-2.
8. Lavergne T, Daubert JC, Chauvin M*, et al.* Preliminary clinical experience with the first dual chamber pacemaker defibrillator. Pacing Clin Electrophysiol 1997;20:182-88.
9. Nair M, Saoudi N, Kroiss D, Letac B. Automatic arrhythmia identification using analysis of the atrioventricular association. Application to a new generation of implantable defibrillators. Participating Centers of the Automatic Recognition of Arrhythmia Study Group. Circulation 1997;95:967-73.
10. Kuhlkamp V, Dornberger V, Mewis C*, et al.* Clinical experience with the new detection algorithms for atrial fibrillation of a defibrillator with dual chamber sensing and pacing. J Cardiovasc Electrophysiol 1999;10:905-15.
11. Deisenhofer I, Kolb C, Ndrepepa G*, et al.* Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillators in reducing inappropriate therapy? A randomized, prospective study. J Cardiovasc Electrophysiol 2001;12:134-42.

12. Wilkoff BL, Cook JR, Epstein AE*, 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.
13. Guidant Corporation. *Physician's system manual, Prizm DR 1860/1861*. St Paul, MN: Guidant Corporation, Cardiac Pacemakers Inc 2000;3-15 – 3-27.
14. Theuns D, Klootwijk AP, Kimman GP*, et al.* Initial clinical experience with a new arrhythmia detection algorithm in dual chamber implantable cardioverter defibrillators. Europace 2001;3:181-86.
15. Liang KY, Zeger S. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13-22.
16. Zeger S, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. Biometrics 1988;44:1049-60.
17. Rosenqvist M, Beyer T, Block M*, et al.* Adverse events with transvenous implantable cardioverter-defibrillators: A prospective multicenter study. Circulation 1998;98:663-70.
18. Sticherling C, Schaumann A, Klingenheben T, Hohnloser SH. First worldwide clinical experience with a new dual chamber implantable cardioverter defibrillator: advantages and complications. Europace 1999;1:96-102.
19. Wilkoff BL, Kuhlkamp V, Volosin K*, et al.* Critical Analysis of Dual-Chamber Implantable Cardioverter- Defibrillator Arrhythmia Detection: Results and Technical Considerations. Circulation 2001;103:381-86.
20. Sadoul N, Jung W, Jordaens L*, et al.* Diagnostic performance of a dual-chamber cardioverter defibrillator programmed with nominal settings: a European prospective study. J Cardiovasc Electrophysiol 2002;13:25-32.
21. Gradaus R, Block M, Brachmann J*, et al.* Mortality, morbidity, and complications in 3344 patients with implantable cardioverter defibrillators: results from the German ICD Registry EURID. Pacing Clin Electrophysiol 2003;26:1511-18.
22. Klein RC, Raitt MH, Wilkoff BL*, et al.* Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. J Cardiovasc Electrophysiol 2003;14:940-48.
23. Israel CW, Gronefeld G, Iscolo N, Stoppler C, Hohnloser SH. Discrimination between ventricular and supraventricular tachycardia by dual chamber cardioverter defibrillators: importance of the atrial sensing function. Pacing Clin Electrophysiol 2001;24:183-90.
24. Kouakam C, Kacet S, Hazard JR*, et al.* Performance of a dual-chamber implantable defibrillator algorithm for discrimination of ventricular from supraventricular tachycardia. Europace 2004;6:32-42.
25. Kuhlkamp V, Wilkoff BL, Brown AB*, et al.* Experience with a dual chamber implantable defibrillator. Pacing Clin Electrophysiol 2002;25:1041-48.

26. Swerdlow CD, Chen PS, Kass RM, Allard JR, Peter CT. Discrimination of ventricular tachycardia from sinus tachycardia and atrial fibrillation in a tiered-therapy cardioverter-defibrillator. J Am Coll Cardiol 1994;23:1342-55.
27. Weber M, Bocker D, Bansch D*, et al.* Efficacy and safety of the initial use of stability and onset criteria in implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 1999;10:145-53.

Chapter 10

Analysis of Stored Electrograms in Implantable Cardioverter-Defibrillators: Application of Blocks with Physiologic Information

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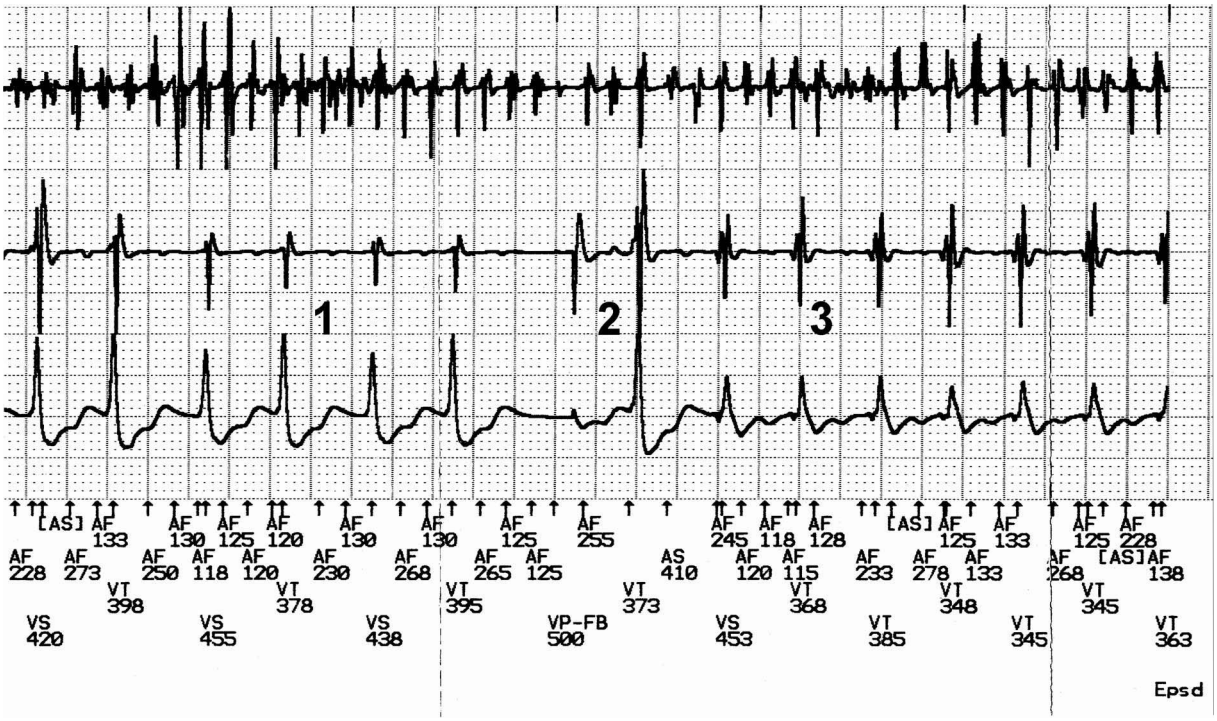
Submitted for publication 2004.



Abstract

Stored electrograms in implantable cardioverter-defibrillators (ICDs) have not only improved our patient management, but also increased our understanding of tachyarrhythmias. Stored electrograms are usually visual analysed by physicians. The analysis can be performed in a methodological way by application of blocks with physiologic information. Each block contains specific timing or morphology based characteristics of arrhythmias. A systematic approach is proposed, which can help physicians and technicians to avoid bias in the analysis.

Introduction

From the time of introduction of the ICD, the device has evolved from a simple shock-box to a complete arrhythmia management device. The improvements in arrhythmia treatment have paralleled the advances in diagnostic information. The current generation of ICDs offers an array of diagnostic information, including stored electrograms. Analysis of this diagnostic information has not only improved the management of patients but also contributed to an increased understanding of triggers precipitating delivered or aborted device therapy.

This article will provide an overview of diagnostic capabilities of stored electrograms. We will present the evolution of diagnostic information in ICD, and we propose the application of blocks with physiologic information for analysis of stored electrograms.

Historical perspective of diagnostic information in ICDs

In the first-generation devices, the definition of “appropriate” therapy relied on the clinical history of the patient, the presence or absence of hemodynamically significant symptoms, or concomitant ECG monitoring. The second-generation ICDs had recording of RR intervals with device activity markers or simply numerical. This storage allowed analysis of the rate of the arrhythmia preceding and following ICD therapy. Differentiation of arrhythmias was based on the regularity of RR intervals. Irregular RR intervals suggested atrial fibrillation (AF), while regular RR intervals could indicate sinus tachycardia, arial flutter, or atrial tachycardia as well as ventricular tachycardia. Interpretation of the appropriateness of therapy was the major limitation in first- and second-generation devices.[1] Appropriate ICD therapy for ventricular arrhythmias without hemodynamically symptoms was demonstrated in patients.[2,3] As a consequence, clinical decision-making in patients treated with the first- and second-generation devices was associated with uncertainty. With third-generation devices, the most significant advance in diagnostic information was the storage of intracardiac electrogram recordings. This diagnostic information included recording of RR intervals preceding and following the arrhythmia, and stored electrograms with real-time marker channels of arrhythmias triggering ICD therapy.

Electrogram sources

The current generation of devices can be programmed to record events from different electrogram sources. The electrograms can be recorded from the pair of electrodes used for rate sensing (near-field), the defibrillation coils (far-field or wide-band) or both. Both electrogram sources have advantages and disadvantages. Near-field ventricular electrograms show no atrial activity, which could result in the inability to discriminate between atrial and ventricular tachyarrhythmias. However, they can provide information on detection problems, such as the presence of over- or undersensing of signals. In contrast, far-field electrograms have the advantage of reflecting atrial activity and electrogram morphology changes, which can be both helpful in arrhythmia diagnosis by the physician. This resembles a surface ECG, which is leaving uncertainty as well.

Visual analysis of stored electrograms

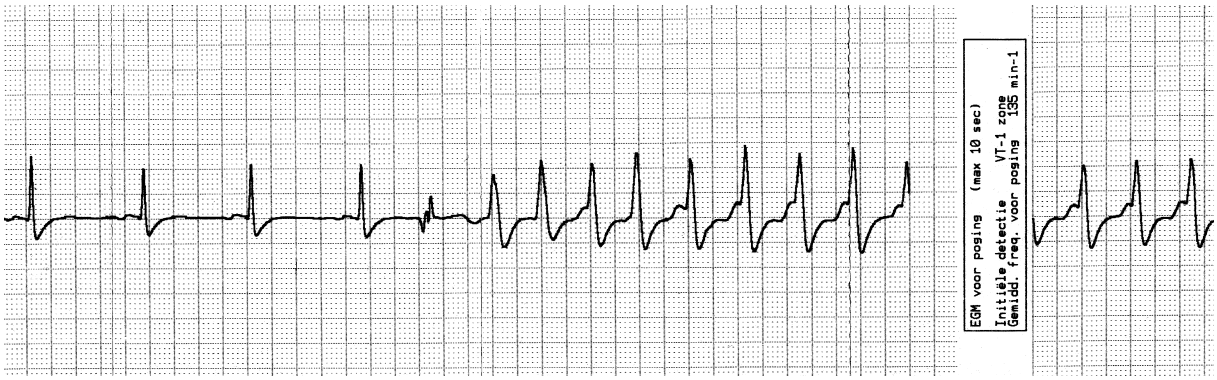
Tachyarrhythmia detection algorithms in devices use combinations of information derived from intracardiac atrial and ventricular events. Tachyarrhythmia detection is generally performed in a stepwise process using “blocks” of physiologically relevant information. Each block has a specific timing or morphological aspect, which contains characteristics of tachyarrhythmias. These blocks with physiological information can be applied in the visual analysis of stored electrograms.

Single chamber devices

In single chamber devices, “blocks” are derived from the sensed ventricular activity. Device activity markers are usually interpreted during visual analysis. Each block has clinical information, but limitations to discriminate between atrial and ventricular tachyarrhythmias are inherent to single chamber devices. The widely used block ‘ventricular electrogram morphology’ is mainly based on the premise that the electrogram morphology will change during ventricular tachyarrhythmias as compared to a supraventricular baseline rhythm (Figure 1). A distinct change in the electrogram morphology was identified in 93% of induced ventricular tachycardias.[4] The analysis of far-field electrograms permits a more accurate arrhythmia classification. However, the development of rate-dependent aberrancy during supraventricular tachycardia alters the electrogram morphology as compared to

baseline sinus rhythm.[5] Specifically, a change in electrogram morphology was predominantly observed at recording sites ipsilateral to the bundle branch block.[6] It was demonstrated that the combined use of electrogram morphology, rate characteristics, and VV interval stability allowed a correct diagnosis in 97% of the events.[7]

Figure 1. *Stored bipolar shock electrogram demonstrating a change in electrogram morphology during ventricular tachycardia as compared to the supraventricular baseline rhythm. (Guidant, model Mini IV)*



The block 'VV interval stability' is used to discriminate between monomorphic ventricular tachycardia, characterized by regular ventricular intervals, and atrial fibrillation characterized by irregular ventricular intervals. The limitation of this block is the regular ventricular response during atrial tachyarrhythmias with fixed N:1 atrioventricular conduction, as 2:1 atrial flutter. Another limitation is the increased stability of VV intervals during atrial fibrillation with fast ventricular response.[8]

The block 'sudden onset' can be used to discriminate sudden onset ventricular tachyarrhythmias from sinus tachycardia, which is characterized by a gradual onset. However, sudden onset may not be specific for atrial or ventricular tachyarrhythmias. Appropriate interpretation of stored electrograms in single chamber devices is not only based on one changes in an information block. In fact, we rather combine the information of the electrogram morphology with information on the rate of the arrhythmia, the onset and the stability of the arrhythmia. The recording of device activity markers (marker channel) provides additional information, which requires fewer computer spare.

Figure 2. *Stored bipolar electrogram showing ventricular tachycardia (VT) with regular ventricular intervals detected in the programmed tachycardia detection zone. The programmed tachycardia detection (TD) is fulfilled and subsequently antitachycardia pacing (ATP) is delivered. The ventricular electrogram morphology is significantly different during tachycardia as compared to the restored baseline rhythm.*
Markers: FS = fibrillation sensing; TD = tachycardia detected; TP = tachycardia pacing; TS = tachycardia sensing; VS = ventricular sensing sensing. (Medtronic Jewel, model 7219)

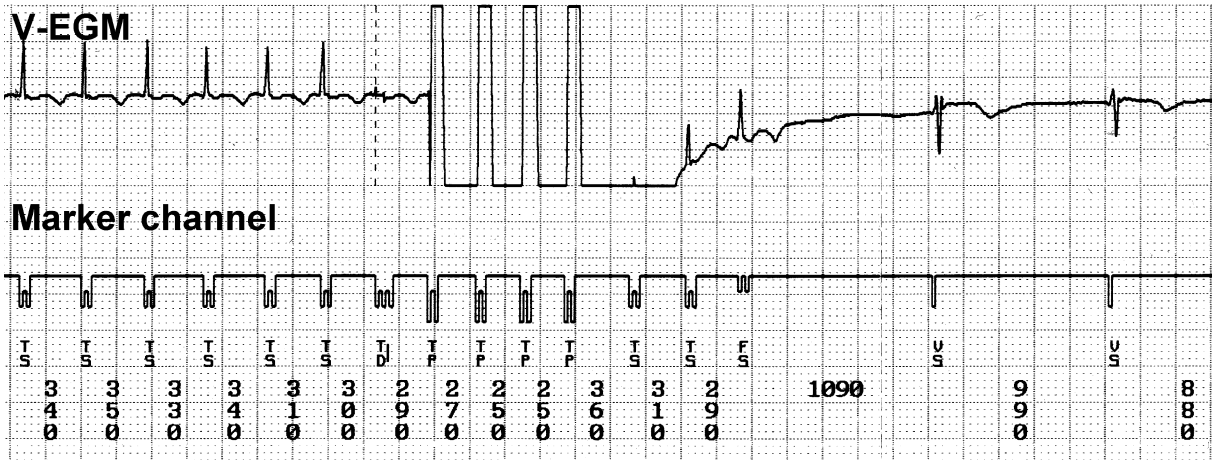
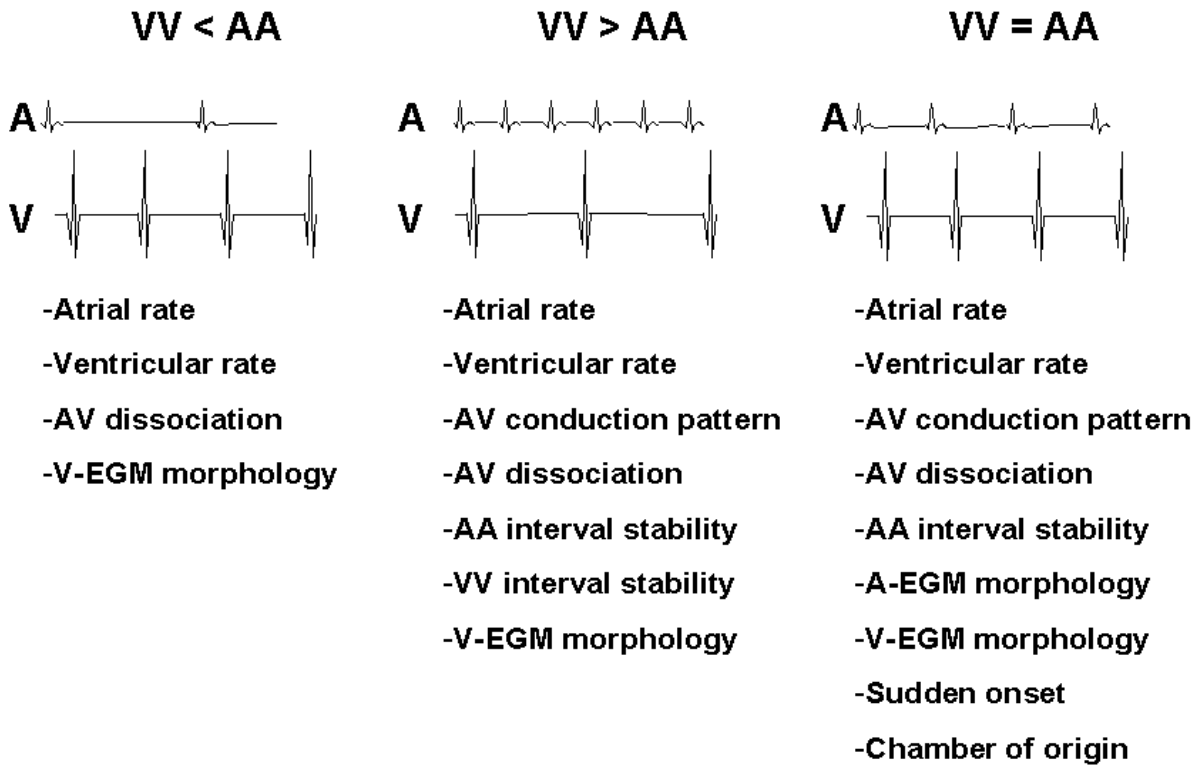


Figure 3*. Application of blocks with physiologic information for presenting arrhythmias in relation to rate branch*



Dual chamber devices

The visual analysis of stored electrograms from dual chamber devices includes blocks based on atrial and ventricular physiological information. Blocks derived from the ventricular activity are similar to those used in single chamber devices. For clinical information of atrial activity, blocks are 'AA stability', 'atrial cycle length', and 'atrial electrogram morphology'. These blocks can be used to identify the presence of atrial tachyarrhythmias. As atrial information is present, analysis of the atrioventricular (AV) relationship can be performed. The first block 'AV conduction pattern' can be used to discriminate between atrial and ventricular tachyarrhythmias with stable AV conduction. The majority of atrial tachyarrhythmias have a consistent AV conduction pattern, but ventricular tachyarrhythmias with stable retrograde 1:1 ventriculoatrial (VA) conduction also have a consistent AV conduction pattern. In the majority of ventricular tachyarrhythmias, the block 'AV dissociation' can be used to identify ventricular tachyarrhythmias. Another helpful block is the 'chamber of origin', which can be used to discriminate between atrial and ventricular tachyarrhythmias with 1:1 AV or VA conduction by identification of atrial activity preceding ventricular activity or vice versa. All blocks with physiologic information can serve as tool for analysis of stored electrograms. The use of specific physiologic blocks and the order or combination of them is dependent on the comparison of atrial and ventricular rate (Figure 3).

Application of physiologic blocks in relation to rate branches

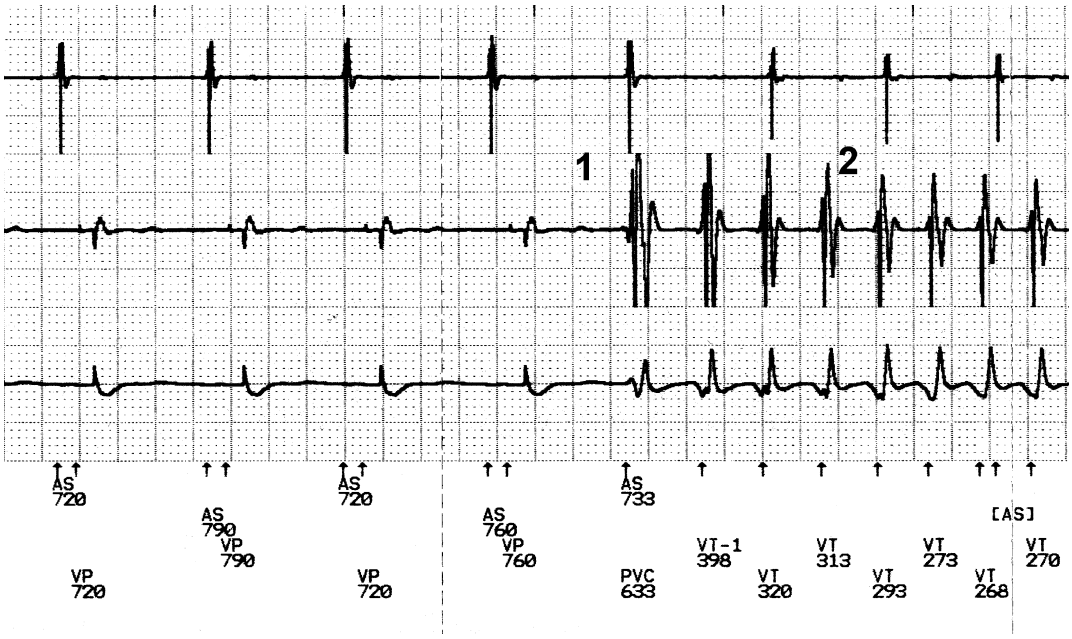
Based on the comparison of atrial and ventricular rate, tachyarrhythmias can be roughly divided into three rate branches: ventricular rate > atrial rate, ventricular rate < atrial rate, and ventricular rate = atrial rate.

Ventricular rate > atrial rate

In the majority of ventricular tachyarrhythmias, the ventricular rate is faster than the atrial rate (Figure 4). In this rate branch, the timing-based physiologic blocks 'atrial rate', 'ventricular rate', 'AV dissociation', and 'VV interval stability' are applicable. The block 'ventricular electrogram morphology' can be used to discriminate between monomorphic and polymorphic ventricular tachycardias. Monomorphic ventricular

tachycardia has a constant cycle length, beat-to-beat variation < 10%, and a uniform electrogram morphology during the tachycardia.[9]

Figure 4. *Stored bipolar electrograms showing ventricular tachycardia (VT). Rhythm strip from top to bottom atrial, ventricular, and shock electrogram. Ventricular premature beat (1) initiates VT (2) with regular ventricular intervals detected in the programmed tachycardia detection zone. During VT, the ventricular rate is faster as compared to the atrial rate. Markers: AS = atrial sensing; PVC = premature ventricular complex; VP = ventricular pacing; VT = ventricular tachycardia window. (Guidant Prizm DR, model 1861)*



Ventricular rate < atrial rate

Compared to 'ventricular rate > atrial rate', the rate branch 'ventricular rate < atrial rate' is more complex. Atrial tachyarrhythmias within this rate branch can be atrial fibrillation, atrial flutter or atrial tachycardia with stable N:1 AV conduction. The occurrence of ventricular tachyarrhythmias in this rate branch is also known as double tachycardia, i.e. atrial fibrillation and ventricular tachycardia. On the atrial level 'atrial rate', 'AA interval stability', and 'AV conduction pattern' blocks are used to identify the type of atrial tachyarrhythmia. A regular atrial response is usually found during atrial flutter or tachycardia.

For the identification of ventricular tachycardia, combinations of blocks 'AV dissociation', 'VV interval stability', and 'ventricular electrogram morphology' are used (Figure 5). The ventricular electrogram morphology and stability of ventricular intervals are applicable for identification of ventricular tachycardia during atrial

fibrillation. The blocks ‘AV dissociation’ and ‘ventricular electrogram morphology’ are suitable for identification of ventricular tachycardia during atrial flutter or tachycardia. Atrial flutter or tachycardia with stable N:1 AV conduction have a consistent AV conduction pattern. This AV conduction pattern will change when ventricular tachycardia is present (Figure 6). The physiologic block ‘VV interval stability’ is not applicable during atrial tachyarrhythmias with stable N:1 AV conduction as the ventricular response is regular.

Figure 5. *Stored bipolar electrograms demonstrating double tachycardia, which is ventricular tachycardia (VT) during atrial fibrillation (AF). Rhythm strip from top to bottom atrial, ventricular, and shock electrogram. The atrial electrogram shows atrial fibrillation. Ventricular premature beat (2) initiates VT (3). During VT, the morphology of the ventricular and shock electrogram changed as compared to baseline rhythm (3). Markers: AF = atrial fibrillation window; AS = atrial sensing; VP-FB = ventricular pacing, fallback; VS = ventricular sensing; VT = ventricular tachycardia window. (Guidant, Renewal II, model H155)*

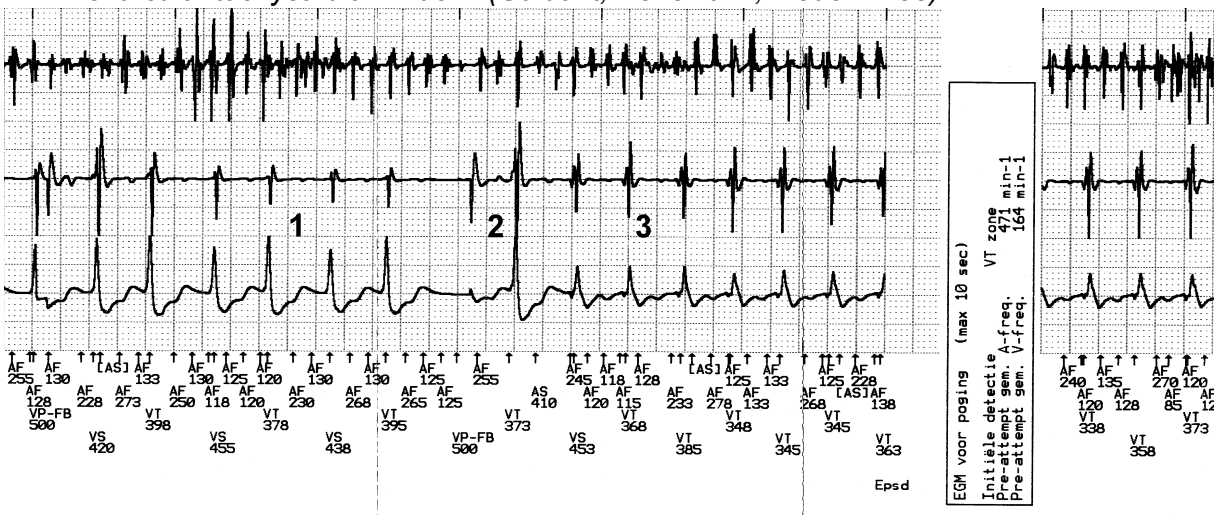
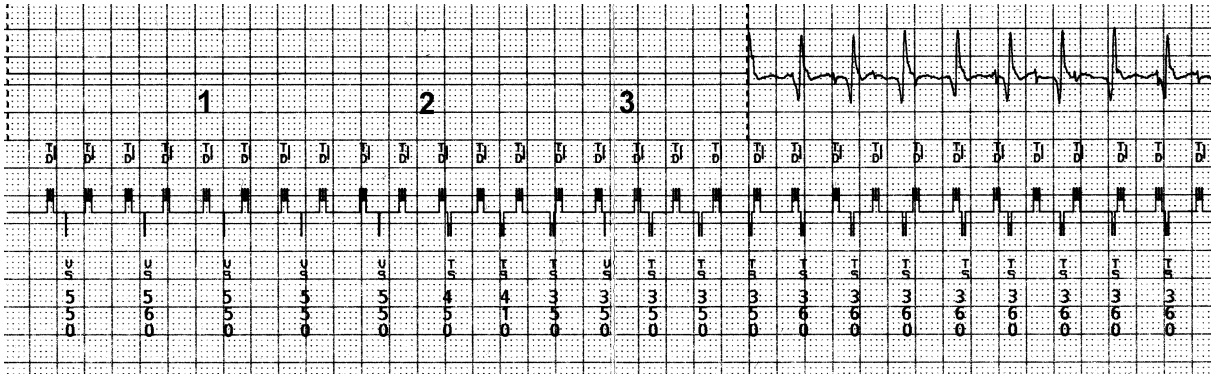


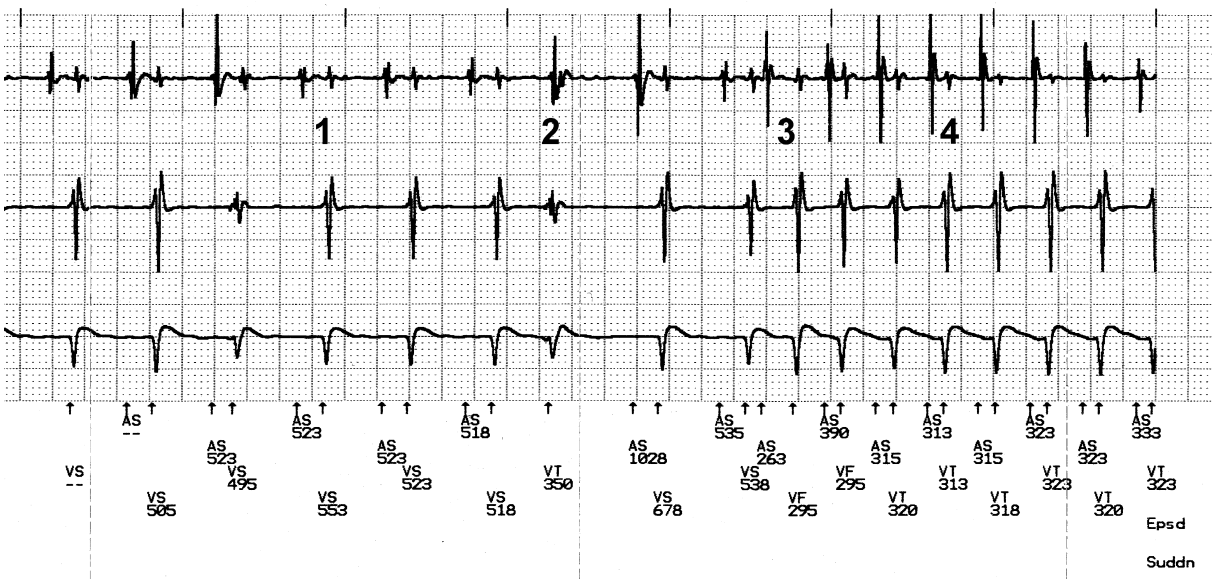
Figure 6. *Detection of double tachycardia, which is ventricular tachycardia (VT) during atrial flutter (AFl). The marker channel demonstrates appropriately detected AFl (1) with a consistent atrioventricular (AV) conduction pattern. A ventricular premature beat (2) initiates VT (3). At the onset of VT, the marker channel demonstrates a change in the AV conduction pattern. During VT, there is AV dissociation. Markers: TD = tachycardia detected; TS = tachycardia sensing; VS = ventricular sensing. (Medtronic Jewel AF, model 7250)*



Ventricular rate = atrial rate

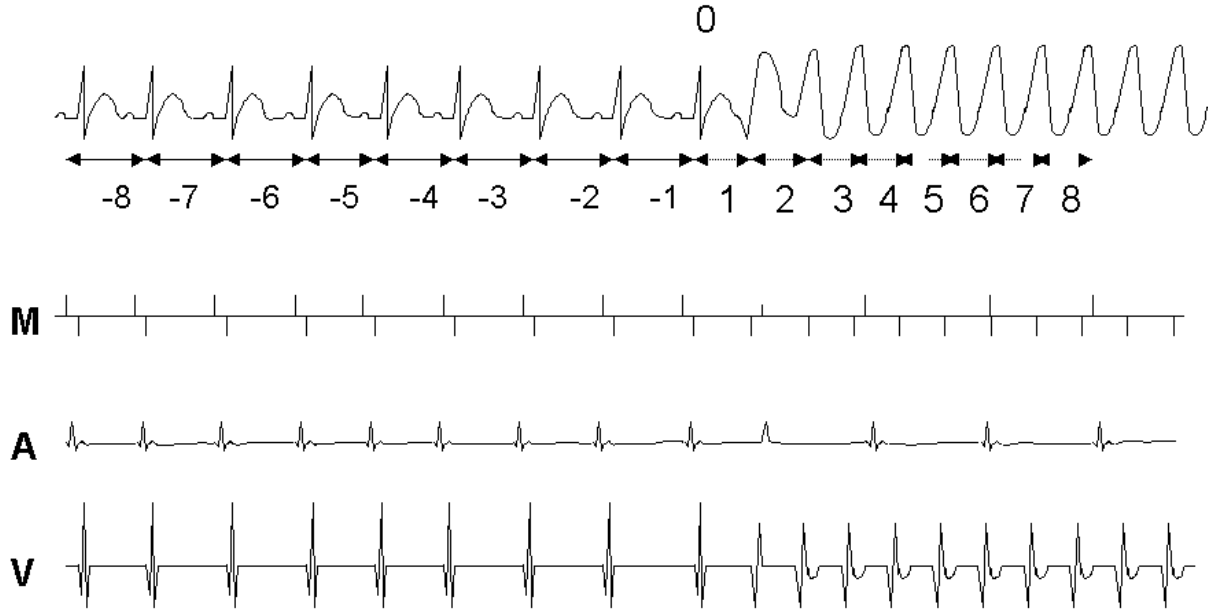
The rate branch 'ventricular rate = atrial rate' consists of tachyarrhythmias with 1:1 AV conduction. In this rate branch, the AV conduction relationship plays an important role. The atrial tachyarrhythmias (i.e. sinus and atrial tachycardia) have a consistent AV conduction pattern. On the other hand ventricular tachyarrhythmias with stable retrograde 1:1 VA conduction also have a consistent AV conduction pattern. To discriminate between atrial and ventricular tachyarrhythmias, the first step is to analyze the onset of the tachyarrhythmia. Sinus tachycardia is characterized by a gradual onset, whereas ventricular tachycardia has a sudden onset. The application of blocks 'chamber of origin' and 'ventricular electrogram morphology' offers additional information for further differentiation between sinus and ventricular tachycardia. The 'chamber of origin' is used to identify the initiating event at the onset of tachycardia. At the onset of ventricular tachycardia, an intrinsic atrial event usually does not occur between the last conducted sinus beat and the first ventricular ectopic event. On the other hand, an atrial event is present before every ventricular event at the onset of atrial tachycardia (Figure 7).

Figure 7. *Stored electrogram showing atrial tachycardia with consistent 1:1 atrioventricular (AV) conduction. Rhythm strip from top to bottom atrial, ventricular, and shock electrogram. After 6 normal conducted ventricular events (2), a ventricular premature beat (1) occurs, which is followed by 2 normal conducted ventricular events. A premature atrial event (3) initiates an atrial tachycardia with stable 1:1 AV conduction (4). 'Chamber of origin' is atrial and no change in 'ventricular electrogram morphology'. Markers: AS = atrial sensing; VF = ventricular fibrillation window; VS = ventricular sensing; VT = ventricular tachycardia window; Epsd: initial tachycardia detection met; Suddn: sudden onset; --: no annotiation of stored events before detection of tachycardia. (Guidant Prizm DR, model 1861)*



The combination of blocks ‘AV conduction pattern’, ‘chamber of origin’, ‘sudden onset’, and ‘ventricular electrogram morphology’ is necessary in challenging tachyarrhythmias with 1:1 AV conduction. Examples are atrial tachycardias with a sudden onset, and sinus or atrial tachycardia with progressive prolonging AV conduction.

***Figure 8**. Schematic approach of the analysis of ventricular tachyarrhythmias. From top-to-bottom are displayed the surface electrocardiogram (ECG), the atrial electrogram (A-EGM), and the ventricular electrogram (V-EGM). The premature ventricular depolarization initiating the tachyarrhythmia is labeled ‘A’. The preceding interval, the last normal conducted beat, is labeled ‘0’. The corresponding intervals for analysis are S_{-1} to S_{-8}, V_1, and T_1 to T_{12}.*



Standardized approach for electrogram analysis

For clinical trials, correct electrogram interpretation is important. In a recent study, the overall performance of physicians in electrogram interpretation was similar to the ICD.[10] However, the composition of the misinterpretation was different, which can have a severe impact on the outcome of clinical trials. To improve the accuracy and reproducibility of electrogram analysis, a standardized approach was developed for a core ICD laboratory (Figure 8). The electrogram corresponding to the first beat of the tachycardia is labeled “A”. The preceding beat, the last “normal” conducted sinus beat is labeled “0”. The coupling interval of the premature depolarization initiating the tachycardia (from beat “0” to beat “A”) was labeled “V_1”. The consecutive intervals of the tachyarrhythmia were numerically sequentially labeled T_1 through T_{12}. The

preceding intervals were labeled S_{-1} through S_{-8}. This approach is now under validation and used in large clinical trial.[11]

Sudden cardiac death

In the eighties, Holter recordings during sudden death were used to analyse the electrical triggering mechanisms leading to this event.[12-15] Despite the fact that these studies were conducted in small populations, important observations were made. It was found that the most frequent cause of sudden death was monomorphic ventricular tachycardia degenerating into ventricular fibrillation.[12-14] In patients with advanced heart failure, bradyarrhythmias were found as the major cause of sudden cardiac death.[15] The majority of ventricular tachyarrhythmias was ventricular fibrillation, usually secondary to ventricular tachycardia.

Stored electrograms of the ICD allows verification of the suspected mode of death. In a large database with follow-up of 834 ICD patients, sudden death due to tachyarrhythmic events with ICD therapy was observed in only 7 patients.[16] Another study confirmed these results with the majority of deaths (69%) being not the result of a tachyarrhythmia.[17] In contrast, another study on the same topic reported that sudden death was associated with ventricular tachyarrhythmias despite device therapy in 66% of the patients.[18] However, the worsening clinical status of their patients suggested ventricular tachyarrhythmias secondary to acute cardiac mechanical dysfunction. The clinical classification of sudden cardiac death is still a challenge in large clinical trials.

Onset mechanisms of ventricular tachyarrhythmias

Stored electrograms provide the unique opportunity to analyse the triggers initiating ventricular arrhythmias, and to unerstand more of the physiology in larger populations. Reentry, triggered activity, or abnormal automaticity are distinct mechanisms for the generation of ventricular tachyarrhythmias.[19] These mechanisms are dependent on the presence of an underlying cardiac substrate and are modified by dynamic factors such as electrolyte imbalance, coronary ischemia, or neurohumoral influences. In the setting of a prior myocardial infarction, reentry around a fixed anatomic scar often results in monomorphic ventricular tachycardia

(MVT).[19,20] Ventricular arrhythmias of different mechanisms may be triggered by different initiation sequences. The majority of MVTs in patients with previous myocardial infarction is preceded by late-coupled ventricular premature beats.[9,21-23]. The mode of onset of MVT in patients with dilated cardiomyopathy was not different as compared to onset of MVT in the setting of coronary artery disease.[24,25]

Torsades de pointes is typically preceded by a “short-long-short” sequence. Some studies reported a “short-long” sequence as initiating mechanism for polymorphic ventricular arrhythmias. Diagnostic information on initiating mechanisms of tachyarrhythmias in new syndromes as the Brugada syndrome and short QT-syndrome can be expected from stored electrograms.[26,27]

References

1. Marchlinski FE, Buxton AE, Flores BF. The automatic implantable cardioverter defibrillator: Followup and complications. In: El-Sherif N, Samet P, eds. Cardiac pacing and electrophysiology. Orlando, FL: Grune and Stratton, 1990:743-758.
2. Fogoros RN, Elson JJ, Bonnet CA. Actuarial incidence and pattern of occurrence of shocks following implantation of the automatic implantable cardioverter defibrillator. *Pacing Clin Electrophysiol* 1989;12:1465-1473.
3. Maloney J, Masterson M, Khoury D, Trohman R, Wilkoff B, Simmons T, Morant V, Castle L. Clinical performance of the implantable cardioverter defibrillator: electrocardiographic documentation of 101 spontaneous discharges. *Pacing Clin Electrophysiol* 1991;14:280-285.
4. Callans DJ, Hook BG, Marchlinski FE. Use of bipolar recordings from patch-patch and rate-sensing leads to distinguish ventricular tachycardias from supraventricular rhythms in patients with implantable cardioverter defibrillators. *Pacing Clin Electrophysiol* 1991;14:1917-1922.
5. Sarter BH, Hook BG, Callans DJ, Marchlinski FE. Effect of bundle branch block on local electrogram morphology: Potential cause of arrhythmia misdiagnosis. *Pacing Clin Electrophysiol* 1992;15:562.
6. Sarter BH, Hook BG, Callans DJ, Marchlinski FE. Effect of bundle branch block on local electrogram morphologic features: implications for arrhythmia diagnosis by stored electrogram analysis. *Am Heart J* 1996;131:947-952.
7. Hook BG, Callans DJ, Kleiman RB, Flores BT, Marchlinski FE. Implantable cardioverter-defibrillator therapy in the absence of significant symptoms. Rhythm diagnosis and management aided by stored electrogram analysis. *Circulation* 1993;87:1897-1906.
8. Kettering K, Dornberger V, Lang R, Vonthein R, Suchalla R, Bosch RF, Mewis C, Eigenberger B, Kuhlkamp V. Enhanced detection criteria in implantable cardioverter defibrillators: Sensitivity and specificity of the stability algorithm at different heart rates. *Pacing Clin Electrophysiol* 2001;24:1325-1333.
9. Saeed M, Link MS, Mahapatra S, Mouded M, Tzeng D, Jung V, Contreras R, Swygman C, Homoud M, Estes NA, 3rd, Wang PJ. Analysis of intracardiac electrograms showing monomorphic ventricular tachycardia in patients with implantable cardioverter-defibrillators. *Am J Cardiol* 2000;85:580-587.
10. Theuns DA, Szili-Torok T, Scholten M, Res J, Kimman G, Ruiter J, Jordaens LJ. Stored electrograms in implantable cardioverter defibrillators: agreement upon analysis by electrophysiologists (abstract). *Circulation* 2002;106:II-322.

11. Brouwer IA, Zock PL, Wever EF, Hauer RN, Camm AJ, Bocker D, Otto-Terlouw P, Katan MB, Schouten EG. Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *Eur J Clin Nutr* 2003;57:1323-1330.
12. Pratt CM, Francis MJ, Luck JC, Wyndham CR, Miller RR, Quinones MA. Analysis of ambulatory electrocardiograms in 15 patients during spontaneous ventricular fibrillation with special reference to preceding arrhythmic events. *J Am Coll Cardiol* 1983;2:789-797.
13. Kempf FC, Josephson ME. Cardiac arrest recorded on ambulatory electrocardiograms. *Am J Cardiol* 1983;53:1577-1582.
14. 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;117:151-159.
15. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;80:1675-1680.
16. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. *Circulation* 1996;93:519-524.
17. Grubman EM, Pavri BB, Shipman T, Britton N, Kocovi DZ. Cardiac death and stored electrograms in patients with third-generation implantable cardioverter-defibrillators. *J Am Coll Cardiol* 1998;32:1056-1062.
18. Pires LA, Hull ML, Nino CL, May LM, Ganji JR. Sudden death in recipients of transvenous implantable cardioverter defibrillator systems: terminal events, predictors, and potential mechanisms. *J Cardiovasc Electrophysiol* 1999;10:1049-1056.
19. Josephson ME, Almentral JM, Buxton AE, Marchlinski FE. Mechanisms of ventricular tachycardia. *Circulation* 1987;75(Suppl III):III-41-III-47.
20. El-Sherif N, Hope RR, Scherlag BJ, Lazzara R. Re-entrant ventricular arrhythmias in the late myocardial infarction period. 2. Patterns of initiation and termination of re-entry. *Circulation* 1977;55:702-719.
21. Hook BG, Marchlinski FE. Value of ventricular electrogram recordings in the diagnosis of arrhythmias precipitating electrical device shock therapy. *J Am Coll Cardiol* 1991;17:989-990.
22. Marchlinski FE, Gottlieb CD, Sarter B, Finkle J, Hook B, Callans D, Schwartzman D. ICD data storage: Value in arrhythmia management. *Pacing Clin Electrophysiol* 1993;16:527-534.

23. Roelke M, Garan H, McGovern BA, Ruskin JN. Analysis of the initiation of spontaneous monomorphic ventricular tachycardia by stored intracardiac electrograms. *J Am Coll Cardiol* 1994;23:117-122.
24. Meyerfeldt U, Schirdewan A, Wiedemann M, Schutt H, Zimmerman F, Luft FC, Dietz R. The mode of onset of ventricular tachycardia. A patient-specific phenomenon. *Eur Heart J* 1997;18:1956-1965.
25. Taylor E, Berger R, Hummel JD, Dinerman JL, Kenknight B, Arria AM, Tomaselli G, Calkins H. Analysis of the pattern of initiation of sustained ventricular arrhythmias in patients with implantable defibrillators. *J Cardiovasc Electrophysiol* 2000;11:719-726.
26. Kakishita M, Kurita T, Matsuo K, Taguchi A, Suyama K, Shimizu W, Aihara N, Kamakura S, Yamamoto F, Kobayashi J, Kosakai Y, Ohe T. Mode of onset of ventricular fibrillation in patients with Brugada syndrome detected by implantable cardioverter defibrillator therapy. *J Am Coll Cardiol* 2000;36:1646-1653.
27. Schimpf R, Wolpert C, Bianchi F, Giustetto C, Gaita F, Bauersfeld U, Borggrefe M. Congenital short QT syndrome and implantable cardioverter defibrillator treatment: inherent risk for inappropriate shock delivery. *J Cardiovasc Electrophysiol* 2003;14:1273-1277.

Part III

Single Chamber, Dual Chamber or Biventricular devices?

Chapter 11

Comparison of Events and Survival in Dual- versus Single-Chamber ICDs

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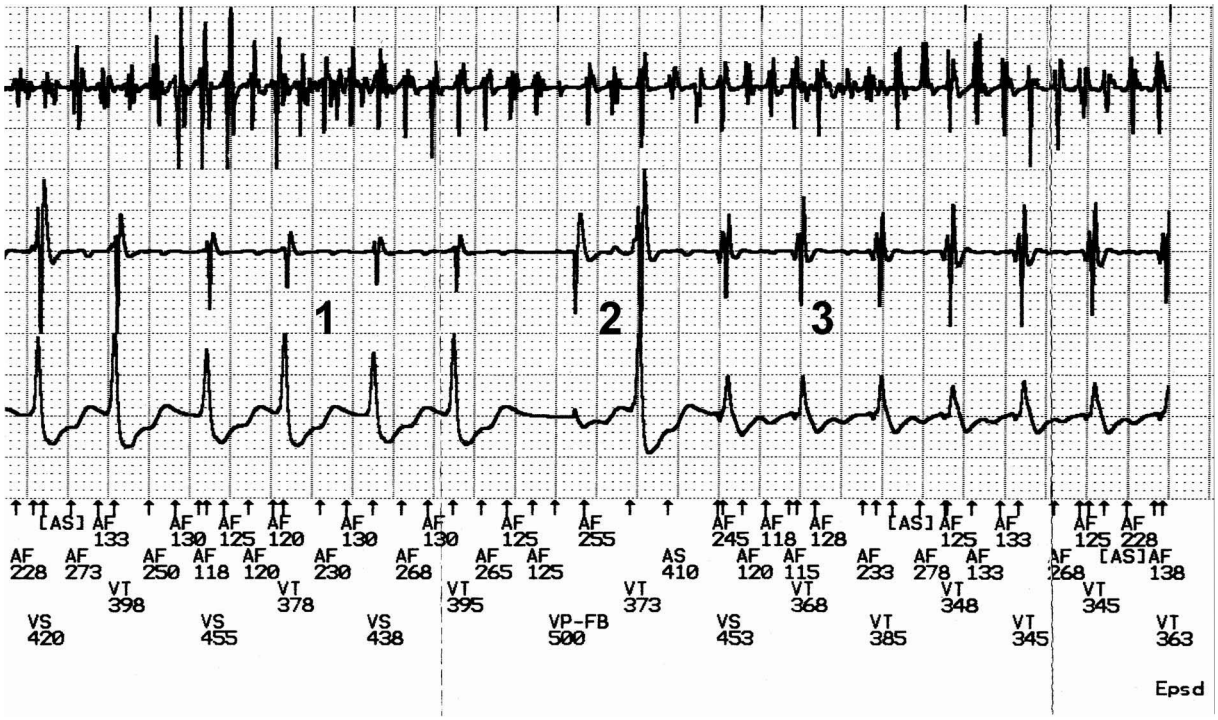
Published: Cardiologie 1999;12:604-608.



Abstract

Background: *Conventional (single lead ventricular) defibrillators (ICDs) often deliver "inappropriate" therapy. It is supposed that algorithms incorporating information about the atrial rhythm, and derived from an additional electrode in the atrium will be helpful in correct recognition of ventricular tachycardia or fibrillation.*

Methods: *We studied factors influencing appropriate therapy and survival (odds ratio and 95% confidence intervals) of 126 patients receiving an ICD. Single-chamber ICD's were implanted in 99 patients, (group 1) while 27 received a dual-chamber ICD (group 2). The groups were comparable for most demographic and clinical variables except for the incidence of complete heart block, which was more frequently observed in group 2, $p<0.01$.*

Results: *Dual-chamber therapy was associated with less inappropriate interventions (a reduction of 12%). The odds for appropriate intervention were higher when a history of atrial fibrillation existed.*

The Kaplan-Meier survival curve showed no significant difference between both groups for mortality, and for event free survival (appropriate and inappropriate therapy).

Conclusion: *While survival was similar for dual- and single-chamber devices, the use of dual-chamber devices will improve the quality of life, as less interventions were necessary, certainly in the long term. Even when interventions were judged as appropriate, previously documented atrial fibrillation was established as being a risk for such interventions.*

Introduction

Conventional (single-lead ventricular) defibrillators (ICDs) often deliver 'inappropriate' therapy for supraventricular arrhythmias, including sinus tachycardia and atrial fibrillation (AF).[1] Some algorithms have been developed to avoid these 'spurious' interventions, but a large number of inappropriate shocks was still mentioned in recent reports.[2] When an atrial lead is implanted, sensing the atrium becomes possible.[3] This information can be integrated in the device. It is assumed that algorithms incorporating information about the atrial rhythm will be helpful in correct recognition of ventricular tachycardia (VT) or fibrillation (VF). As dual-chamber ICDs can pace the atrium, they can be used in patients with bradycardia and a poor left ventricular function, because they will not compromise the function by ventricular pacing alone. This can also help prevent atrial fibrillation, and therefore become important in avoiding inappropriate therapy.[4]

Dual-chamber pacing is also associated with less congestive heart failure and an improved survival in some patient groups. It is, therefore, anticipated that dual-chamber defibrillators share this advantage with dual-chamber pacemakers over single-chamber systems.[5]

Aim

In this study, we wanted to test the hypothesis that dual-chamber ICDs diminish the number of events (appropriate and inappropriate) compared with conventional single-chamber ICDs. Further, the short-term impact on survival of dual-chamber devices will be assessed.

Methods

Centres

This study was a two-centre study (Departments of Electrophysiology, University Hospital Ghent, Belgium, and the Heart Centre, Universtity Hospital, Rotterdam, The Netherlands), with prospective collection of clinical follow-up data.

Patient population

A total number of 100 consecutive patients with a single-chamber device and 27 patients with a dual-chamber defibrillator were selected for this comparative, retrospective analysis. All patients with a dual-chamber device from both centres were included. Single-chamber patients were selected consecutively,with selection commencing as soon as the first dual-chamber ICD was implanted, so that contemporary patients were studied. The general approach of implantation and follow-up did not change during the study period and was similar in both hospitals. The implantation methodology has been extensively described, and was slightly different for a dual-chamber device, as an atrial lead was implanted as well, in the high right atrium.[6,7] The atrial lead was always from a type with active fixation (Medtronic). All patients underwent defibrillation threshold testing and a pre-hospital discharge test with reinduction of ventricular fibrillation. Programming was tailored to individual patient needs. `Rate regularity` (the most widely studied preventive algorithm, based upon the RR intervals, enhancing discrimination between regular tachycardia and irregular atrial fibrillation) was always programmed if a history of atrial fibrillation was available.[2]

Follow-up

Follow-up was defined as the time from ICD implantation until the last visit, heart transplantation or death. Patients were followed at regular intervals. An interrogation of the device memory was performed every three months. If the first spontaneous arrhythmia or intervention occurred before this visit, the memory of the device was interrogated as soon as possible. Events were defined as antitachycardia pacing or shocks. Classification of interventions as appropriate and inappropriate was performed with the device electrograms and all other available means. For five patients (one in the dual-chamber and four in the VVI single-chamber group), data concerning inappropriate intervention were too unreliable to include in the analysis. Vital statistics were complete, except for one patient from the single-chamber group, reducing this group to 99 patients.

Statistical methods

Patients were compared for clinical baseline variables. Endpoints were appropriate, inappropriate therapy and mortality. Univariate analysis was performed with confidence interval analysis comparing both groups. Multivariate analysis and Kaplan-Meier survival curves were performed with SPSS 8, using all available data to analyse whether dual-chamber devices were associated with less endpoints. A result was considered as significant for p values <0.05.

Results

Comparison between both groups

The comparison for the base-line variables is given in table 1. The two groups were comparable for most demographic and clinical variables, except for the incidence of complete heart block (more frequently observed in the dual-chamber group, p<0.01). Follow-up duration was not completely equal: the mean duration was longer in the single-chamber group, as initially only few patients could receive a dual-chamber device because of limited availability and socio-economic considerations (table 2).

Table 1. *Patient data*

	All (n=126)	Dual (n=27)	Single (n=99)	Difference (%) and 95% CI		p value
Age > 75 years	43	12	31	13	(-7 to 34)	NS
Male gender	108	20	88	-15	(-33 to 3)	< 0.06
Coronary artery disease	90	18	72	-6	(-26 to 14)	NS
Ejection fraction <25%	30	7	23	4	(-15 to 23)	NS
Ventricular tachycardia	77	18	59	7	(-13 to 27)	NS
Ventricular fibrillation	47	9	38	-5	(-25 to 15)	NS
Complete heart block	9	7	2	24	(7 to 41)	< 0.01
Previous atrial fibrillation	47	12	35	10	(-11 to 32)	NS

CI = confidence interval

Table 2. *Follow-up*

	All (n=126)	Dual (n=27)	Single (n=99)	Difference (%) and 95% CI		p value
Mean duration (days)	502 ± 368	169 ± 593	593 ± 354			< 0.001
Appropriate interventions	49/125	7/27	42/98	-17	(-36 to 2)	NS
Inappropriate therapy	17/121	1/26	16/95	-12	(-2 to –23)	< 0.05
Mortality	12/126	3/27	9/99	2	(-11 to 15)	NS
Days to appr. intervention	121 ± 155	38 ± 29	135 ±164			NS
Days to inappr. therapy	473 ± 397	63	57 ± 91			NS

Appr. = appropriate; CI = confidence interval; inappr. = inappropriate

Interventions

The relative risk for appropriate intervention was similar for dual- and single-chamber devices. The chances for inappropriate therapy were reduced for dual-chamber ICDs. The Kaplan-Meier survival curve (figures 1 and 2) showed no significant differences for intervention-free survival (both for appropriate and appropriate therapy).

Figure 1. *Kaplan-Meier survival for intervention-free survival for single- and dual- chamber defibrillators (appropriate therapy, antitachycardiapacing and shocks).*

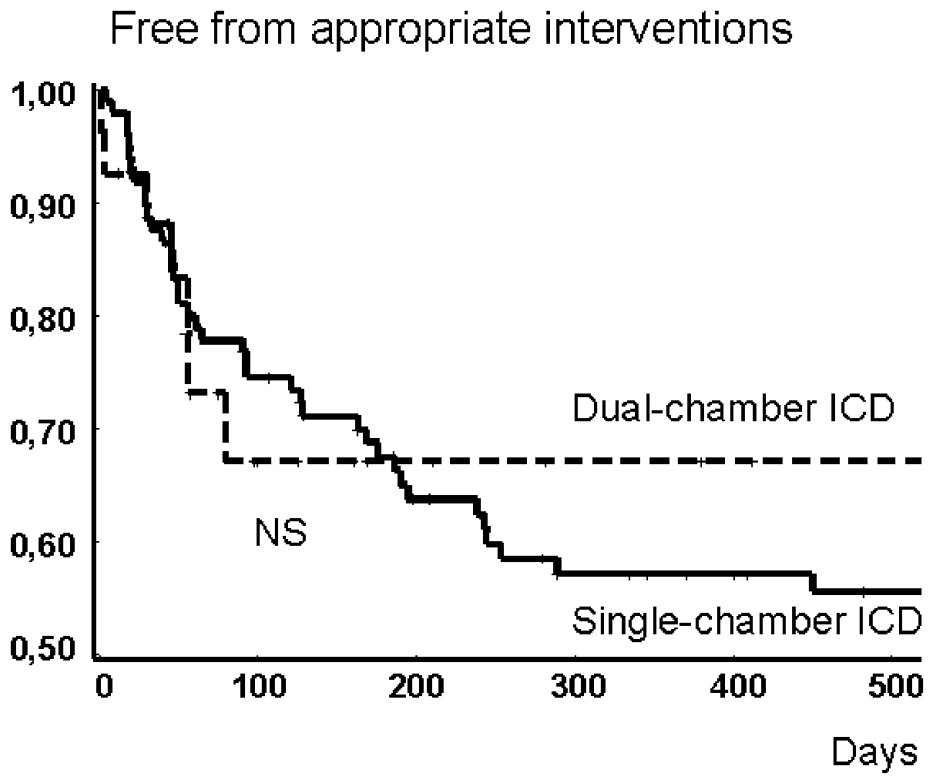
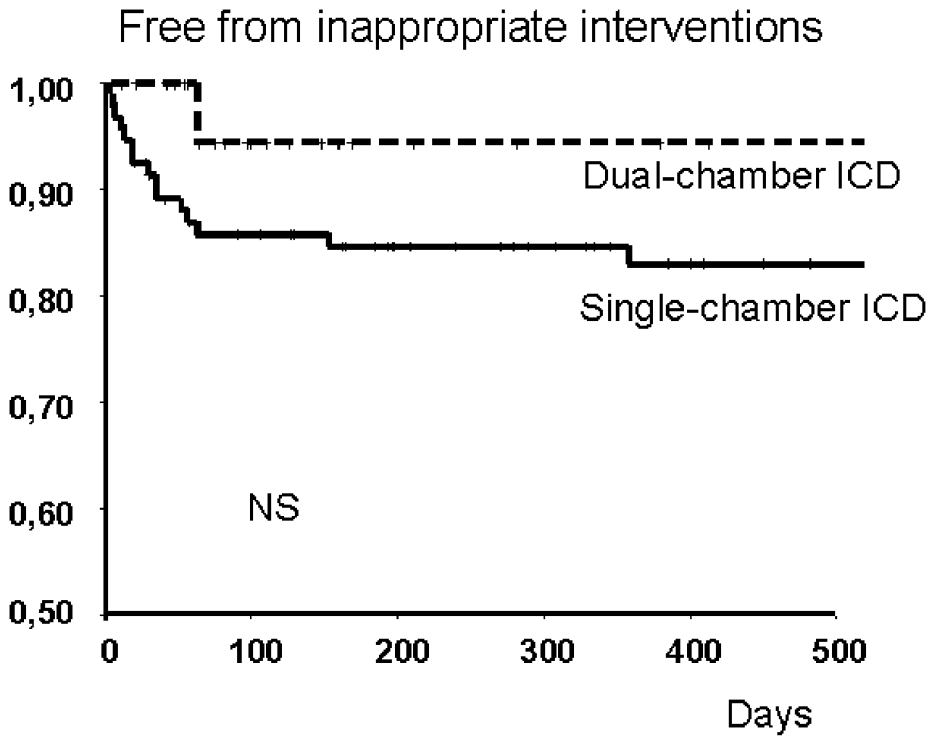


Figure 2. *Kaplan-Meier survival for intervention-free survival for single- and dual-chamber defibrillators (inappropriate therapy, antitachycardiapacing and shocks).*



In multivariate analysis, using logistic regression analysis, the odds for appropriate intervention tended to be higher when VT was the presenting arrhythmia ($p<0.08$). The only significant factor was previous AF: the chance of receiving appropriate therapy was higher ($p<0.02$). No factors were related to inappropriate therapy. Dual-chamber or single-chamber device was not related to both intervention types (table 3).

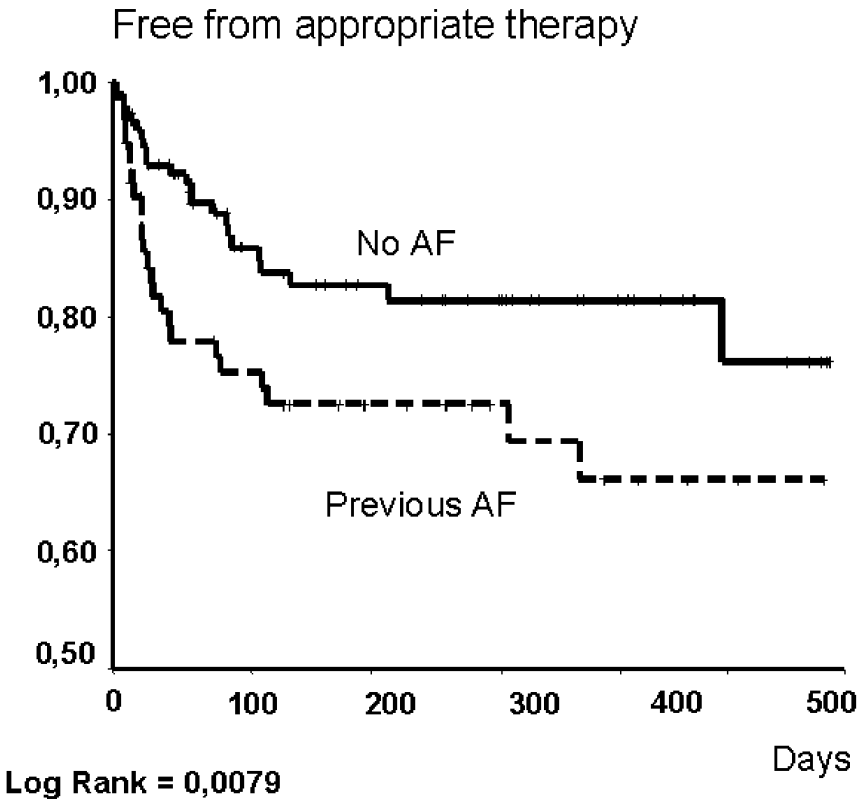
Table 3. *Results from multivariate analysis.*

Variable	Factors	p	R
Appropriate therapy	Previous AF	< 0.02	15%
	VT	< 0.08	8%
Inappropriate therapy	-		
Mortality	CAD	< 0.099	10%

AF = atrial fibrillation; CAD = coronary artery disease; VT = ventricular tachycardia

When a Kaplan Meier analysis was performed for the total group, with previous AF as discriminating factor, a history of AF was indeed a significant predictor of appropriate, and not for inappropriate therapy (figure 3). This was observed for single-chamber (log rank = 0.0226), but in a much less significant way for dual-chamber devices (log rank = 0.096).

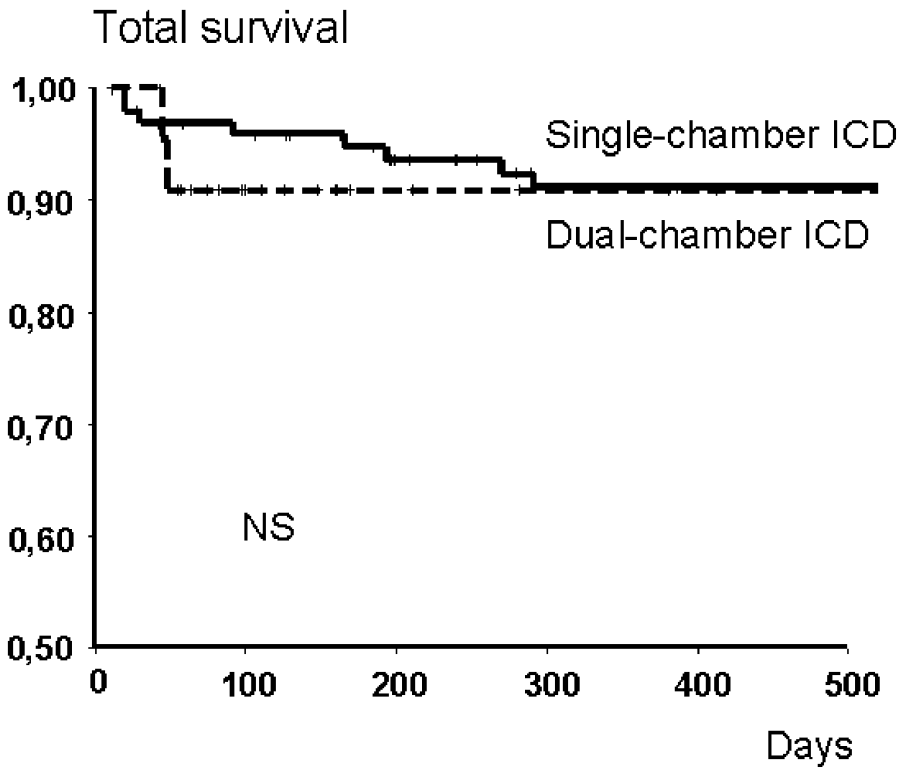
Figure 3. *Kaplan-Meier survival for intervention-free survival (from appropriate therapy, in relation to preexisting AF).*



Mortality

In univariate and multivariate analysis, no influence of the device group was observed. The Kaplan-Meier survival curve showed no significant difference between both groups (figure 4).

Figure 4. *Kaplan-Meier survival for mortality (all causes) for single and dual chamber defibrillators.*



Discussion

Dual-chamber ICDs and inappropriate interventions

Inappropriate interventions (both ATP and shocks) have been a problem from the early ICD era,[8,9] which is not surprising, as atrial fibrillation is the most frequently encountered arrhythmia.[10] Atrial fibrillation is indeed the most frequent reason for 'spurious' shocks. Attempts to avoid intervention have been undertaken, and in the early days they included the selection of non-programmable devices with a high cut-off rate. When these devices became programmable, high cut-off rates could be programmed to avoid triggering by high ventricular rates. Alternatives for avoiding unnecessary shocks were prescription of drugs, depressing AV-nodal conduction, or even ablation of the AV-node.[11] Further preventive measures became available when algorithms as rate regularity and the electrogram width were developed.[2,12] The first option has the disadvantage that polymorphic ventricular tachycardia is not well recognised, and the second option that aberrant conduction over the bundle branches is recognised as ventricular tachycardia. However, most experts believe that the number of spurious interventions is reduced when electrical information from the atrium (i.e. electrograms, or the P-wave) is used for decision making in

arrhythmia recognition.[3,7] The first algorithm for dual-chamber devices uses the relation of the atrial and ventricular electrogram (association and relative number of each) and decides whether atrial fibrillation is present or not using other information. Other algorithms have been developed and are under clinical investigation. Most available data suggest that ventricular arrhythmias are recognised with a high sensitivity, but that specificity (avoiding therapy for supraventricular arrhythmias) remains somewhat problematic.[13]

Therefore, our study (using four different brands of devices and not testing a specific algorithm) is important as it is the first showing that dual-chamber devices reduce the number of inappropriate interventions. Apart from the intelligent dual-chamber algorithms, other factors could play a role. One might assume that atrial pacing as such could already be enough to prevent supraventricular arrhythmias.[14] Further, it is speculative that the presence of more patients with heart block could have been a reason for less interventions; however, heart block had no relation with AF, and it did not have a significant outcome in uni- and multivariate analysis in relation to ICD interventions.

Other sources of inappropriate therapy are T-wave sensing and hardware-related problems.[15] The most important one is lead fracture. While this can be theoretically more frequent (with two leads per patient), it was not observed in our study.

Dual-chamber ICD's appropriate interventions, and mortality.

It can be expected that dual-chamber pacing reduces the number of events, by electrophysiological mechanisms (preventing reentry), and by improving the haemodynamic situation of the patient.[16,17] If congestive heart failure is prevented, mortality should be reduced. No reduction in the number of correctly treated events was observed. The same was observed for mortality. One can assume that patients are selected for dual-chamber devices when their general condition is poorer. This might counterbalance the possible benefit in this study. On the other hand, no differences in ejection fraction were observed.

It is no surprise that AF is related with appropriate interventions. That atrial arrhythmias can lead to ventricular arrhythmias is also well known.[18] Furthermore, in particular conditions AF can have the same consequences as ventricular arrhythmias, so a shock that is technically considered inappropriate might be appropriate from a clinical point of view.

Limitation and complications of dual-chamber defibrillators

It is often thought that dual-chamber devices are associated with more morbidity during implantation. While this was not specifically addressed in this study, it was not our experience. However, the complex hardware and software used for such ICDs is borne to yield more problems. For example, at least 20 out of 69 AV defibrillators in a clinical trial were replaced because shock delivery resulted in a marked increase in atrial lead impedance.[19] Until now, we have encountered no such problems. However, as these devices have only recently been released, we feel that some caution in their use remains necessary.

Conclusions

Dual-chamber ICDs did not influence the amount of appropriate interventions for arrhythmias, but did reduce the number of inappropriate therapies. This is important for the quality of life; it could extend the longevity of pulse generators and is an additional argument for using dual-chamber devices in all patients prone for atrial fibrillation. Mortality was not influenced in this study, which comprised a small number of patients and was not randomised. Furthermore, the data analysis was retrospective and has a rather short follow-up. Surprisingly, a history of atrial fibrillation predisposed to a higher risk of appropriate shocks, emphasising again the importance of this common arrhythmia. Prospective, multicentre studies addressing the importance of dual-chamber defibrillators are certainly needed, as we are already facing an era of more complex devices as biventricular defibrillators, which will only make our approach even more difficult.

References

1. Grimm W, Flores BF, Marchlinski FE. Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. PACE 1992;15:1667-1673.
2. Swerdlow C; Chen P, Kass R, Allard J, Peter C. Discrimination of ventricular tachycardia from sinus tachycardia and atrial fibrillation in a tiered-therapy cardioverter-defibrillator. J Am Coll Cardiol 1994;23:1342-1355.
3. Lavergne T, Daubert JC, Chauvin M, Dolla E, Kacet S, Leenhardt A, Mabo P, Ritter P, Sadoul N, Saoudi N, Henry C, Nitzsche R, Ripart A, Murgatroyd F Preliminary clinical experience with the first dual chamber pacemaker defibrillator. PACE 1997; 20:182-188.
4. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet 1994;344:1523-8.
5. Alpert MA, Curtis JJ, Sanfelippo JF, et al. Comparative survival following permanent ventricular and dual-chamber pacing for patients with chronic symptomatic sinus node dysfunction with and without congestive heart failure. Am Heart J 1987;113:958-965.
6. Jordaens L, Vertongen P, Provenier F, Trouerbach JW, Poelaert J, Herregods L. A new transvenous internal cardioverter-defibrillator: Implantation technique, complications and short term follow-up. Am Heart J 1995;129:251-258.
7. Tavernier R, Nitszché R, Jordaens L. What are the expected clinical benefits of the DDD implantable defibrillator ? Cardiac Arrhythmias. Raviela A, ed. Springer Verlag, Milano, 1997:33-36.
8. Jordaens L, Hamerlynck R, Clement DL. Efficacy of an implanted automatic defibrillator which had induced atrial fibrillation. Br Heart J 1985;54:605-608.
9. Jordaens L, Waleffe A, Derom F, Rodriguez LM, Clement DL, Kulbertus H. First experience with the implantable cardioverter-defibrillator : 90 patient-months of follow-up. Acta Clin Belg 1988;43:209-218.
10. Pritchett EL. Management of atrial fibrillation. N Engl J Med 1992;326:1264-71.
11. Jordaens L, Caenepeel A, Calle P. His-bundle ablation for supraventricular arrhythmias to avoid spurious shocks of an implanted defibrillator. Clin Cardiol 1992;15:693-695.
12. Jung W, Spehl S, Esmailzadeh B, Wolpert C, Schneider C, Korte T, Lewalter T, Hagendorff A, Lüderitz B. New detection enhancement for arrhythmia classification with a pectoral dual-chamber implantable cardioverter defibrillator(abstract). PACE 1997;20:1168.

13. Wilkoff B, Kühlkamp V, Gillberg JM, Brown AB, Cuipers A, DeSouza CM. Performance of the dual chamber detection algorithm (PR Logic ^{TM}) based on the worldwide Gem DR clinical results (abstract). PACE 1999;22:720.
14. Saksena S, Prakash A, Hill M, Krol RB, Munsif AN, Mathew PP, Mehra R.Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 1996; 28:687-94.
15. Hutse W, Tavernier R, Jordaens L. Inappropriate shocks in a patient treated with a cardioverter defibrillator. Heart 1997;77:386-387.
16. Moss AJ, Liu JE, Gottlieb S, Locati EH, Schwartz PJ, Robinson JL. Efficacy of permanent pacing in the management of high-risk patients with long QT syndrome. Circulation 1991;84:1524-9.
17. Fananapazir L, Epstein ND, Curiel RV, Panza JA, Tripodi D, McAreavey D. Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy: evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. Circulation 1994;90:2731-42.
18. Zipes DP, Foster PR, Troup PJ, Pedersen DH. Atrial induction of ventricular tachycardia: reentry versus triggered automaticity. Am J Cardiol 1979;44:1-8.
19. Mehmanesh H, Lange R, Brachmann J, Hagl S, Gilkerson J. First report on surgical experience with a new implantable cardioverter defibrillator providing dual-chamber pacing and sensing (abstract). PACE 1997;20:1079.

Chapter 12

Biventricular Pacing: A Promising Therapeutic Alternative for Patients with Severe Congestive Heart Failure

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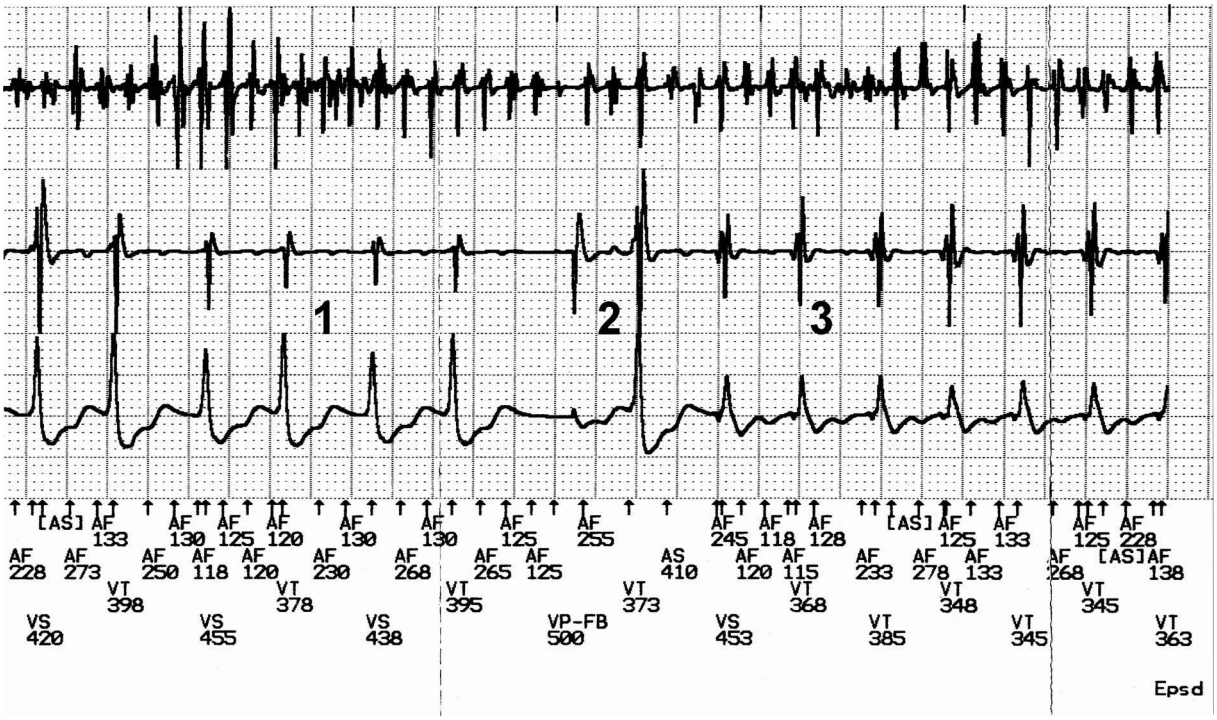
Published: Progress in Biomedical Research 2001;6:353-357.



Summary

Biventricular pacing is a novel therapy for patients with heart failure and severely diminished left ventricular function associated with intracardiac conduction delay. The primary aim of biventricular pacing is to re-synchronize the ventricular activation pattern and to improve hemodynamics. Results of early and recent studies including large-scale, multicenter, randomized trials demonstrated the efficacy of this treatment modality showing improved hemodynamics, exercise tolerance and quality of life in patients with severe heart failure. Preliminary data suggest that patients with atrial fibrillation may also benefit. There is a growing evidence showing that the frequency of life-threatening arrhythmias is decreased using biventricular pacing in this patient population. However, the effect of biventricular pacing on mortality is still unknown. Important ongoing trials will clarify the important issues regarding the influence on mortality and the problem of appropriate patient selection

.

Introduction

Heart failure is a highly prevalent disease and despite recent advances in medical therapy it remains a growing health problem [1]. Intraventricular conduction delay is an independent predictor of mortality in patients with severe congestive heart failure (CHF) [2]. Multisite or biventricular pacing was recently developed as a possible novel pacing modality for patients with CHF and intraventricular conduction delay [3]. In patients with drug refractory heart failure and a severely diminished left ventricular function associated with significant intracardiac conduction delay biventricular pacing can be used to improve mechanical synchrony [4]. Results of available controlled and uncontrolled studies show improvement in hemodynamics, exercise tolerance, and quality of life in patients with heart failure [3-7]. The aim of this review is to summarize the current knowledge regarding biventricular pacing as well as the potential mechanism of the effectiveness of this pacing modality, including the evaluation of the optimal pacing sites. Furthermore, on the basis of our experience, we provide a description of the implantation technique. The possible role of a combined biventricular pacing and ICD therapy is also discussed, particularly the influence of biventricular pacing on the recurrence of ventricular tachyarrhythmias.

Rationale for biventricular pacing

A considerable proportion of the patients with severe CHF often has significant intraventricular conduction delay and left bundle branch block [2]. This intraventricular conduction delay -indicated by prolonged QRS duration- may cause an abnormal contraction pattern recognized as ventricular dyssynchrony [4]. Segments of the left and right ventricle contract in different times. Ventricular dyssynchrony results in abnormal interventricular septal wall motion, decreased contractility (dP/dt), reduced diastolic filling times, and prolonged duration of mitral regurgitation causing significant mechanical disadvantage for the failing heart [8,9]. Theoretically, multisite or biventricular pacing may resynchronize the contraction pattern of the ventricles [3-5]. This idea serves as a rationale for biventricular pacing in this severely ill patient population. Re-coordination of the activation pattern can normalize the so called functional mitral regurgitation and may optimize left ventricular filling [4]. However, the trend towards a superior hemodynamic benefit has to be interpreted with caution, because the atrioventricular delay was optimized in

most of the studies, which has had a major impact by itself [10]. Recent data suggest that patients in atrial fibrillation may also benefit, but to achieve sufficient pacing time, radiofrequency catheter ablation of the atrioventricular node is often required [11].

A number of randomized trials have provided information on the efficacy and safety of biventricular pacing. Patients with severe heart failure (NYHA III or IV) and wide QRS complex were included in the PATH-CHF trial (Pacing THerapy in Congestive Heart Failure). During implantation invasive testing was performed and patients were then randomized to a one-month period of either univentricular pacing, no pacing, or biventricular pacing. The study utilized a three-month crossover period between pacing modes. The chronic pacing mode was optimized according to the results of crossover period. Results showed a 40% increase in the six-minute walking distance and a 50% improvement in quality of life with biventricular and preferred univentricular (usually left ventricular) pacing. The Multisite Stimulation in Cardiomyopathies (MUSTIC) trial randomized 67 patients with severe heart failure associated with a QRS duration > 150ms. This single-blind, randomized, controlled crossover study compared the responses of patients during two different pacing situations: three months of inactive pacing and three months of atriobiventricular pacing. The study concluded that although the procedure is technically complex, atriobiventricular pacing significantly improves exercise tolerance and quality of life in patients with chronic heart failure and significant intraventricular conduction delay [6]. These results were confirmed by the Multicenter InSync Randomized Clinical Evaluation Trial (MIRACLE) [12], which was presented at the 2001 Scientific Session of the American College of Cardiology. The MIRACLE trial statistically proved the therapeutic benefit of cardiac resynchronization therapy. The functional status of the patients significantly improved; this was quantified by objective measures such as a reduction in systolic and diastolic volumes, increase in left ventricular ejection fraction and reduction of mitral regurgitation.

Selection of the optimal right and left ventricular pacing sites

Despite the strong theoretical basis, a considerable proportion of patients does not respond to biventricular pacing therapy even if a decreased QRS complex is achieved. Different approaches are used to select patients who will benefit most from

biventricular pacing. In our center, a conventional electrophysiological induction study is combined with an acute hemodynamic evaluation of biventricular pacing. Standard diagnostic catheters are used to stimulate the high right atrium and the right ventricle at different sites. The coronary sinus is cannulated with a specially designed vascular sheath (Vue Port, Cardima, USA) that contains an inflatable balloon that is capable of performing a venogram without the need of a separate balloon catheter (Figure 1). After the anatomical situation is assessed and recorded for future use, a very thin 1.5 F multipolar electrode catheter (Pathfinder, Cardima) is inserted into the CS to perform the pacing study (Figure 2). At least two different side branches - that seem feasible according to the venogram - are cannulated by this multipolar electrode catheter. Intracardiac electrograms are recorded and the pacing threshold is evaluated at each site at different atriobiventricular pacing rates and atriventricular delays. A non-invasive, continuous photoplethysmograph with an option of model flow analysis (Portapres, TNO Biomedical Instrumentation, Amsterdam) that measures complex hemodynamics throughout the whole study including cardiac output, stroke volume and total peripheral resistance is connected to the patient. A transthoracic echocardiography that assesses transmitral flow completes the setup. The optimal pacing site is selected according to the results of acute hemodynamic measurements. There is growing evidence showing the disadvantageous effect of right ventricular apical pacing on left ventricular function [13]. Therefore, in the case of a non-responding patient, the right ventricular lead is repositioned from the right ventricular apex to alternative pacing sites (i.e., right ventricular outflow tract), and the measurements are repeated. However, improved acute hemodynamics does not necessarily mean an improved clinical outcome including a reduction in mortality. The evaluation of this issue necessitates large-scale randomized trials.

Figure 1. *Occlusion venogram of the distal coronary sinus shows appropriate side branches (arrow) for biventricular pacing.*

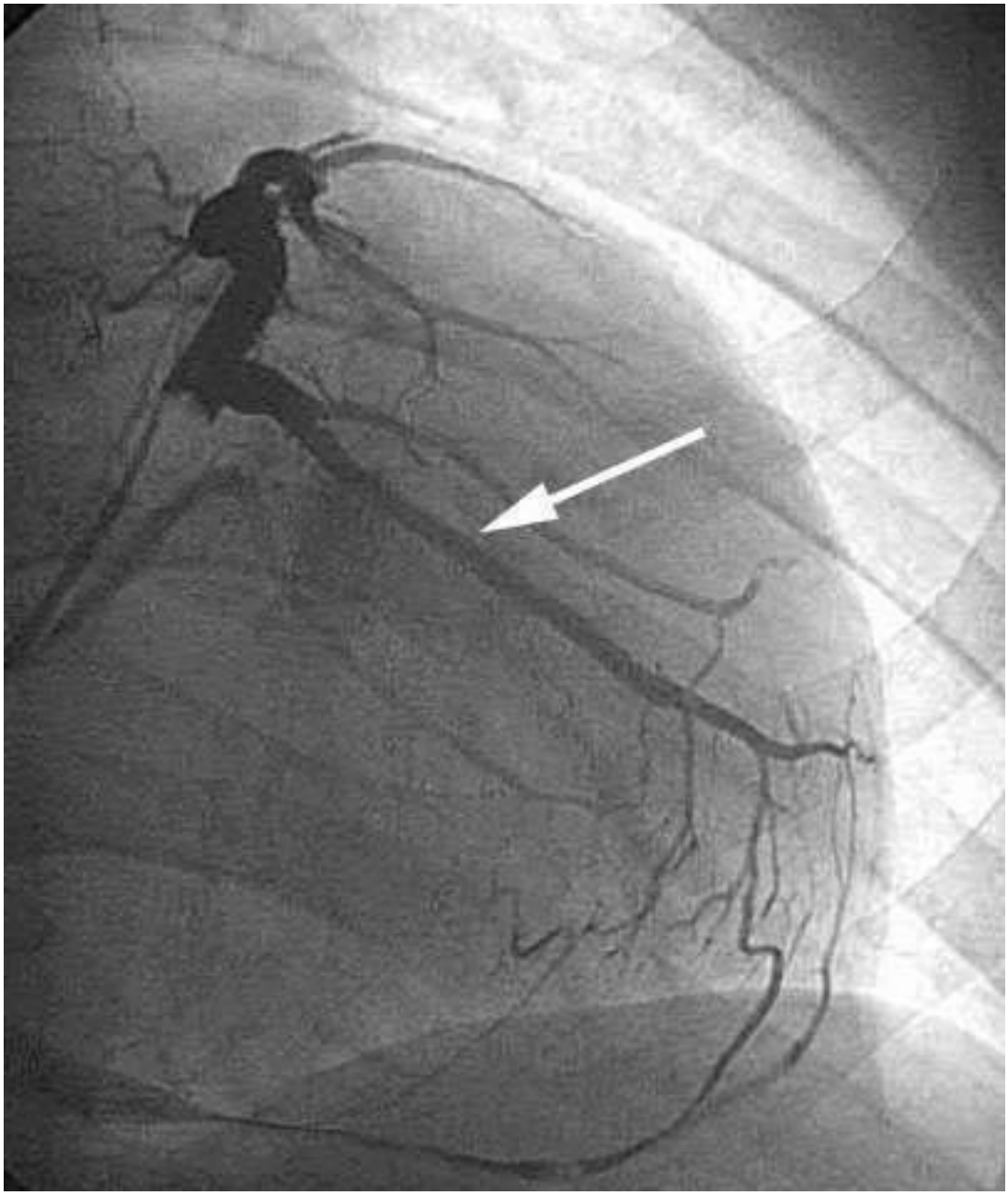
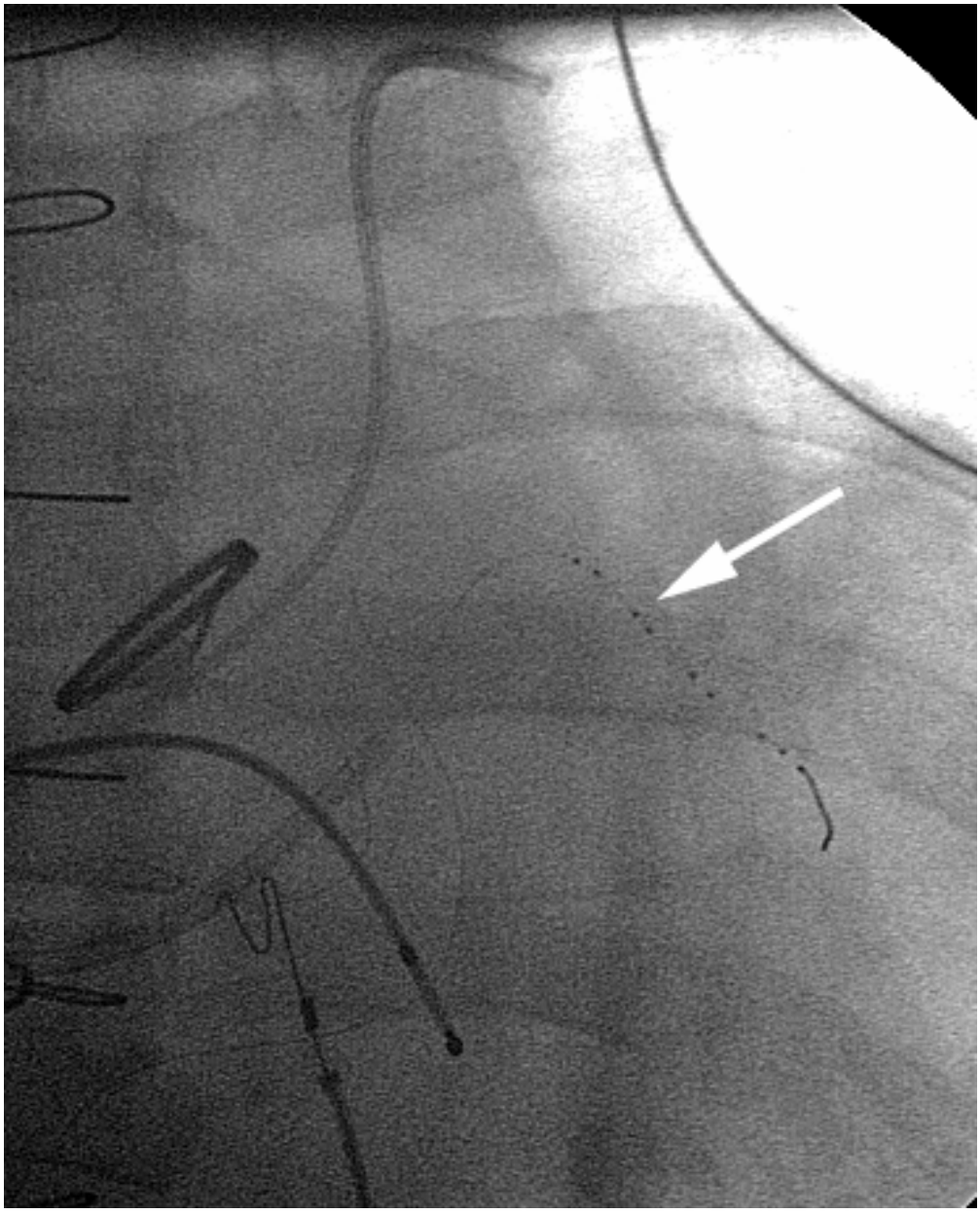


Figure 2. *Temporary multipolar electrode catheter (arrow) is used for acute hemodynamic study.*



The technique of left ventricular lead positioning

Transvenous implantation of the left ventricular lead via the coronary sinus (CS) is well- developed, however there is still a need to describe the optimal implantation technique. The methodology developed at the Thorax Center in Rotterdam, the Netherlands, is based on our own, as well as adopted international experience. After puncture of the subclavian vein, the CS is cannulated with a non-steerable diagnostic catheter using a combined electrophysiologic and anatomical approach. After successful cannulation of the CS, a 9 F delivery sheath is placed over the catheter distal to the CS, providing a stable and multipurpose access to the targeted vein which is selected according to the acute hemodynamic study (see above). The “peel away” sheath is then used to deliver a permanent, unipolar pacing lead, preferably at the lateral wall, midway between the apex and the base. Other lateral and posterior sites are also acceptable, but the great cardiac vein and the middle cardiac vein are used only when the other veins are not available.

Biventricular ICD therapy and recurrences of ventricular tachyarrhythmias

Although most of the recent studies demonstrated the beneficial effects of biventricular pacing on this patient population, the mortality rate still remains fairly high [14]. Nevertheless, none of the studies mentioned above aimed to assess the mortality in a randomized fashion. The high mortality rate suggests the natural course of this severe, advanced stage of heart failure disease because this pacing modality is used mainly for very sick patients with CHF, which is usually refractory to drug therapy. Since the incidence of sudden cardiac death accounts for 30 - 50% in this patient population [14], combined biventricular pacemaker and defibrillator therapy should be considered. Improved hemodynamics with biventricular pacing may reduce the need for interventions by the device. This possible and logical synergistic effect was proposed and studied by Higgins and his colleagues [15]. They reported that biventricular pacing diminished the need for ICD therapy for patients with tachyarrhythmias [15]. The decreased number of interventions by the ICD was possibly related to the improved hemodynamics. A decrease in ventricular conduction delay with biventricular pacing reduces macro-reentry and pause-dependent tachyarrhythmias because the dispersion of refractoriness is decreased, comparing with right ventricular pacing [15,16]. The decrease in plasma nor-

epinephrine levels and decreased sympathetic activity may also play role [17,18]. Zagrodzky et al. showed that acute biventricular pacing decreases the inducibility of sustained monomorphic tachycardias in patients with ischemic cardiomyopathy [16]. In contrast, in a retrospective study conducted by Theuns et al., the time between the implantation and the first recurrence of ventricular tachyarrhythmias was not modified by biventricular pacing in a virtually identical patient population [19]. Furthermore, subgroup analysis revealed a slightly earlier recurrence of ventricular tachyarrhythmias with a cycle length slower than 350 ms in the group treated with biventricular pacing, compared with groups having a dual-chamber ICD either with a narrow or broad QRS complex [19]. According to these results, the proarrhythmic effect of left ventricular lead can not be excluded. However, this potential and probably temporary disadvantage of this therapy's effect exists in the peri-procedural period. There is no available data comparing the late recurrence of the same arrhythmias with the recurrence of index arrhythmias.

Future considerations

So far, biventricular pacing is based on a modified conventional pacing setup. The placement of a permanent endocardial left ventricular lead using a transseptal technique seems technically feasible; however, the potential for life-threatening, thrombo-embolic complications has not yet been investigated. The enhanced hemodynamic response of multisite, left ventricular pacing in various clinical circumstances, such as the adjusted right ventricular-left ventricular stimulation delay, also necessitates further controlled studies.

References

1. Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med*. 1997;337:1360-1369.
2. Shamim W, Francis DP, Yousufuddin M, Varney S, Pieopli MF, Anker SD, Coats AJ. Intraventricular conduction delay: a prognostic marker in chronic heart failure. *Int J Cardiol*. 1999;70:171-178.
3. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, Mundler O, Daubert JC, Mugica J. Four chamber pacing in dilated cardiomyopathy. *Pacing Clin Electrophysiol*. 1994;17:1974-1979.
4. Kerwin WF, Botvinick EH, O'Connell JW, Merrick SH, DeMarco T, Chatterjee K, Scheibly K, Saxon LA. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. *J Am Coll Cardiol*. 2000;35:1221-1227.
5. Leclercq C, Cazeau S, Le Breton H, Ritter P, Mabo P, Gras D, Pavin D, Lazarus A, Daubert JC. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. *J Am Coll Cardiol*. 1998;32:1825-1831.
6. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873-880.
7. Merkely B, Vago H, Zima E, Geller L. Multichamber pacing in patients with an implantable cardioverter defibrillator. *Prog Biomed Res*. 2001;6:17-24.
8. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. *Br Heart J*. 1991;66:443-447.
9. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. *Circulation*. 1989;79:845-853.
10. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation*. 1999;99:2993-3001.
11. Leclercq C, Victor F, Alonso C, Pavin D, Revault d'Allones G, Bansard JY, Mabo P, Daubert C. Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. *Am J Cardiol*. 2000;85:1154-1156.

12. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *J Card Fail*. 2000;6:369-380.
13. Tantengco MV, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. *J Am Coll Cardiol*. 2001;37:2093-2100.
14. Gras D, Mabo P, Tang T, Luttikuis O, Chatoor R, Pedersen AK, Tscheliessnigg HH, Deharo JC, Puglisi A, Silvestre J, Kimber S, Ross H, Ravazzi A, Paul V, Skehan D. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. *Pacing Clin Electrophysiol*. 1998;21:2249-2255.
15. Higgins SL, Yong P, Sheck D, McDaniel M, Bollinger F, Vadecha M, Desai S, Meyer DB. Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. *J Am Coll Cardiol*. 2000;36:824-827.
16. Zagrodzky JD, Ramaswamy K, Page RL, Joglar JA, Sheehan CJ, Smith ML, Hamdan MH. Biventricular pacing decreases the inducibility of ventricular tachycardia in patients with ischemic cardiomyopathy. *Am J Cardiol*. 2001;87:1208-1210.
17. Saxon LA, De Marco T, Chatterjee K, Boehmer JP, Investigators ftV-C. The magnitude of sympathoneural activation in advanced heart failure is altered with chronic biventricular pacing (abstr). *Pacing Clin Electrophysiol*. 1998;21.
18. Hamdan MH, Zagrodzky JD, Joglar JA, Sheehan CJ, Ramaswamy K, Erdner JF, Page RL, Smith ML. Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. *Circulation*. 2000;102:1027-1032.
19. Theuns D, Klootwijk P, Szili-Torok T, Kimman G, Jordaens L. Ventricular tachyarrhythmias in patients with biventricular ICDs (abstr). *Europace*. 2001;Suppl.B:74.

Chapter 13

Outcome in Patients with an ICD Incorporating Cardiac Resynchronization Therapy: Differences between Primary and Secondary Prophylaxis

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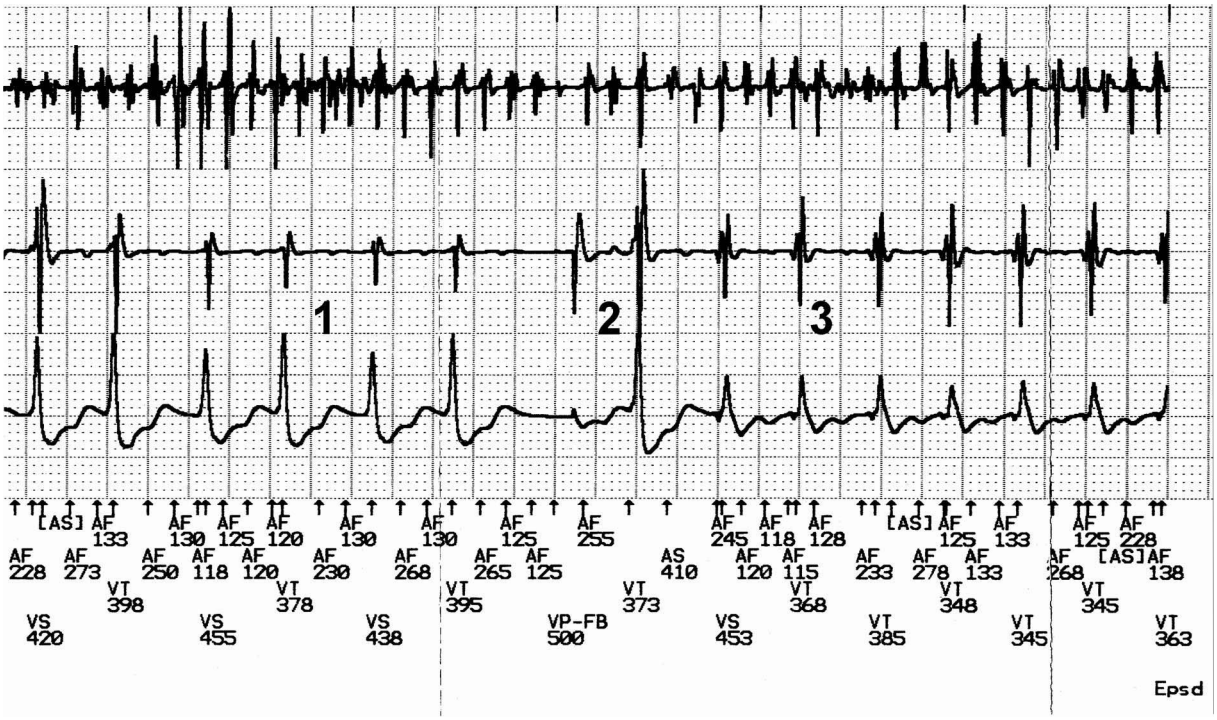


Abstract

Background: *The incidence of ventricular tachyarrhythmias in ICD patients with cardiac resynchronisation therapy (CRT-D) is not well studied.*

Aim: *To analyse event free survival in CRT-D patients with a primary or a secondary prophylactic ICD indication*

Methods: *Prospective, single centre. Eighty-six patients, 44% with a primary prophylactic indication. Actuarial event-free rates for mortality and arrhythmias were calculated.*

Results: *Baseline clinical characteristics were not significantly different between primary and secondary prophylaxis. Primary prophylaxis patients tended to have more often NYHA class III. Over 21 months, 724 ventricular events with therapy occurred in 36 patients (42%). The actuarial event-free rates, at 1 and 3 years, from appropriate ICD therapy were higher (P < 0.001) for primary (79.0% and 67.8%) than for secondary prophylaxis (45.6% and 27.0%). Appropriate ICD therapy occurred more in NYHA class II compared to class III (P = 0.016). Underlying disease (ischemic versus non-ischemic) and functional class did not play a role in multivariate analysis.*

Conclusion: *Important arrhythmic events in patients with congestive heart failure, and CRT-D occur at a very high rate when the indication is secondary prophylaxis. Patients with primary prophylaxis have an annual event rate of 10%, even when they tend to have a worse heart failure class.*

Introduction

Congestive heart failure (CHF) is reported to occur in 1% to 5% of the European population.[1] The long-term prognosis still remains poor.[2] Mortality is high, due to deterioration of left ventricular function and sudden death.[3] Arrhythmic sudden death is diverse and includes ventricular tachycardia (VT), ventricular fibrillation (VF), and bradycardic events, including some unrecognized hemodynamic situations leading to electromechanic dissociation or asystole. The prevention of life-threatening ventricular arrhythmias as such is a major goal in the management of patients with CHF. In multiple randomised studies, the implantable cardioverter-defibrillator (ICD) has demonstrated to be effective for life-threatening ventricular arrhythmias and to prevent sudden cardiac death in patients with reduced left ventricular function.[4-10] Although ICD treatment prolongs life in patients at risk, it does not improve quality of life or symptoms of CHF. Recent data demonstrated that cardiac resynchronisation therapy (CRT) has the potential to improve hemodynamic parameters and symptoms in heart failure patients, thereby potentially preventing disease progression and prolonging life.[11-13] The latter however, has never been proven in randomised trials. Recent trials demonstrated that CHF patients have a mortality benefit with ICD therapy.[10,14] This benefit can be achieved with conventional, single chamber ICDs, whereas patients with a profile suitable for resynchronisation show lower morbidity after receiving a combined device with CRT as well.

The aim of this study was to analyse the outcome and incidence of ventricular tachyarrhythmias in patients with congestive heart failure, treated with a cardiac resynchronisation ICD (CRT-D).

Methods

Patient population

The study population consisted of patients who received a CRT-D in combination with a transvenous approach. Indications for ICD therapy were a history of symptomatic sustained ventricular tachyarrhythmia or aborted sudden death without reversible cause (secondary prophylaxis). The primary prophylaxis group included patients with ischemic and nonischemic heart diseases, which were considered for cardiac transplantation, and patients who fulfilled criteria as described in the first Multicenter Automatic Defibrillator Implantation Trial or MADIT I [LVEF < 30%, nonsustained ventricular tachycardia (NSVT), inducible, but without rechallenge after

drugs].[4] All patients met CRT criteria: symptomatic CHF, inter- or intraventricular conduction delay (QRS duration ≥ 120 ms), LVEF ≤ 35%, and left ventricular end-diastolic diameter of more than 55 mm. Nonischemic dilated cardiomyopathy was diagnosed after exclusion of coronary artery disease by the absence of a Q wave myocardial infarction, and/or exclusion of significant luminal stenosis in one or more coronary arteries. The clinical characteristics of the patients are summarised in Table 1.

Implantation procedure and programming

Implantations were performed preferably with a single left pectoral incision, a left cephalic vein cutdown and a left subclavian puncture. Defibrillation leads were positioned in the right ventricular apex. The LV pacing lead was placed in a tributary of the coronary sinus. A postero-lateral branch was used in 39 patients (45%), an anterior branch in 20%, and a lateral branch in 10% of patients. The lowest effective defibrillation energy was less than 15 J in 49/56 tested patients. The selected devices were InSync 7272 and 7279 (Medtronic Inc., Minneapolis, MN, USA), Contak CD, Renewal I, and Renewal II (Guidant Inc., St. Paul, MN, USA), and Epic HF (St Jude Medical, Sylmar, CA, USA). ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation. The mean ventricular tachycardia detection rate was 383 ± 40 ms, the mean fibrillation detection interval was 290 ± 22 ms. Biventricular pacing was monitored by 12-lead surface ECG during threshold testing. At the 3-month visit, the mean programmed AV delay was 106 ms and the ventricular output to ensure biventricular capture was programmed at 3.6 V. The maximum ventricular output was programmed in only 9 patients (10%) at this interval.

Data collection and tachyarrhythmia classification

Follow-up started at the time of ICD implantation. All patients were followed at 3-monthly intervals and were advised to contact our out-patient clinic as soon as possible after a symptomatic event. At each visit, arrhythmic events were retrieved from the device's memory. The stored electrograms (EGMs) were visually analysed by 2 investigators to assess the type of the recurrent arrhythmia. In case of disagreement between the 2 reviewers about the stored EGMs, a third one was

consulted to reach a final agreement. The stored arrhythmias were classified as (1) ventricular tachyarrhythmia or (2) atrial tachyarrhythmia without a coexistent ventricular arrhythmia. As the atrial electrogram was present, the presence of atrioventricular dissociation was used to diagnose ventricular tachycardia. Otherwise, a ventricular tachyarrhythmia was defined as an event with a sudden increase in rate combined with a change in electrogram morphology from the baseline rhythm. Ventricular arrhythmias were classified as “sustained” or “nonsustained”. A “sustained ventricular tachyarrhythmia” was defined as a ventricular event lasting long enough to allow delivery of device therapy. “Nonsustained” events were defined as events, not long enough for triggering device therapy, and were excluded from analysis.

Statistical analysis

Continuous variables are expressed as mean ± SD if normally distributed, or otherwise by median. Continuous variables were analysed with Student’s *t*-test. Categorical data are summarised as frequency (percentage). Chi-square test was used for analysis of categorical variables. Estimated survival and the actuarial event-free rates were calculated according to the Kaplan-Meier method and were compared by use of the log-rank test. Survival time was defined as the date from ICD implantation to the date of death or last follow-up. Patients undergoing cardiac transplantation were censored from the moment of transplantation. The actuarial event-free rates from ventricular tachyarrhythmias triggering ICD therapy were measured from the date of ICD implantation to the date of the first ventricular tachyarrhythmia triggering ICD therapy or last follow-up; deaths and cardiac transplantation were treated as censored observations. Covariates previously identified to be independently associated with the occurrence of appropriate ICD therapy were used in a Cox proportional-hazards model. A P value < 0.05 was considered statistically significant.

Table 1. *Clinical characteristics of the patients*

Characteristics	Total (n=86)	Primary prophylaxis (n=38)	Secondary prophylaxis (n=48)	P value
Age (years)	61 ± 10	60 ± 9	63 ± 11	0.25
Male gender	77%	68%	83%	0.09
LVEF (%)	23 ± 8	24 ± 10	23 ± 8	0.77
Cardiac disease				
Coronary artery disease	59%	51%	65%	0.27
Dilated cardiomyopathy	41%	49%	35%	
Heart failure class				
NYHA II	26%	11%	38%	0.006
NYHA III	74%	89%	62%	
Bridge-to-transplant	24%	34%	17%	0.08
Pharmacological treatment				
Amiodarone	50%	34%	63%	0.016
Betablockade	71%	66%	75%	0.47
Digoxin	30%	34%	27%	0.63
ACE inhibitor	93%	94%	94%	1.00
Diuretics	89%	94%	87%	0.46
Lipid-lowering drug	54%	57%	52%	0.66
History of atrial tachyarrhythmias	27%	24%	29%	0.40
Presenting arrhythmia				
Ventricular fibrillation	20%	0	35%	NA
Sustained VT	36%	0	65%	NA
Nonsustained VT	44%	100%	0	NA
Median follow-up (days)	556	404	636	0.001

Data are given as mean ± SD. Categorical data are shown as percentage.
ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NA = not applicable; NS = non significant; NYHA = New York Heart Association

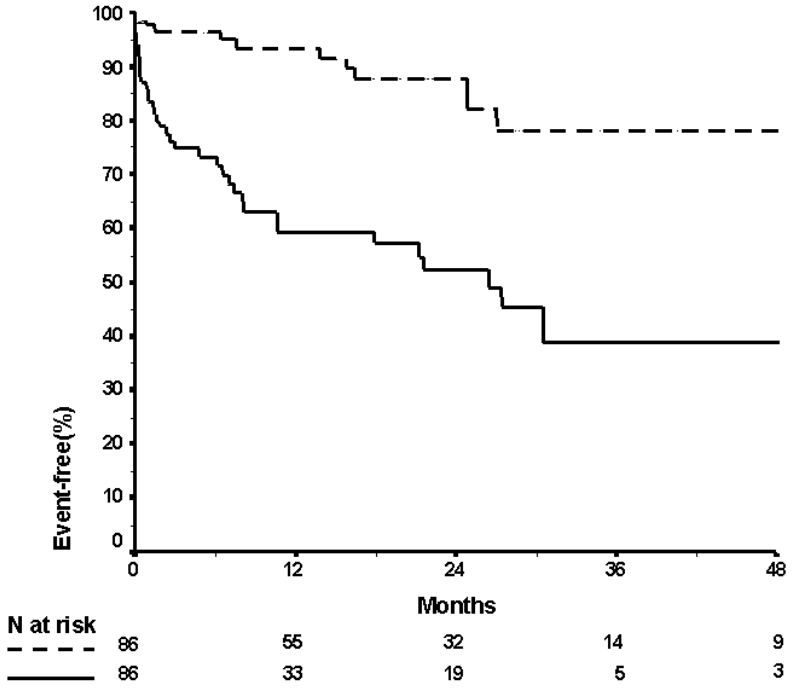
Results

Patient population

A total number of 86 patients received a CRT-D. Clinical characteristics and demographic data are listed in Table 1. The underlying cardiac disease was coronary artery disease (CAD) in 50 patients (58%). Mean QRS duration was 174 ± 31 ms. The ICD was indicated as secondary prophylaxis for 48 patients (56%), and as primary prophylaxis in 38 patients (44%). Twenty-one patients were formally listed for cardiac transplantation, 8 belonging to the secondary prophylaxis, 13 to the primary prophylaxis group.

The mean follow-up duration was 21 months, with a cumulative follow-up of 1772 months. During this follow-up, a total of 11 deaths were reported. Of these deaths, 5 (45%) were attributed to progressive heart failure, 2 (18%) were arrhythmic, and 2 (18%) were non-cardiac. Operative mortality, defined as death from any cause within 30 days of the implant procedure, was documented in 1 (9%) patient. The cause of death was unknown in 1 patient. Eight patients underwent successful heart transplantation. The actuarial mortality was 6.7% and 21.9%, at 1 and 4 years, respectively (Figure 1).

***Figure 1**. Actuarial event-free curves from all-cause mortality (dashed line) and from ventricular tachyarrhythmias triggering ICD therapy (solid line).*



Spontaneous ventricular tachyarrhythmias

During the follow-up period, 869 episodes with ventricular tachyarrhythmias were recorded in 40 patients (46.5%). Of the 869 episodes, 145 episodes of nonsustained ventricular tachyarrhythmias were excluded from analysis. Thus 724 episodes were eligible for analysis in 36 patients (range 1 to 92 episodes per patient). The first appropriate therapy occurred at a median interval of 63 days after ICD implantation. The actuarial event-free rates from appropriate ICD intervention were 59.4% and 38.8% at 1 and 4 years, respectively (Figure 1). Seventy episodes (10%) were treated with shock therapy (18 patients, range 1 to 12 episodes per patient). Antitachycardia pacing therapy was delivered in 654 episodes (90%) occurring in 23 patients (range 1 to 91 episodes per patient).

Clinical characteristics of patients with and without ventricular tachyarrhythmias during follow-up are summarised in Table 2. Ventricular tachyarrhythmias occurred in only 7 out-of-38 patients with a primary prophylactic indication against in 29 out-of-48 patients with a secondary prophylactic indication ($P < 0.001$). In a univariate model, male gender, lower NYHA class, and a secondary prophylactic indication correlated with a higher recurrence rate for ventricular tachyarrhythmias. To evaluate clinical predictors of appropriate device therapy, univariate covariates with P value ≤ 0.10 were entered in a Cox proportional hazards model adjusted for difference in follow-up time. This multivariate model with “appropriate device therapy” as the dependent variable revealed the prophylactic indication as the only independent predictor ($P = 0.009$).

Primary and secondary prophylaxis

Of the 86 patients, a total of 38 patients had a primary prophylactic indication and 48 patients a secondary prophylactic indication for ICD implantation. Demographic and clinical variables for both groups are listed in Table 1. Underlying cardiac disease was not different between the 2 groups. Proportionally, patients with NYHA Class III were significantly higher in the primary prophylactic group. Amiodarone as antiarrhythmic drug treatment was significantly higher for patients with secondary prophylaxis. The Kaplan-Meier curves illustrating time to first appropriate ICD intervention for patients in both groups are shown in Figure 2. The actuarial event-free rates from appropriate ICD intervention were lower in the secondary prophylaxis

group (79.0% and 67.8% for primary versus 45.6% and 27.0% for secondary prophylaxis, at 1 and 3 years, respectively; P = 0.001).

Twelve patients (14%) experienced ventricular tachyarrhythmias with cycle length (CL) ≤ 250 ms, and 19 patients (22%) had ventricular tachyarrhythmias with CL > 350 ms. For the primary prophylactic group, 75% of ventricular tachyarrhythmias had CL ≤ 350 ms, for the other group it was 52%.

Inappropriate therapy

Inappropriate tachyarrhythmia detection was observed in 17 patients (20%). The first inappropriate therapy occurred at a median interval of 194 days after ICD implantation. Six patients experienced inappropriate device therapy for atrial fibrillation or atrial flutter, and 12 patients received inappropriate therapy for sinus or atrial tachycardia. Inappropriate detection was not significantly different between the primary and secondary prophylaxis group.

***Figure 2**. Actuarial event-free rates from first appropriate ICD intervention for patients with primary prevention indication and patients with secondary prevention indication*

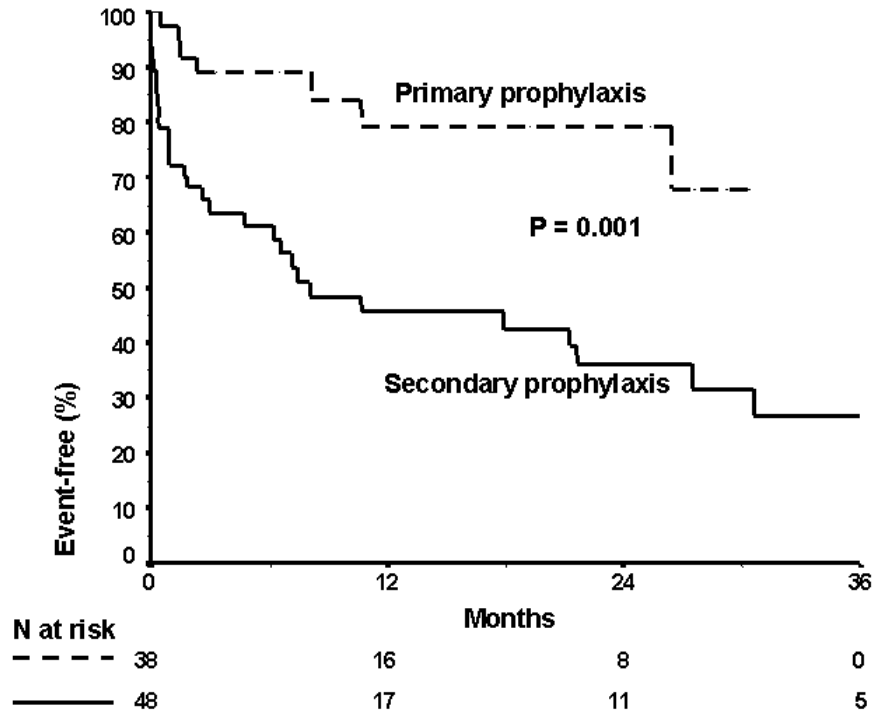


***Table 2**. Clinical characteristics of patients with and without ventricular tachyarrhythmias triggering appropriate device therapy*

Characteristics	Ventricular Tachyarrhythmias (n=28)	No ventricular tachyarrhythmias (n=32)	P value univariate	P value multivariate
Age (years)	62 ± 11	61 ± 9	0.47	
Male gender	89%	68%	0.037	0.25
LVEF (%)	23 ± 8	24 ± 9	0.65	
Prevention indication				
Primary	19%	62%	0.001	0.009
Secondary	81%	38%		
Cardiac disease				
Coronary artery disease	67%	53%	0.27	
Dilated cardiomyopathy	33%	47%	0.27	
Heart failure class				
NYHA II	36%	19%	0.085	0.48
NYHA III-IV	64%	81%		
Pharmacological treatment				
Amiodarone	53%	48%	0.83	
Betablockade	75%	68%	0.63	
Digoxin	34%	27%	0.63	
ACE inhibitor	91%	96%	0.65	
Diuretics	89%	92%	0.72	
Lipid-lowering drug	54%	54%	1.00	

Data are given as mean ± SD. Categorical data are shown as percentage.
Abbreviation as in Table 1.

Discussion

The present study addresses the incidence of appropriate ICD interventions in CHF patients with either a primary or secondary prophylactic indication for ICD therapy using a CRT-D. The major finding of this study is that recurrent ventricular tachyarrhythmias triggering device therapy are more common in patients with secondary prophylactic indications as compared to patients with a primary prophylactic indication for ICD implantation. However, the annual event rate in the primary prophylactic group remains 10% which is a generally accepted criterion for defining very high risk. The interpretation is difficult as it was suggested that patients with a MADIT I profile would have the same recurrence rate as secondary prophylaxis patients. On the other hand, the more advanced CHF patients in the primary prophylactic group (as suggested by their NYHA classification) are expected to die rather from heart failure than from arrhythmias.

Heart failure and secondary prophylaxis for arrhythmias

ICD therapy has demonstrated an improvement in survival after sudden cardiac death in high-risk patients.[6-8] Meta-analysis of secondary prophylactic trials demonstrated a significant benefit from ICD therapy for patients with LVEF $\leq$ 35% as compared to those with LVEF > 35%.[15] The ICD can be regarded as the treatment of choice in heart failure patients with life-threatening ventricular tachyarrhythmias. In the present study, we observed a very high incidence of ventricular tachyarrhythmias triggering device therapy in CHF patients with a secondary prophylactic indication. Almost all patients had a recurrence after 2 years. The benefit of ICD therapy was observed in patients with ischemic heart disease as well in patients with nonischemic heart disease. These findings reconfirm the guideline to implant an ICD in patients who already experienced a life-threatening ventricular arrhythmia, and demonstrate the frightening high recurrence rate of ventricular tachyarrhythmias.

Heart failure and primary prophylaxis for arrhythmias

The first primary prophylactic trials showed that patients with ischemic heart disease, a poor left ventricular function, NSVT, and inducible sustained ventricular tachyarrhythmias benefit from prophylactic ICD implantation.[4, 5] In contrast, the benefit from prophylactic ICD implantation was not proven in patients with nonischemic heart disease.[16, 17] The presence of NSVT is common in patients

with CHF and does not always predict sudden cardiac death.[18] The presence of NSVT in functional class III patients is rather a marker of worse prognosis related to poor left ventricular function than an indication for sudden cardiac death. The MADIT II trial reported a 31% reduction in all-cause mortality for post-myocardial infarction patients with LVEF ≤ 30%, even without NSVT an effect that was enhanced as a function of QRS duration.[9] This was confirmed with data from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), showing that a simple back-up ICD reduces overall mortality with 23%.[10] Adding CRT will provide more quality of life, and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial confirmed again the superiority of CRT-D over pacing alone in patients with a primary indication.[14] Wilkoff et al. reviewed recently the difference in tachyarrhythmia detection between primary and secondary prophylaxis in patients with resynchronization therapy.[19] Patients with a primary prophylaxis were much less likely to develop ventricular tachyarrhythmias; when they did, it was at significantly faster cycle lengths compared to patients with secondary prophylaxis. We confirmed their findings of ventricular tachyarrhythmias in our series. We observed an annual recurrence rate of 10%, which is very high, given the prophylactic indication. The majority of ventricular tachyarrhythmias in the primary prophylactic group had a cycle length ≤ 350 ms.

It has always been thought that sudden cardiac death comes early in the course of cardiac disease, while non-sudden cardiac death comes later, i.e. in stages of more advanced heart failure.[20] This finding is supported by the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), in which sudden death was more common in patients with NYHA class II.[21] This is also in harmony with our data, as appropriate device therapy occurred more frequently in patients with NYHA class II. These patients had more often a secondary prophylactic indication. It should be noted that the rate of interventions in the other group remains high in spite of resynchronisation therapy.

Limitations of the study

The present study was a retrospective analysis in a highly selected group of patients with CHF. However, both groups were followed prospectively on a regular basis at the out-patient clinic. We selected primary prophylactic patients with ischemic heart disease who fulfilled MADIT I criteria or when considered for cardiac transplantation,

as was also the case for nonischemic patients. In spite of the small numbers in the subgroups, a support for the policy to add the ICD component to CRT was observed for the primary prophylaxis group.

Conclusion

Ventricular tachyarrhythmias triggering device therapy appear extremely frequent in patients with CHF receiving the ICD after a first symptomatic arrhythmia or sudden death, in spite of CRT which was well delivered in our study. Further, patients selected for primary prophylactic indication, using MADIT I criteria, or when waiting for cardiac transplantation face a high recurrence rate.

The decision-making process to implant an ICD in CHF patients for primary prophylactic of sudden cardiac death now becomes a clinical decision based on low LVEF plus heart failure. This will probably result in a lower recurrence rate (SCD-HeFT). The uncertainty remains the option of cardiac resynchronisation: SCD-HeFT improved survival without CRT. COMPANION had no arm without CRT and yet a simple ICD. Till these questions are answered, our policy to combine both ICD and CRT in the field for primary prophylaxis remains an option, which is open for discussion.

References

1. Cowie M, Mosterd A, Wood D, et al. The epidemiology of heart failure. Eur Heart J 1997;18:208-223.
2. Erikson H. Heart failure: a growing public health problem. J Intern Med 1995;237:135-141.
3. Cleland J, Massie BM, Packer M. Sudden death in heart failure: Vascular or electrical? Eur J Heart Fail 1999;1:41-45.
4. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-1940.
5. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 2000;342:1937-1945.
6. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
7. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-1302.
8. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748-754.
9. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883.
10. Bardy G, Lee KL, Mark DB, et al. for the Investigators of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-337.
11. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-880.
12. Abraham W, Fisher A, Smith A, et al. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-1853.

13. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111-118.
14. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-2150.
15. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071-2078.
16. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator:randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia--AMIOVIRT. J Am Coll Cardiol 2003;41:1707-1712.
17. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453-1458.
18. Teerlink JR, Jalaluddin M, Anderson S, et al. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. Circulation 2000;101:40-46.
19. Wilkoff BL, Hess M, Young J, Abraham WT. Differences in tachyarrhythmia detection and implantable cardioverter defibrillator therapy by primary or secondary prevention indication in cardiac resynchronization therapy patients. J Cardiovasc Electrophysiol 2004;15:1002-1009.
20. Myerburg RJ, Interian A, Jr., Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 1997;80:10F-19F.
21. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-2007.

Summary

During the past 25 years, the implantable cardioverter-defibrillator (ICD) has evolved from the treatment of last resort to the gold standard for patients at high risk for life-threatening ventricular tachyarrhythmias. Patients at high risk include those who survived life-threatening ventricular tachyarrhythmias, and patients with cardiac diseases who carry an increased risk for these tachyarrhythmias. We performed a clinical assessment during implantation and follow-up of our patients in Rotterdam.

Part I Prognosis and follow-up of patients with an ICD

In **Chapter 1**, the clinical benefit of ICD therapy, survival, and adverse events of patients who received an ICD at the Erasmus MC Rotterdam are described. Our data confirm the benefit from ICD implantation, especially for those patients with a poor left ventricular function.

In **Chapter 2**, defibrillation efficacy testing is investigated. The role of a second defibrillation threshold test after implantation appears questionable. With the advances in ICD technology, defibrillation thresholds are low and stable, which changed the mode of death in ICD patients from instantaneous arrhythmic death to heart failure. Our data demonstrate that despite the advanced ICD technology, a subset of patients may require a second defibrillation efficacy test to confirm a poor prognosis.

The feasibility of remote monitoring of ICD therapy is discussed in **Chapter 3**. The expanding indications for ICD therapy and the complexity of current devices have a high impact on follow-up policy. Currently, the quality of medical supervision only depends on scheduled regular follow-up visits, which is time consuming and expensive. Too long follow-up intervals may have the disadvantage of a delay in the awareness of changes of the clinical course of the underlying disease or in the technical status of the device. Transmission of stored ICD data can overcome this problem and thus offers the potential to improve patient care.

Finally, a case of Twiddler's syndrome, which was detected by home monitoring is presented in **Chapter 4**.

Part II Rhythm discrimination by the ICD

The primary goal of the ICD is to detect and subsequently terminate ventricular tachyarrhythmias. The secondary goal is to deliver therapy only when necessary. Inappropriate therapy due to atrial tachyarrhythmias is the most common adverse

event in ICD patients. In this second part of the thesis, rhythm discrimination by the ICD is investigated.

Chapter 5 describes a confusing stored ICD electrogram. This electrogram demonstrates an apparent induction of ventricular tachycardia after appropriate pacing by the ICD. However, accurate analysis demonstrated an artefact representing a ventricular premature beat initiating the ventricular tachycardia.

The initial clinical experience with a new dual-chamber algorithm, SMART, is discussed in **Chapter 6**. This new algorithm is based on comparison of atrial and ventricular rates, which divide tachyarrhythmias into 3 rate branches. Next, applicable single- and dual-chamber arrhythmia discriminators are applied in order to classify the tachyarrhythmia. In our series, the SMART algorithm achieved a sensitivity of 100%, with a positive predictive value of 95.6% for all ventricular arrhythmias. The majority of misclassified episodes appeared to be atrial tachyarrhythmias with stable atrioventricular conduction.

In **Chapter 7**, the evolution of timing-based detection algorithms in ICDs is studied. Over the last 25 years, ICDs base arrhythmia discrimination on timing-based detection criteria in order to avoid inappropriate therapy for atrial tachyarrhythmias. Original single-chamber detection criteria have been implemented as such in dual-chamber devices. Atrial signals can be reliably recognized with atrial leads and improved arrhythmia discrimination algorithms based on atrial signals were developed. However, this did not reduce the incidence of inappropriate therapy over time with the development of algorithms as was proven with comparative studies.

Chapter 8 evaluated whether clinical characteristics can predict inappropriate therapy due to atrial tachyarrhythmias. We identified a history of atrial tachyarrhythmias and recurrent slow ventricular tachycardias, rate < 170 bpm, as independent predictors of inappropriate therapy. Whether device selection should depend on the knowledge of a history of atrial tachyarrhythmias still is open for debate, as inappropriate therapy equally occurs in patients with single- and dual-chamber devices.

The results of our prospective, randomized study comparing the performance of tachyarrhythmia detection algorithms in single- and dual-chamber devices are presented in **Chapter 9**. During a mean follow-up of 12 months, the investigators classified 653 tachyarrhythmia episodes with stored electrograms: 391 episodes were ventricular tachyarrhythmias and 262 epsiodes were atrial tachyarrhythmias.

Overall, no significant difference in tachyarrhythmia detection, atrial or ventricular, between single- and dual-chamber devices was observed. Not sinus tachycardia or atrial fibrillation were a problem, but atrial tachyarrhythmias with stable N:1 atrioventricular conduction remain a problem for both devices.

In **Chapter 10**, a systematic approach for the analysis of stored electrograms is proposed. Stored electrograms in ICDs have not only improved our patient management, but also contributed to our understanding of tachyarrhythmias. Stored electrograms are usually visually analyzed, but the analysis can also be performed in a methodological way by application of blocks containing physiologic information.

Part III Single-chamber, dual-chamber or biventricular devices

In **Chapter 11**, we studied factors influencing appropriate therapy and survival in ICD patients with single- and dual-chamber devices, in an era that dual chamber devices were only implanted for patients with bradycardia indication. Survival analysis demonstrated no significant difference between patients with single- and dual-chamber devices for mortality and for event-free rate of appropriate therapy. A tendency to less inappropriate interventions was observed in a small series of dual chamber devices. In addition, it was observed that a history of atrial fibrillation contributed to appropriate therapy.

Resynchronization therapy by means of biventricular pacing is a novel therapy for patients with heart failure and severely diminished left ventricular function associated with intracardiac conduction delay. In **Chapter 12**, we present a brief review of early trials evaluating the therapeutic effect of biventricular pacing. Furthermore, we propose a method to select the optimal right and left ventricular pacing sites together with a technique of left ventricular lead positioning.

The incidence of ventricular tachyarrhythmias in ICD patients with resynchronization therapy is presented in **Chapter 13**. Event-free survival was analyzed for patients with either a primary or a secondary prevention indication for ICD therapy. Ventricular tachyarrhythmias are very common for congestive heart failure patients with a secondary prevention indication. Patients with primary prophylaxis have an annual event rate of 10%, even when they tend to have a worse heart failure class. The decision-making process to implant an ICD in heart failure patients for primary prophylaxis of sudden cardiac death has presently become a clinical decision, based on low left ventricular ejection fraction plus heart failure.

Samenvatting

Het concept van de implantable cardioverter-defibrillator (ICD) heeft de afgelopen 25 jaar een grote ontwikkeling doorgemaakt. De eerste generatie defibrillatoren was uitsluitend in staat om ventrikelfibrilleren te herkennen en te onderbreken door middel van een elektrische shock. De volgende generaties defibrillatoren werden uitgerust met functies om verschillende ritmestoornissen te herkennen en te behandelen. Vanuit klinisch oogpunt is er een verschuiving opgetreden van secundaire preventie naar primaire preventie van plotse dood ten gevolge van ventriculaire ritmestoornissen. Dit proefschrift beschrijft zowel de klinische als technische aspecten van defibrillator therapie.

Deel 1 Prognose en follow-up van ICD patiënten

Hoofdstuk 1 beschrijft zowel het klinische voordeel als de potentiële complicaties van defibrillator therapie bij patiënten, bij wie een ICD in het Erasmus MC werd geïmplanteerd.

De rol van het testen van de defibrillatie effectiviteit wordt in **Hoofdstuk 2** behandeld. Door de technische vooruitgang kunnen ventriculaire ritmestoornissen effectief met lage energie gedefibrilleerd worden. Vanuit dit technisch oogpunt is een tweede defibrillatie test niet nodig, echter vanuit klinisch oogpunt kan deze test een slechte prognose bij een kleine groep patiënten bevestigen.

Veranderingen in de klinische status van de ICD patiënt worden vaak pas vastgesteld bij het volgende poliklinisch bezoek. In **Hoofdstuk 3** wordt de mogelijkheid van het op afstand waarnemen van zowel klinische als technische aspecten van defibrillator therapie beschreven. Het verzenden van opgeslagen data in de ICD heeft een potentiële meerwaarde voor de klinische follow-up van de patiënt.

Ter illustratie wordt in **Hoofdstuk 4** een voorbeeld van het op afstand waarnemen van ICD data gepresenteerd. Bij interpretatie van de ontvangen data werd een malfunctie van de ventriculaire elektrode vastgesteld.

Deel 2 Onderscheiden van ritmestoornissen door de ICD

Hoofdstuk 5 behandelt een voorbeeld van een opgeslagen registratie van een ventriculaire ritmestoornis, die na nauwkeurige analyse een ander ontstaansmechanisme heeft dan het op eerste oog doet lijken.

In **Hoofdstuk 6** wordt een nieuw tweekamer detectie algoritme, SMART, geëvalueerd. Na de vergelijking van de atriale en ventriculaire frequentie worden enkelkamer detectie criteria toegepast om een ritmestoornis te classificeren. Ventriculaire ritmestoornissen worden met behulp van dit algoritme betrouwbaar waargenomen. Ondanks een goede discriminatie tussen atriale en ventriculaire ritmestoornissen, worden atriale ritmestoornissen met een stabiele atrioventriculaire geleiding vooral verkeerd geclassificeerd.

De ontwikkeling van detectie algoritmen om onterechte therapie ten gevolge van atriale ritmestoornissen te vermijden, wordt in **Hoofdstuk 7** gepresenteerd. De classificatie van de ritmestoornis door de ICD is primair gebaseerd op de timing van ventriculaire signalen. De originele eenkamer detectie algoritmen zijn in de tweekamer ICD geïmplementeerd. De toevoeging van atriale informatie heeft tot betere en geavanceerde detectie algoritmen geleidt. Echter, onderzoeken die eenkamer met tweekamer detectie algoritmen vergeleken, lieten geen afname van onterechte therapie zien.

Hoofdstuk 8 gaat over klinische variabelen die een verhoogd risico op onterechte therapie kunnen voorspellen. Uit onderzoek blijkt dat de aanwezigheid van atriale ritmestoornissen in het verleden en het voorkomen van trage ventriculaire ritmestoornissen, beide een verhoogd risico op onterechte therapie voorspellen. De beslissing om een tweekamer defibrillator bij patiënten met atriale ritmestoornissen te implanteren is een open vraag. Onterechte therapie werd namelijk in gelijke mate bij zowel eenkamer als tweekamer defibrillatoren waargenomen.

Een gerandomiseerd onderzoek tussen eenkamer en tweekamer detectie algoritmen wordt in **Hoofdstuk 9** gepresenteerd. De resultaten van dit onderzoek laten geen verschil zien in de discriminatie van ritmestoornissen tussen beide detectie algoritmen. Ventriculaire ritmestoornissen worden betrouwbaar door beide detectie algoritmen waargenomen. Van de atriale ritmestoornissen zijn zowel sinustachycardie als atriumfibrilleren geen probleem voor eenkamer en tweekamer detectie algoritmen. Atriale ritmestoornissen met een stabiele atrioventriculaire geleiding blijven een probleem voor beide defibrillator detectie algoritmen.

Een systematische methode voor de beoordeling van opgeslagen elektrogrammen wordt in **Hoofdstuk 10** gepresenteerd. Opgeslagen elektrogrammen geven inzicht in ritmestoornissen en bepalen het klinisch beleid van de patiënt. De toepassing van

blokken met fysiologische informatie, die kenmerken beschrijven van ritmestoornissen, is een methodiek voor het analyseren van ritmestoornissen.

Deel 3 Enkel kamer, dubbel kamer of biventriculaire ICDs

In **Hoofdstuk 11** worden factoren die invloed hebben op terechte ICD therapie en overleving onderzocht in een groep patiënten met eenkamer en tweekamer defibrillatoren. Er wordt geen verschil in terechte therapie en overleving gevonden tussen patiënten met een eenkamer of een tweekamer defibrillator. Een trend tot minder onterechte therapie werd waargenomen bij de kleine groep patiënten met een tweekamer systeem. Patiënten met atriale ritmestoornissen hebben een groter risico op terechte therapie voor ventriculaire ritmestoornissen.

In **Hoofdstuk 12** wordt een nieuwe toepassing beschreven: resynchronisatie therapie bij patiënten met hartfalen en een intra- of interventriculaire geleidingsstoornis. Een kort overzicht van onderzoeken over resynchronisatie therapie wordt gepresenteerd. Verder wordt in dit hoofdstuk een methode voorgesteld om de beste positie van de rechter en linker ventrikel elektrode te bepalen.

Hoofdstuk 13 gaat in op een klinisch vraagstuk van patiënten die in aanmerking komen voor resynchronisatie therapie. Een hoge incidentie van ventriculaire ritmestoornissen wordt waargenomen bij patiënten met hartfalen en een indicatie voor resynchronisatie therapie. Bij patiënten die eveneens een ICD indicatie hebben op basis van secundaire preventie is de incidentie van ventriculaire ritmestoornissen hoger ten opzichte van patiënten met een primaire preventie indicatie voor ICD therapie. Echter, de jaarlijkse incidentie van ventriculaire ritmestoornissen in de primaire preventie groep bedraagt 10%, ongeacht het stadium van hartfalen. Profylactische ICD therapie bij patiënten met hartfalen is een klinische beslissing op basis van de lage linker ventrikel ejectiefractie en hartfalen.

Dankwoord

Dit proefschrift is opgedragen aan mijn dochters Maria en Lauren. De toekomst heeft zijn wortels in het verleden. ‘Young as a flood after the rain, old as the course it follows’

Allereerst gaat mijn dankbetuiging uit naar Prof.dr. Hein Wellens, een eminent wetenschapper en leermeester. Mijn interesse in de klinische elektrofysiologie en vooral het analyseren van ritmestoornissen is ontstaan tijdens mijn jaren in het Academisch Ziekenhuis Maastricht. Bedankt voor de samenwerking en de inspiratie.

Mijn promotor Prof.dr. Luc Jordaens dank ik voor alle kansen die hij mij heeft geboden. Beste Luc, je bent altijd meer geweest dan alleen een collega. Het idee “PINAPP” ontstond tijdens het nuttigen van een Belgisch biertje op het terras van café Coenen. Jouw enorme drive en enthousiasme hebben de klinische elektrofysiologie van het Erasmus MC een nationaal en een internationaal gezicht gegeven. Het deel uitmaken van de initiële kleine groep mensen, die een afdeling vanuit het niets heeft opgebouwd, betekent veel voor mij.

Mijn co-promotor Dr. Peter Klootwijk wil ik bedanken voor de samenwerking tijdens de afgelopen jaren. Peter, de constructieve kritiek en discussies zijn altijd erg stimulerend geweest om het onderste uit de kan te halen.

Gaarne wil ik de leden van de beoordelingscommissie en de promotiecommissie, Prof.dr. P.J. de Feyter, Prof.dr. J.L.R.M. Smeets, Dr. C.C. de Cock, Prof.dr. M.L. Simoons, Prof.dr. D. Poldermans, en Prof.dr. N. van Hemel bedanken voor de tijd en aandacht die ze hebben besteed aan het beoordelen van het manuscript.

Prof.dr. J.L.R.M. Smeets, beste Joep bedankt voor de uurtjes in onze Maastrichtse jaren. Het fundament van het kritisch analyseren van ritmestroken heb ik van jou geleerd.

Mijn paranimfen, Geert-Jan Kimman en Andrew Thornton. Geert, we hebben samen heel wat uren doorgebracht in het Erasmus MC. Bedankt voor de mooie tijd. De “reentry” in “je AVNRT” is nu beschreven en dit zal resulteren in een mooi proefschrift.

Andrew, de hypermoderne technieken in diagnostiek en behandeling van ritmestoornissen, dit is jouw grote uitdaging. Laat de “magnetic navigation” de juiste route uitzetten voor je promotieonderzoek.

De artsen van de afdeling Klinische Elektrofysiologie, Marcoen Scholten a.k.a. mister atrial fibrillation, veel succes met je nieuwe uitdaging, bedankt voor de samenwerking in de afgelopen jaren en veel succes met je promotie onderzoek. Jan Res, bedankt voor de implantaties en de samenwerking tijdens elektrofysiologische onderzoeken en ablaties. Wellicht, zien we weer nieuwe aspecten van ons werk om nader te onderzoeken. Joris Mekel, veel succes met je opleiding tot klinisch elektrofysioloog. Maximo Rivero Ayerza, veel enthousiasme en nieuwe impulsen, onze samenwerking is nog maar net begonnen.

Tamas Szili-Torok, thanks for your critical notes. Your drive for research is inspiring.

De technici van de afdeling Klinische Elektrofysiologie, Paul Knops, Ronald Luyten, Max Miltenburg, Ronald van der Perk en Roel de Ruiter, worden bedankt voor hun werk tijdens de implantaties en de poliklinische controles. Het poliklinisch controleren van de ICD is tijdens de kritische situaties een bundeling van krachten op technisch en klinisch gebied. Ik ben erg trots op onze technische groep omdat zij het klinische aspect van ICD therapie centraal stellen. Bedankt, we gaan ervoor, op naar de volgende uitdaging a.k.a. morfologie.

De verpleegkundigen van de afdeling klinische Elektrofysiologie, Lara Emilsdottir, Wilma van de Kerke, Richard Alloway, Agnes Muskens-Heemskerk, en Hans van Schendel, worden bedankt voor hun inzet bij implantaties en psycho-sociale begeleiding van onze ICD dragers. Petter Janse, bedankt voor de samenwerking tijdens de onderzoeksprojecten van onze afdeling. De ex-verpleegkundige van de afdeling, Esther Zwanenburg, bedankt de samenwerking en het opvangen na mijn vogelvlucht resulterend in 2 gebroken armen.

Laura Bom en Anneke Stam, bedankt voor het coördineren van afspraken en het plannen van procedures. Het secretariaat van de afdeling is te vergelijken met het crisiscentrum van het Pentagon.

Annet Louw, bedankt voor het navigeren in het bureaucratische doolhof tijdens het eindstadium van het promotie traject. Jouw hulp en inzet is erg belangrijk voor promovendi om ze door dat tijdschema te krijgen.

De volgende mensen van Cardialysis wil ik bedanken. De analisten van het ICD Corelab in Cardialysis, Heather, where are you?, Ellie en Lali, bedank ik voor de prettige samenwerking in de afgelopen jaren. Gerrit-Anne, Yvonne en Claudia bedank ik voor het randomiseren van mijn PINAPP patiënten. Dick, bedankt voor het uitzoeken van de GEE statistische methode, ik hoop dat we in de toekomst nog vele leuke statistische analyses kunnen uitvoeren. Veel succes met je eigen promotie traject.

De medewerkers van de desbetreffende ICD fabrikanten wil ik bedanken voor de prettige samenwerking tijdens de afgelopen jaren. Jongens, dit is nog maar het begin. Een kritisch blik moet geen deuren sluiten, maar juist openen voor verdere progressie in de diagnostiek en de therapie van de ICD.

Jan Tuin en Paula Delfos, bedankt voor de grafische ondersteuning. De posters van het Thoraxcentrum zijn een plaatje om te zien.

Zoals bij ieder proefschrift, er zijn altijd diepte- en hoogtepunten. Muziek van bijvoorbeeld, Cradle of Filth, Dimmu Borgir, Dream Theater, en Slipknot hebben mij energie gegeven. Thanks mates, for writing and playing this insane stuff, which is torturing my fingers as a trained classical guitar player.

Pa en ma, bedankt dat jullie mij altijd gesteund hebben in mijn ontwikkeling.

Het laatste woord is gericht aan mijn partner. Marianne, mijn dank die ik aan jou verschuldigd ben is het grootst. Jij bent degene die ondanks je eigen drukke baan in staat is om mijn tekortkomingen in ons gezin op te vangen. Mijn dank en gevoel zijn niet in woorden uit drukken. In Rotterdam beter bekend als, ‘geen woorden, maar daden’.

Curriculum Vitae

Curriculum Vitae

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Profession

1992 - 1998:	Cardiology, University Hospital Maastricht
1998 - :	Clinical Electrophysiology, Erasmus MC Rotterdam
	Position: Scientist and supervisor ICD clinic
1999 - :	Cardialysis, Rotterdam
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Member

1999:	Dutch Society of Cardiology
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Topics of interest

Implantable defibrillator therapy

- Rhythm discrimination, timing-based and morphology-based
- Congestive heart failure
- Risk stratification

Cryothermal mapping and ablation

Biomedical statistics

Publications

1. Habets JHM, **Theuns DAMJ**, Scheerder COS. Klinische evaluatie van disposable ECG-elektroden. TG 1996;1,11-12.
2. Jordaens LJLM, **Theuns D**, Flamee M, Oostindjer A, De Ronde W, Bijl M, Roelandt JRTC. Intrathoraric conversion of 'refractory' atrial fibrillation. The Thoraxcentre Journal 1999; 11(1): 16-19.
3. Jordaens LJ, Kimman GJ, **Theuns D**, Simoons ML, Roelandt JRTC. Early experience with implantable dual chamber defibrillators. The Thoraxcentre Journal 1999; 11(2): 24-28.
4. Tavernier RH, Kimman GP, **Theuns DAMJ**, Klootwijk PJ, Kazmierczak J, Jordaens LJLM. Comparison of events and survival in dual- versus single-chamber ICDs. Cardiologie 1999; 12: 604-608.
5. **Theuns D**, Kimman GJ, Jordaens L. Apparent induction of ventricular tachycardia after "appropriate pacing" by an implantable dual chamber defibrillator: confusing ICD electrograms. Heart 2000;84:36.
6. Szili-Torok T, Res J, De Ruiter R, **Theuns D**, D'hondt L, Schilderman B, Muskens-Heemskerk A, Kimman GJ, Jordaens L. Transseptal ablation of a left-sided accessory pathway guided by intracardiac echocardiography. The Thoraxcentre Journal 2000; 12(3): 72-74.
7. Kimman GP, **Theuns DAMJ**, Vantrimpont P, Dall 'Agatha A, Jordaens LJLM. Een aanhoudende linker kamertachycardie en een gedilateerde cardiomyopathie: Een kwestie van de kip of het ei? Cardiologie 2001;8:67-72.
8. **Theuns D**, Klootwijk AP, Kimman GJ, Szili-Torok T, Roelandt JRTC, Jordaens L. Initial clinical experience with a new arrhythmia detection algorithm in dual chamber implantable cardioverter defibrillators. Europace 2001;3:181-186.
9. **Theuns DAMJ**, Klootwijk APJ, Kimman GP, Simoons ML, Roelandt JRTC, Jordaens LJLM. Clinical benefit, survival, and adverse events in patients with an implantable cardioverter defibrillator: The initial Rotterdam experience. Netherlands Heart Journal 2001;9:216-221.
10. Szili-Torok T, **Theuns D**, Klootwijk P, Scholten MF, Kimman GP, Jordaens LJ. Biventricular pacing: A promising therapeutic alternative for patients with severe congestive heart failure. Progress Med Res 2001;6:353-357.
11. Szili-Torok T, Kimman G, **Theuns D**, Res J, Roelandt JR, Jordaens LJ. Transseptal left heart catheterisation guided by intracardiac echocardiography. Heart 2001;86:E11.
12. Kimman GP, Szili-Torok T, **Theuns DAMJ**, Jordaens L. Transvenous cryothermal catheter ablation of a right anteroseptal accessory pathway. J Cardiovasc Electrophysiol 2001;12:1415-1417.

13. Szili-Torok T, Klootwijk P, Van den Brand M, Ruiter R, **Theuns D**, Jordaens L. A rare complication: Ossification around the pacing leads after medial subclavian venapuncture. Cardiologica Hungarica 2001;2:162-164.
14. Szili-Torok T, Kimman GP, **Theuns D**, Poldermans D, Roelandt JRTC, Jordaens LJ. Deterioration of left ventricular function following atrio-ventricular node ablation and right ventricular apical pacing in patients with permanent atrial fibrillation. Europace 2002;4:61-65.
15. Szili-Torok T, **Theuns D**, Verblaauw A, Scholten M, Kimman GP, Res J, Jordaens LJ. Transthoracic defibrillation of short-lasting ventricular fibrillation: A randomised trial for comparison of the efficacy of low enenrgy biphasic rectilinear and monophasic damped sine shocks. Acta Cardiol 2002;57:329-334.
16. Kimman GP, Szili-Torok T, Nieuwdorp M, **Theuns DAMJ**, Scholten MF, Jordaens L. Hybrid pharmacologic and ablative therapy for the management of symptomatic atrial fibrillation. Netherland Heart J 2002;10:8-12.
17. Al Hashimi H, Al Windy NYY, **Theuns DAMJ**, Jordaens LJLM. Sudden death of unknown origin. The Thoraxcentre Journal 2002;14:6-9.
18. Scholten M, Szili-Torok T, Kimman GJ, Res J, **Theuns D**, Jordaens L. Case report: Right linear ablation for paroxysmal AF guided by intracardiac echocardiography. The Thoraxcentre Journal 2002;14:27-29.
19. Szili-Torok T, Kimman GP, **Theuns D**, Res J, Roelandt JRTC, Jordaens LJ. Visualisation of intracardiac structures and radiofrequency lesions using intracardiac echocardiography. European J Echocardiography 2002;4:17-22.
20. Kimman GP, **Theuns DAMJ**, Jordaens LJ. A cool ablation. J Cardiovasc Electrophysiol 2002:13;839.
21. Szili-Torok T, **Theuns DAMJ**, Verblaauw A, Scholten M, Jordaens LJ. Transseptal cryoablation of a left-sided accessory pathway guided by a novel three-dimensional navigation system. The Thoraxcentre Journal 2002:14;37-39.
22. Szili-Torok T, Kimman GJ, Scholten MF, Ligthart J, Bruining N, **Theuns DA**, Klootwijk PJ, Roelandt JR, Jordaens LJ. Interatrial septum pacing guided by three-dimensional intracardiac echocardiography. J Am Coll Cardiol 2002;40:2139-2143.
23. Szili-Torok T, **Theuns DAMJ**, Verblaauw A, Scholten M, Jordaens LJ. Transseptal cryoablation of a left-sided accessory pathway guided by a novel three-dimensional navigation system. Heart Views.2002;3:172-176.
24. Szili-Torok T, **Theuns DAMJ**, Scholten MF, Kimman GP, Jordaens LJ. An “atypical” case of “typical” AVNRT? Pacing Clin Electrophysiol 2003;26:630-631.
25. **Theuns DAMJ**, Res JCJ, Jordaens LJ. Feasibility of home monitoring in ICD therapy. Europace 2003;5:139-142.

26. Kimman GP, Szili-Torok T, **Theuns DAMJ,** Res JC, Scholten MF, Jordaens LJ. Comparison of radiofrequency versus cryothermy catheter ablation of septal accessory pathways. Heart 2003;89:1091-1092.
27. Scholten MF, Kimman GP, Janse PA, Thornton AS, **Theuns DAMJ**, Jordaens LJ. Electrical isolation of pulmonary veins using cryothermal energy: study design and initial results. Neth Heart J 2003;9:341-346.
28. Engelen DM, Gressin V, Krucoff MW, **Theuns DA**, Green C, Cheriex EC, Maison-Blanche P, Dassen WR, Wellens HJ, Gorgels AP. Usefulness of frequent arrhythmias after epicardial recanalization in anterior wall acute myocardial infarction as a marker of cellular injury leading to poor recovery of left ventricular function. Am J Cardiol 2003;92:1143-1149.
29. **Theuns DAMJ**, Kimman GP, Szili-Torok T, Res JCJ, Jordaens LJ. Ice mapping during cyothermal ablation of accessory pathways in WPW: The role of the temperature time constant. Europace 2004;6:116-122.
30. Scholten MF, Thornton AS, **Theuns DAMJ**, Jordaens LJ. Twiddler's syndrome detected by home monitoring device. Pacing Clin Electrophysiol 2004;27:1151-1152.
31. Krenning BJ, Szili-Torok T, Voormolen MM, **Theuns DA**, Jordaens LJ, Lancee CT, De Jong N, Van Der Steen AF, Ten Cate FJ, Roelandt JR. Guiding and optimization of resynchronization therapy with dynamic three-dimensional echocardiography and segmental volume-time curves: a feasibility study. Eur J Heart Fail 2004;6:619-625.
32. Pedersen SS, Van Domburg RT, **Theuns DAMJ**, Jordaens L, Erdman RAM. Type D Personality is Associated with Increased Anxiety and Depressive Symptoms in Patients with an Implantable Cardioverter Defibrillator and their Partners. Psychosomatic Medicine 2004;66:714-719.
33. Kimman GP, **Theuns DAMJ**, Szili-Torok T, Scholten MF, Res JC, Jordaens LJ. CRAVT: A prospective, randomised study comparing transvenous Cryothermal and Radiofrequency Ablation in AtrioVentricular nodal reentrant Tachycardia. Eur Heart J 2004;25:2232-2237.
34. **Theuns DAMJ**, Klootwijk APJ, Goedhart DM, Jordaens LJ. Prevention of inappropriate therapy in implantable cardioverter-defibrillators: Results of a prospective, randomized study of tachyarrhythmia detection algorithms. J Am Coll Cardiol 2004;44:2362-2367.
35. **Theuns DAMJ**, Klootwijk APJ, Simoons ML, Jordaens LJ. Clinical variables predicting inappropriate use of implantable cardioverter-defibrillator in patients with coronary artery disease or non-ischemic cardiomyopathy. Am J Cardiol 2005;95:271-274.
36. Pedersen SS, Van Domburg RT, **Theuns DAMJ**, Jordaens L, Erdman RAM. Concerns about the implantable cardioverter-defibrillator: A determinant of anxiety and depressive symptoms independent of experienced shocks. Am Heart J (accepted).

37. **Theuns DAMJ**, Thornton AS, Klootwijk APJ, Scholten MF, Vantrimpont PJMJ, Balk AHMM, Jordaens LJ. Outcome in patients with an ICD incorporating cardiac resynchronization therapy: Difference between primary and secondary prophylaxis. (accepted).
38. **Theuns DAMJ,** Szili-Torok T, Jordaens LJ. Defibrillation efficacy testing – Long-term follow-up and mortality. (accepted).

Financial contribution for the production of this thesis is gratefully acknowledged from the following companies:

Bard Benelux B.V.

Biotronik Nederland B.V.

Cardialysis

ELA Medical Nederland B.V.

Guidant Nederland B.V.

Medtronic B.V.

St Jude Medical Nederland B.V.

Vitatron