Risk stratification and management of patients with sustained ventricular tachycardia or ventricular fibrillation.

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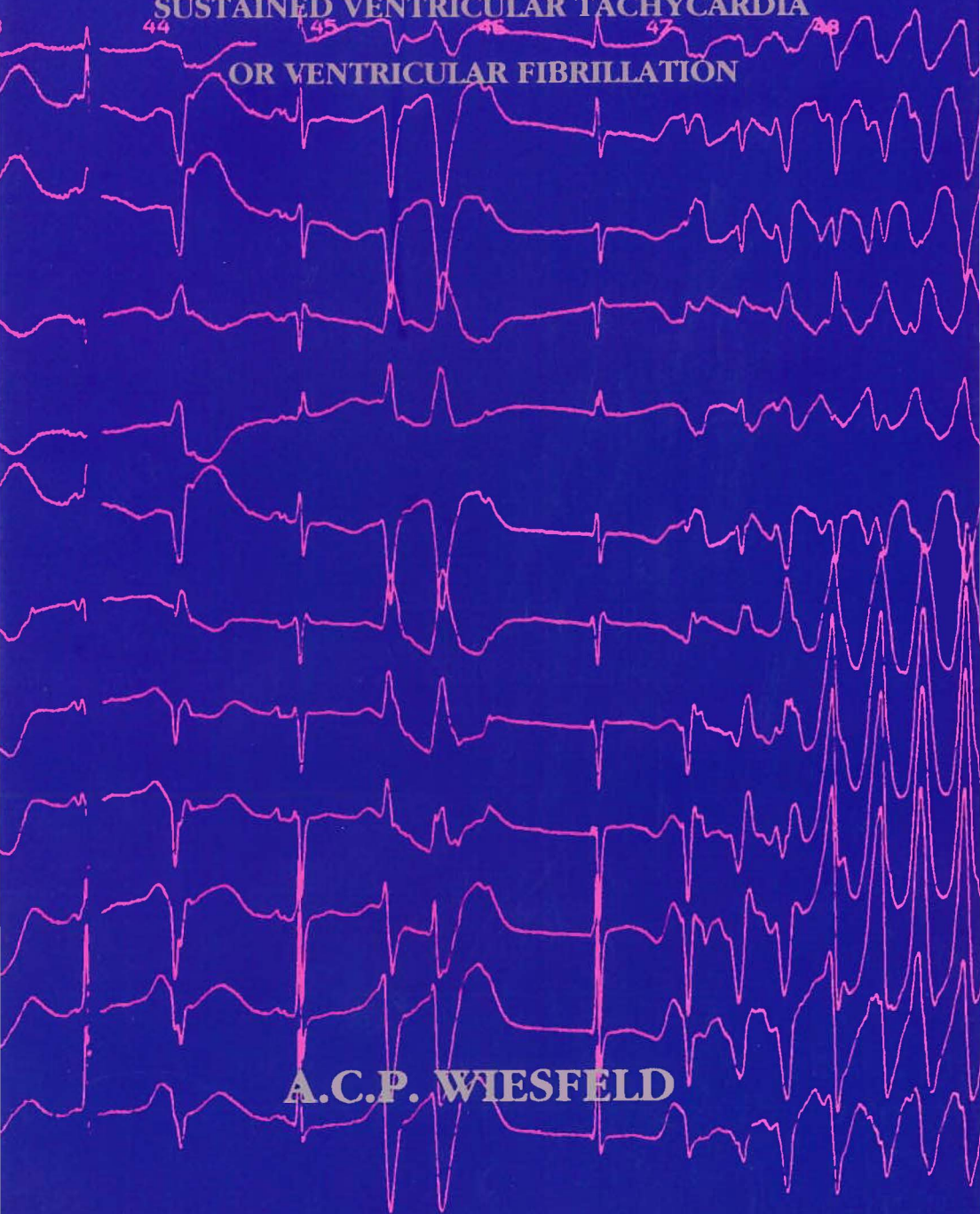

A.C.P. WIESFELD

RISK STRATIFICATION AND MANAGEMENT OF PATIENTS WITH SUSTAINED VENTRICULAR TACHYCARDIA OR VENTRICULAR FIBRILLATION

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Stellingen behorende bij het proefschrift

Risk stratification and management of patients with sustained ventricular tachycardia or ventricular fibrillation

1. Het coronair angiogram speelt een centrale rol bij het instellen van anti-ischemische therapie bij post-infarct VT/VF patiënten.

2. Bij de behandeling van levensbedreigende kamerritmestoornissen nemen anti-ischemische en anti-decompensatoire interventies een belangrijkere plaats in dan anti-aritmische.

3. Bij de definitie van idiopathisch ventrikelfibrilleren dient de endomyocardiale biopsie betrokken te worden.

4. Bij de behandeling van sustained ventriculaire tachycardieën of ventrikelfibrilleren worden beta-blokkers ondergewaardeerd.

5. Delayed rectifier blockers kunnen een sterkere werking op de atria dan op de ventrikels vertonen, hetgeen hun therapeutische breedte vergroot.

6. Bij de predictie van torsades de pointes dient de aandacht eveneens gericht te worden op TU golf veranderingen van het normaal voortgeleide complex na een kamerextrasystole.

7. Pure klasse 3 anti-aritmica zullen de wereld niet veroveren.

8. Het beoordelen van effectiviteit en veiligheid van een anti-aritmicum dient minimaal geëvalueerd te worden door een inspanningstest.

9. Goede patiëntenvoorlichting over het te verwachten resultaat van een ingestelde behandeling zal het aantal gerechtelijke vervolgingen van artsen reduceren.

10. Ook wisselende patiënt-arts contacten zijn ongezond.

11. Tropenartsen hebben aan alles gebrek behalve aan patiënten.

12. Wandelen is de manier om de wereld van je af te zetten.

13. Wijsheid komt niet met de jaren.

14. 'Jederein haet zenne vasteloavend'.

A.C.P. Wiesfeld
Groningen, 6 juli 1994

Rijksuniversiteit Groningen

RISK STRATIFICATION AND MANAGEMENT OF PATIENTS WITH SUSTAINED VENTRICULAR TACHYCARDIA OR VENTRICULAR FIBRILLATION

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'Veur de Mam en de Pap'

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Chapter 1

Introduction

1.1. General introduction

Sustained ventricular tachycardia and ventricular fibrillation (VT/VF) are the most unexpected and life-threatening cardiac events in a person's life. An enormous number of investigations has been performed and will be performed to identify the population at risk and to prevent arrhythmia recurrence.

The last decade the role of antiarrhythmic drugs has changed tremendously. The finding that prognosis after myocardial infarction did not improve with conventional antiarrhythmic drug treatment discouraged the use of these drugs (Furberg 1983). Possible explanations for the unfavorable findings could be either inappropriate study designs, including patient populations with a low risk profile, or true inefficacy of the antiarrhythmic drugs. In addition, it was suggested that negative effects in the patients with impaired left ventricular function might have outweighed beneficial effects in those with a preserved function. This followed the notion that prophylactic treatment in acute myocardial infarction with lidocaine was not associated with improved survival (Lie 1974, MacMahon 1988, Hine 1989a, Antman 1992). New expectations were raised by the clinically available class 1c drugs. Unfortunately, comparable to the class 1a and 1b antiarrhythmic drugs, these drugs were not accompanied by greater clinical safety. Although these drugs showed high antiarrhythmic efficacy (Salerno 1990, Singh 1993a), proarrhythmia (Herre 1990) and negative inotropism (Gottlieb 1990) are also their unfavorable characteristics. The enthusiasm in favor of the class 1c antiarrhythmic drugs tempered further because of the results of the Cardiac Arrhythmia Suppression Trial (CAST 1989). In this trial the 'suppression hypothesis', i.e. eradication of ventricular ectopy may prevent sudden death, was the starting point. However, prophylactic treatment of postinfarct patients with class 1c drugs was associated with a higher mortality compared to those treated with placebo. In addition, meta-analyses revealed deleterious effects of class 1 antiarrhythmic drugs in postinfarct patients (Hine 1989b, Teo 1993). By contrast, more favorable results were noted using the class 3 drugs sotalol (Julian 1982) or amiodarone (Burkart 1990, Cairns 1991, Ceremuzynski 1992, Nademanee 1993, Pfisterer 1993). The use of these class 3 agents was encouraged by their efficacy (Nademanee 1990) and less negative inotropic effects (Josephson 1988). Moreover, in the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) sotalol was more effective in suppressing sustained arrhythmias and preventing sudden death than class 1 agents

(ESVEM 1989, Mason 1993a). In the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation study (CASCADE), empiric amiodarone therapy in survivors of cardiac arrest was superior to class 1 antiarrhythmic drug therapy in preventing arrhythmia recurrences (CASCADE 1991, 1993). As a consequence clinical investigations in VT/VF patients nowadays focus on class 3 antiarrhythmic drugs (the future will show if this is justified). The beneficial effects of amiodarone and sotalol may also relate to their beta adrenergic blocker activity. The beneficial effect of beta blockade in postinfarct patients is unquestioned (Yusuf 1985). This holds in particular for patients with depressed left ventricular function (Chadda 1986, Kennedy 1993). More evidence becomes available that sustained VT/VF patients benefit also from solitary or adjuvant beta blocker therapy (Wiesfeld 1994).

The changing role of antiarrhythmic drugs was paralleled by an increasing use of noninvasive diagnostic techniques, like simultaneous 12-lead surface electrocardiography, ambulatory monitoring, signal-averaged electrocardiography (Tobé 1992a) and measurement of heart rate variability (Dreifus 1993). In addition, body surface mapping may be clinically applicable in the future (SippensGroenewegen 1990, Spekhorst 1990, Muilwijk 1994). Also improvement of invasive diagnostic techniques occurred. Programmed electrical stimulation and mapping techniques improved, resulting in better insight in electrophysiologic arrhythmogenic mechanisms (Franz 1991, Mohabir 1991, Zipes 1991). In vitro observations could be related to in vivo (either in the animal experiment or in humans) observations and vice versa (El-Sherif 1988, 1989, 1991). As a result, identification of high risk VT/VF patients has improved. Also, detection of underlying arrhythmogenic mechanisms is enhanced, enabling a targeted approach when using antiarrhythmic drugs or invasive treatment. Last but not least, our understanding of proarrhythmia has increased.

The disappointing results of the class 1 drug trials and the improvement of diagnostic techniques encouraged the development of invasive nonpharmacological antiarrhythmic therapies. Besides direct current ablation of the origin of the ventricular tachycardia, transcoronary ablation (Brugada 1988, 1989a) and radiofrequency ablation became clinically applicable (Scheinman 1991, Avitall 1993). An important development is the implantable cardioverter-defibrillator, especially since the transvenous form became available. Besides their efficacy, these cardioverter-defibrillators make it possible to perform randomized placebo-controlled trials in VT/VF patients with a cardioverter-defibrillator as back-up. Moreover, the ambulatory monitoring possibilities of cardioverter-defibrillators contributes to a more profound understanding of initiating mechanisms of VT/VF.

As a consequence of the latest developments reorientation in the evaluation and treatment of VT/VF patients was necessary. Before initiating treatment in VT/VF patients extensive clinical evaluation should be performed to identify underlying heart disease and arrhythmogenic mechanisms. This may result in

improved risk stratification and improved individualized treatment. The therapeutic approach of VT/VF patients should be based on the understanding of the pathophysiologic and electrophysiologic mechanisms rather than being empiric. Therefore, in the University Hospital Groningen a standardized approach of patients with sustained ventricular tachycardia and ventricular fibrillation was started in January 1989, *'The Groningen VT/VF protocol'*.

1.2. Aims of the thesis

As a consequence of the abovementioned new insights in diagnosis and therapy, reorientation on the clinical evaluation and treatment of patients with sustained ventricular tachycardia or fibrillation was mandatory. Therefore, the first aim of this thesis was to re-evaluate the role of underlying heart disease in patients with sustained ventricular tachycardia or fibrillation. In this context, the prognostic role of generally accepted parameters of left ventricular function in VT/VF patients was further studied. Also, the clinical significance of ischemia in postinfarct VT/VF patients was elaborated. In addition, this thesis focuses on the definition of idiopathic ventricular fibrillation, i.e. VF in the absence of structural heart disease. Obviously, this diagnosis is made by exclusion and depends on the type of diagnostic investigations performed. In this respect, endomyocardial biopsy plays an undervalued role and this thesis investigates its diagnostic value in revealing unexpected heart disease.

The second aim was to study clinically significant arrhythmogenic factors in VT/VF patients, including ischemia, congestive heart failure, enhanced sympathetic tone and proarrhythmic effects of antiarrhythmic drugs. Treatment was individualized according to the identified mechanism and efficacy was evaluated in a nonrandomized observational fashion.

The third aim was to (re)consider the role of beta adrenergic blockade and selective potassium channel blockers (drugs delaying refractoriness) in the management of VT/VF patients. This was done against the background of the abovementioned individualized treatment and was carried out in an animal experimental setting as well as in a randomized double blind study in postinfarct patients suffering from complex ventricular arrhythmias. Safety aspects of drugs delaying repolarization, in particular with respect to proarrhythmia, were studied in an international retrospective case-control multicenter study on drug-induced long QT-related arrhythmias. The aim of that study was to identify the clinical and electrocardiographic profile of the patient at risk for torsades de pointes on this class of drugs.

1.3. Definitions

In this thesis generally accepted definitions of ventricular tachyarrhythmias and sudden cardiac death (Myerburg 1988) will be used.

Nonsustained ventricular tachycardia
: ventricular tachycardia of at least 6 ventricular beats with a rate above 100 beats per minute and lasting for less than 30 seconds without hemodynamic collapse.

Sustained ventricular tachycardia
: ventricular tachycardia with a rate above 100 beats per minute and lasting for more than 30 seconds or requiring an intervention within 30 seconds because of a hemodynamic collapse.

Sudden cardiac death (Myerburg 1988)
: natural death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 hour after onset of symptoms or during sleep, in the absence of increasing angina or overt heart failure.

Early ventricular tachycardia or ventricular fibrillation
: within 48 hours after onset of an acute myocardial infarction.

Late ventricular tachycardia or ventricular fibrillation
: at least 48 hours after an acute myocardial infarction.

Appropriate discharge of a cardioverter-defibrillator
: discharges preceded by syncope or presyncope.

1.4. The Groningen VT/VF protocol

Between January 1989 and January 1992 136 VT/VF patients were admitted to the University Hospital Groningen or referred from other centers (19%). After successful termination of a sustained ventricular tachycardia or successful resuscitation, patients were admitted to the coronary care unit and underwent the investigations mentioned in Table 1.

Table 1. Investigations in the Groningen VT/VF protocol

1.	Serial 12-lead electrocardiography
2.	Serial laboratory evaluations
	a. cardiac enzymes
	b. electrolytes
	c. plasma level of the antiarrhythmic drug
3.	Echocardiography
	a. ventricular dimensions
	b. valvular abnormalities
4.	Determination of left ventricular ejection fraction with a radionuclide technique
5.	Ambulatory monitoring
	a. incidence of arrhythmias
	b. mechanism of arrhythmias
	c. (silent) ischemia
6.	Signal-averaged electrocardiography
7.	Bicycle exercise testing
8.	Peak oxygen consumption determination
9.	Coronary angiography and left ventricular angiography
10.	Programmed electrical stimulation

Patients with VT/VF in the setting of an acute myocardial infarction were not included in 'The VT/VF protocol', because the favorable prognosis of VT/VF in the initial stages of acute infarction is beyond any doubt (Schaffer 1975). Also, patients with VT/VF due to electrolyte disturbances were excluded (Podrid 1990a, Gettes 1992, Arsenian 1993) as well as those with VT/VF on antiarrhythmic drugs (proarrhythmia).

Investigations. As a rule, a 12-lead electrocardiogram of the ventricular tachycardia was recorded as well as a continuous 12-lead electrocardiogram during intravenous administration of an antiarrhythmic drug to record different morphologies and initiation or termination of VT. An acute myocardial infarction was excluded by serial 12-lead electrocardiograms and serial determination of the enzymes released from the myocardium. If the patient was using an antiarrhythmic drug at admission, the plasma level of the antiarrhythmic drug was determined.

Echocardiography was done to evaluate left ventricular function and valvular abnormalities. In the absence of left ventricular disease, the wall motion of the right

ventricle was evaluated carefully (appendix 3,4). The left ventricular ejection fraction was determined with a radionuclide technique.

Ambulatory monitoring was performed to evaluate the incidence of supraventricular and ventricular arrhythmias. Special attention was given to initiating mechanisms, for example ST segment depression before the start of ventricular arrhythmias, rate dependence of arrhythmias (tachycardia-, bradycardia-, or pause-dependent), or initiation of ventricular arrhythmias by supraventricular arrhythmias (appendix 8,9).

Signal-averaged electrocardiography identifies low-amplitude, high frequency signals in the terminal part of the QRS complex, i.e. a ventricular late potential (Simson 1981, Lander 1992, appendix 4,8). A late potential is a marker for the presence of an area of slow and inhomogeneous conduction in the ventricle, which is one of the prerequisites for the development of arrhythmias based on reentry (Engel 1989, Breithardt 1991, Tobé 1992a, Dunbar 1993, Engel 1993, Gomes 1993). Apart from risk stratification (Tobé 1993, appendix 4), signal-averaged electrocardiography was used to evaluate antiarrhythmic drug effects on intraventricular conduction and repolarization (appendix 7,8).

Exercise testing was performed to uncover ischemia (appendix 1), but also to evaluate the initiating mechanism of VT/VF (Tuininga 1993, appendix 4,6,9). Peak oxygen consumption was determined for evaluation of exercise tolerance to compare its prognostic value with the other parameters of exercise tolerance and left ventricular function (appendix 2).

After the noninvasive tests, patients underwent coronary angiography to evaluate the role of ischemia in the arrhythmic event (appendix 1). Left ventricular angiography was performed to determine the angiographic left ventricular wall motion score (CASS 1981, Schwartz 1989, appendix 2). In the absence of coronary artery disease or any other structural heart disease the patients underwent an ergonovine spasm provocation test (Heupler 1987, appendix 4). In the latter patients also right ventricular angiography was done (Daubert 1988, appendix 3,4).

Programmed electrical stimulation was performed to evaluate inducibility (Wellens 1986). In case of noninducibility, the stimulation protocol was repeated during isoproterenol infusion (appendix 4,5,6).

Treatment. In VT/VF patients with a definite provoking arrhythmogenic factor, which could be treated effectively either using noninvasive or invasive treatment, no antiarrhythmic therapy was prescribed. In case of adrenergic-dependent VT/VF beta blocker therapy was prescribed and evaluated with exercise testing.

The patients with coronary artery disease as coexistent factor were treated for ischemic heart disease including beta blocker therapy before prescribing antiarrhythmic therapy. Patients with congestive heart failure as coexistent factor received diuretics, digoxin and angiotensin converting enzyme inhibitors before

prescribing antiarrhythmic therapy. In those patients tolerating beta blockade, this agent was given to reduce neurohumoral activation and its arrhythmogenic consequences.

In the absence of provoking factors and adequate treatment for coexistent coronary artery disease and congestive heart failure, serial antiarrhythmic drug testing was the first option. Efficacy of antiarrhythmic drug treatment was evaluated with exercise testing, ambulatory monitoring and programmed electrical stimulation. Using programmed stimulation (Wellens 1986), patients were considered responders if they were not inducible (complete responders) or only to nonsustained ventricular tachycardias of less than 30 seconds duration without hemodynamic consequences. Partial responders were those patients in whom a hemodynamically stable ventricular tachycardia could be induced which was more 'difficult' to induce (i.e. at a shorter pacing cycle length or using more extrastimuli) and that showed an increase of tachycardia cycle length. After ≥ 2 antiarrhythmic drug tests, we considered amiodarone or nonpharmacological alternatives, i.e. arrhythmia surgery or implantation of a cardioverter-defibrillator. In selected patients implantation of a cardioverter-defibrillator was performed as first choice therapy in the setting of a Dutch randomized multicenter trial (Wever 1992).

Chapter 2

Underlying cardiac disease in sustained ventricular tachycardia and ventricular fibrillation and its role in risk stratification

VT/VF is the result of an interplay between substrate, triggers and modulating factors. The underlying causes of VT/VF are numerous (Myerburg 1988, Zipes 1988). To prevent too many subgroups with a too small number of patients, the classification as mentioned in Table 2 was used in the VT/VF protocol.

Table 2. Baseline characteristics and outcome of 136 patients in the Groningen VT/VF protocol included between 1989 and 1992. Outcome is given after a mean follow-up of 20±12 months (mean±SD). A small restgroup of 3 patients (2%) is not included in this overview

Underlying heart disease	CAD	CMP	Id VT/VF
N (%)	94 (69%)	28 (21%)	11 (8%)
Age (years, mean±SD)	63±10	49±19	44±15
Sex (male/female, %)	80/20%	61/39%	82/18%
Presenting arrhythmia VT/VF (%)	54/46%	79/21%	27/73%
NYHA classification for exercise tolerance ≥ III (%)	18%	25%	0%
LVEF (%, mean±SD)	33±15	47±18	66±5
Nonfatal arrhythmia recurrences (n)	15	8	2
Total mortality (n)	20	4	-
Sudden cardiac death (n)	14	2	-
Death because of CHF (n)	2	2	-
Other (n)	4	-	-

CAD: coronary artery disease; *CHF:* congestive heart failure; *CMP:* cardiomyopathy; *Id VT/VF:* idiopathic ventricular tachycardia/ventricular fibrillation; *LVEF:* left ventricular ejection fraction; *N.:* number of patients; *NHYA:* New York Heart Association.

The history and clinical presentation of a VT/VF patient can give some clues to the underlying cause of the arrhythmic event. For example, angina pectoris may suggest ischemia as the main cause of postinfarct VF. Patients may present with either VT or VF, but this does not provide much information concerning the type and severity of underlying heart disease. In this respect it is important to note that ventricular tachycardia frequently precedes fibrillation (Gradman 1977, Lahiri 1979, Nikolic 1982, Panidis 1983, Pratt 1983, Kempf 1984, Bayés de Luna 1989). In VF patients the left ventricular ejection fraction appeared to be lower (Saxon 1989), higher (Adhar 1988, Denniss 1988) or equal to the ejection fraction in the patients presenting with VT (Hamer 1984, Stevenson 1985). Parameters related to cardiac arrest rather than hemodynamically tolerated sustained VT were syncope in the history or rate of VT in a study by Hamer et al. (1984). Also, it is generally accepted that patients with ischemia present more frequently with VF (Meissner 1991a, appendix 1). Nevertheless, it may be concluded that the presentation with either VT or VF gives only limited information about the underlying disease and has no direct relation to left ventricular function.

In postinfarct VT/VF, the initial presentation can be used for risk stratification. In these patients the following factors were identified as being unfavorable for long-term outcome: cardiac arrest at initial presentation, New York Heart Association class for exercise tolerance $\geq$ III or the presence of more than 1 infarct in the history (Brugada 1989b). In a study of the Interuniversity Cardiology Institute of the Netherlands (ICIN) the following parameters were independently predictive of total mortality: older than 70 years in age, Killip III or IV in the semi-acute phase of the infarction ($<$ 6 weeks), first arrhythmic event in the semi-acute phase of the infarction, cardiac arrest at initial presentation, Q wave infarcts, history of multiple infarcts and anterior localization of the infarction prior to the arrhythmia (Willems 1990). The latter study proposed an algorithm for calculation of arrhythmia recurrence risk. Both studies emphasize the importance of depressed left ventricular function for risk stratification of postinfarct patients (Brugada 1989b, Willems 1990).

In the absence of invasive facilities the presenting circumstances are more or less helpful in the identification of underlying disease. However, this is associated with a low sensitivity and a low specificity. Extensive (non)invasive evaluation is required for adequate treatment. The most frequent cause of VT/VF is coronary artery disease and the most powerful prognostic parameter in patients with cardiac disease is left ventricular function. Hence, the first parameter of utmost importance to evaluate is the presence of coronary artery disease and its role in the arrhythmic event. The second parameter to evaluate, independent of presence of coronary artery disease, is left ventricular function.

2.1. Role of ischemia.*

The most frequent underlying heart disease in VT/VF patients is coronary artery disease. Symptomatic and asymptomatic ischemia is considered to be a risk factor for cardiac death (Mulcahy 1992, Reis 1992). However, clinicians often are not unanimous on the role of ischemia preceding VT/VF. During ambulatory monitoring of VT/VF events, asymptomatic ischemia preceded these life-threathening arrhythmias only in a subset of patients (Hong 1987, Hohnloser 1988, Bayés de Luna 1989, Olshausen 1991, Pepine 1991). In addition, during exercise testing after the arrhythmic event, ST segment depression is absent in more than half of the cardiac arrest patients with coronary artery disease (Weaver 1982, Sharma 1987) and ischemia is unlikely to be found during ambulatory monitoring (Mulcahy 1992, Reis 1992). Moreover, most sudden cardiac deaths do not occur in the setting of strenuous exercise (Schaffer 1975, Weaver 1982). On the basis of these noninvasive techniques a relation between ischemia and sudden death may only be suggested in a subgroup of coronary artery disease patients with VT/VF (Sellers 1987, Gomes 1989). However, most patients with VT/VF have an old infarct. In postinfarct patients without overt angina pectoris the incidence of silent ischemia during ambulatory monitoring may be as high as 46% (Mulcahy 1992). Therefore, despite the absence of a clear relation between ischemia and the arrhythmic event it can never be excluded that ischemia plays a role in relatively many postinfarct VT/VF patients. To study ischemia it seems appropriate to perform thallium-201 scintigraphy (Jordaens 1988) and coronary angiography in VT/VF patients.

Coronary artery disease patients with VT/VF are studied frequently as a homogeneous population. However, besides the possibility of an acute myocardial infarction (which was excluded from the VT/VF protocol) coronary artery disease may be present in several forms in VT/VF patients (Goldstein 1990, Meissner 1991a, appendix 1). Important subgroups can be identified necessitating differential treatment. The cause of the arrhythmic event may have been coronary artery spasm or a significant stenosis without an old infarct. Most of the VT/VF patients have had a myocardial infarction previously. In the presence of an old infarct reversible ischemia may be highly arrhythmogenic, much more than either an old infarct or ischemia alone (Myerburg 1982, Patterson 1982, Garan 1988). In postinfarct VT/VF patients the arrhythmogenic role of ischemia may be of 3 sorts: it may be the definite cause of the event, it may be a coexistent factor merely facilitating the onset of arrhythmia, or it plays no additional role (appendix 1). As mentioned above noninvasive techniques are insufficient to evaluate the role of ischemia in VT/VF

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* The reader is also referred to 'The ventricular arrhythmias of ischemia and infarction. Electrophysiological mechanisms' by A.L. Wit and M.J. Janse (eds.), Futura Publishing Company, Inc., New York, U.S.A., 1993.

patients. We decided to combine accepted noninvasive techniques, like exercise testing and thallium-201 scintigraphy with coronary angiography to identify prospectively the incidence and clinical significance of ischemia in 82 postinfarct VT/VF patients (appendix 1). Ischemia was considered the definite cause of the event in 17% of the patients, a coexistent factor in 16% and played no role in 67%. Treatment was directed to the cause of the tachyarrhythmic event, and was either antiischemic alone or combined with antiarrhythmic therapy, or antiarrhythmic therapy alone. With this approach VT/VF patients with definite ischemia had an excellent long-term outcome without arrhythmia recurrences during a mean follow-up of 21 months. Prognosis in the other 2 groups were comparable, with a 2-year arrhythmia-recurrence rate of 47% (appendix 1). Our findings support the contention that VT/VF patients with definite ischemia as the cause for the arrhythmic event may be successfully treated simply by preventing recurrence of ischemia (Garan 1983, Kelly 1990).

It is tempting to speculate that antiischemic therapy as single treatment may be sufficient in postinfarct VT/VF in whom ischemia plays a role. Most investigators would disagree and will prescribe additional antiarrhythmic drugs. It may be argued however, that in the setting of breakthrough ischemia, antiarrhythmic drugs may become arrhythmogenic and offset the protective effects of antiischemic therapy.

The role of programmed stimulation in the evaluation of stand alone antiischemic therapy may be limited. Usually it is advised to perform programmed stimulation before and after antiischemic therapy (Garan 1983, Kelly 1990). However, programmed stimulation before antiischemic therapy certainly provokes ischemia facilitating the induction of VT/VF, potentially reducing the specificity of the test (Morady 1986, 1987). On the other hand, after adequate antiischemic therapy these postinfarct VT/VF patients may be considered comparable to the general postinfarct patients without VT/VF. In the latter patients inducibility of VT/VF during programmed stimulation is about 30-40% of the patients while only in a small portion VT/VF will occur spontaneously (Richards 1983, Denniss 1985, Denniss 1986, Cripps 1989, Vorperian 1989, Iesaka 1990). Inducibility is even higher in the patients with depressed left ventricular function (Kowey 1990, Wilber 1990, Bourke 1991). These circumstances limit the predictive value. Hence, programmed stimulation as evaluation method after antiischemic therapy may be considered only of prognostic value if the patient is not inducible.

Ischemia causes ventricular fibrillation rather than ventricular tachycardia (Meissner 1991a). Kelly et al. (1990) emphasized that ventricular fibrillation patients are more likely to become noninducible after bypass surgery than ventricular tachycardia patients. If the preoperative induced arrhythmia is monomorphic or if left ventricular function is severely depressed, the likelihood of suppressing arrhythmia by coronary revascularization alone is small (Kelly 1990). However, as reported in appendix 1, 29% of the postinfarct VT/VF patients with definite

ischemia presented with monomorphic ventricular tachycardia and antiischemic treatment was effective in these patients. This is in seeming discrepancy with previous studies, which may relate to the fact that our patients received additional beta blockade after the intervention as part of the general postinfarct strategy. Possibly this prevented further monomorphic ventricular arrhythmias.

As mentioned above, late monomorphic ventricular tachycardia due to ischemia is relatively rare. It may be explained by assuming that in the setting of an old infarct a subtle area of ischemia may be the final (conduction slowing) part to complete the already (partially) present reentrant circuit, as result of altered local membrane electrophysiologic properties by ischemia induced hyperkalemia and acidosis.

In appendix 1, the group of postinfarct VT/VF patients with concomitant ischemia (group B) had a similar prognosis as found in those without ischemia (group C). This implies that adequate antiischemic therapy in patients with coexistent ischemia does not improve prognosis compared to postinfarct patients without additional ischemia. Possible explanations could be that the impact of low left ventricular ejection fraction was too large (Swerdlow 1983a, Lampert 1988, Wilber 1988), which also precluded beta blocker treatment (Chadda 1986, Steinbeck 1992). In addition, coronary bypass surgery or percutaneous transluminal angioplasty was not feasible in all of these patients (Holmes 1986, Every 1992). Finally, proarrhythmic effects could have outweighed the beneficial effects of the antiischemic interventions (Podrid 1992).

Appendix 1 shows that coronary angiography can be important in determining the arrhythmogenic role of ischemia and its prognostic implications in postinfarct VT/VF patients. It is possible to identify a low risk group suitable for antiischemic therapy. In how far additional antiischemic therapy prevents arrhythmias in patients with coexistent ischemia is unclear at present. Randomization after implantation of a cardioverter-defibrillator may give insight into the relative efficacy of antiischemic versus antiarrhythmic therapy.

The severity of a stenosis found during coronary angiography may not directly reflect the potential for developing ischemia since more dynamic factors such as coronary artery spasm, transient intraluminal thrombus (Warnes 1984, Davies 1992) and myocardial oxygen demand might contribute also. To prevent this as much as possible exercise testing with or without thallium-201 scintigraphy should be performed. Special attention should be given at acute coronary lesions or intraluminal thrombi maybe using new techniques like coronary angioscopy. In the future, thallium-201 scintigraphy may be replaced by positron emission tomography (Bonow 1991). Preliminary results from our institution indicate that postinfarct VT/VF patients without ischemia using the conventional (non)invasive parameters, still showed signs of ischemia using this sophisticated tool.

In summary, the role of ischemia varies in the occurrence of VT/VF in

postinfarct patients. Using coronary angiography, we could identify a subgroup of postinfarct VT/VF patients with ischemia as definite arrhythmogenic factor. This group had an excellent prognosis with single antiischemic treatment. Prognosis of postinfarct VT/VF patients with coexistent or no additional ischemia was comparable unfavorable, despite optimal antiarrhythmic treatment with or without antiischemic treatment.

2.2. Role of left ventricular function

Impaired left ventricular function is prognostically unfavorable in VT/VF patients (Swerdlow 1983a, Wilber 1988, Brugada 1989b, Furukawa 1989, Wellens 1989, Leclercq 1991, Kim 1992). Several methods are used to characterize left ventricular function (Table 3). In general, the ejection fraction is the most frequently used objective parameter.

Table 3. Methods for evaluation of left ventricular function

Exercise tolerance
Classification of exercise tolerance according to the New York Heart Association
Bicycle exercise testing
Measurement of peak oxygen consumption
Left ventricular ejection fraction
Radionuclide
Echocardiographic
Angiographic
Left ventricular wall motion score
Echocardiographic
Angiographic

In postinfarct VT/VF patients depressed left ventricular ejection fraction was identified as one of the factors associated with arrhythmia recurrence (appendix 1). However, left ventricular ejection fraction gives only an impression of global left ventricular function (Braunwald 1992). A left ventricular wall motion score incorporating local differences in contractility may be superior to left ventricular

ejection fraction as predictor for arrhythmia recurrence (Meizlish 1984, Schwartz 1989, Van Hemel 1989, Nath 1993a, 1993b). Ejection fraction and wall motion score give only an index of resting left ventricular function. By contrast, the classification for exercise tolerance of the New York Heart Association and measurement of peak oxygen consumption reflect the functional capacity of the patient (Weber 1982, Franciosa 1984). As such the latter dynamic parameters might have an additional value in predicting long-term prognosis. In previous studies peak oxygen consumption measurement has never been used in the evaluation of VT/VF patients. The measurement of oxygen consumption is better reproducible and more objective compared to New York Heart Association class (Weber 1982, Franciosa 1984, Lipkin 1987). Peak oxygen consumption is a powerful predictor of mortality in patients with congestive heart failure (Szlachcic 1985, Cohn 1987, Willens 1987, Cohn 1988). In appendix 2 the prognostic importance of parameters of functional capacity and resting left ventricular function were compared in 69 VT/VF patients. Arrhythmia recurrence was associated with parameters of resting left ventricular function rather than functional capacity. Of both resting parameters left ventricular wall motion score predicted arrhythmia recurrence better than left ventricular ejection fraction. We found this result rather fascinating. In other words, dynamic factors such as exercise tolerance did not add to the prognostic influence of resting left ventricular ejection fraction concerning prediction of arrhythmia recurrence. It may be argued however that exercise tolerance reflects more than the condition of the left ventricle alone, which confounds the prediction of arrhythmia recurrence. From our study we cannot tell whether another dynamic index of left ventricular function, e.g. ejection fraction during exercise would be a better predictor. On the other hand, most arrhythmias occur at rest, unrelated to physical exercise, which argues against a role for dynamic tests.

Congestive heart failure is associated with neurohumoral activation (Parmley 1989, Ferguson 1993). The elevation of catecholamine plasma levels is an important arrhythmogenic factor (Podrid 1990b). Plasma venous norepinephrine is equivalent to exercise tolerance or left ventricular ejection fraction as a prognostic indicator in patients with mild to moderate heart failure and is superior to other routinely obtained clinical indices in heart failure subjects with more advanced disease (Cohn 1984). Therefore, catecholamine plasma levels may be important in the future evaluation of VT/VF patients.

New therapeutic approaches may change left ventricular function in the cardiac patient population. The full impact of thrombolytic therapy has not emerged yet. Early and complete restoration of coronary flow through the infarct related artery will result in improved left ventricular ejection fraction and lower mortality rates among patients with myocardial infarction ('open-artery' hypothesis) (Braunwald 1993). In addition, early initiation of angiotensin converting enzyme inhibitors after myocardial infarction is associated with improved left ventricular

function and subsequent reduction of mortality (Pfeffer 1992, SOLVD 1992, Goldman 1993). These new therapeutic strategies will lead to changes in the clinical presentation of the VT/VF population (Wiesfeld 1992, Tobé 1993).

2.3. Absence of structural heart disease

In a small subgroup of VT/VF patients no structural heart disease can be found. Prognosis in this particular subgroup depends on the clinical presentation. In idiopathic VT patients outcome is usually good (Brooks 1988, Trappe 1988, Almendral 1992, Belhassen 1993). Controversy exists about the risk for arrhythmia recurrence in idiopathic VF (Trappe 1988, Lemery 1989, Viskin 1990, Wever 1993, appendix 3,4). In part this may be explained by the lack of consensus about the definition for idiopathic VF (Viskin 1990, Waldo 1992, Wellens 1992). One prerequisite is the absence of any abnormality using conventional (non)invasive investigations. The minimally required investigations are those mentioned in Table 1. However, additional noninvasive and invasive investigations should be performed to uncover underlying structural heart disease not expected on the basis of standard studies. First, right ventricular angiography and echocardiography to evaluate right ventricular wall motion (Robertson 1985, Daubert 1988, Scognamiglio 1989a, 1989b, Daliento 1990). Secondly, an ergonovine provocation test for coronary arterial spasm should be performed (Heupler 1978, Théroux 1982, Harding 1992). Myerburg et al. (1992) could establish a relation between coronary arterial spasm and potentially fatal ventricular arrhythmias in 5 out of 13 patients without structural heart disease. Thirdly, programmed electrical stimulation can focus on induction not only of ventricular but also supraventricular arrhythmias (Zipes 1979, Wellens 1980, Belhassen 1982, German 1983). Two of our idiopathic VF patients (appendix 3,4) were inducible to a supraventricular tachyarrhythmia. It has been shown that atrioventricular nodal reentrant tachycardia may be associated with severe hypotension potentially causing sudden death (Wang 1991). Cardiac arrest because of atrial fibrillation was only noted in patients with structural heart disease and enhanced atrioventricular nodal conduction or in the presence of an accessory atrioventricular connection (Wang 1991). However, these characteristics were not present in our 2 patients. Therefore the induced supraventricular arrhythmias were considered unrelated to the cardiac arrest. Fourthly, in case of noninducibility during baseline programmed electrical stimulation it is important to repeat the stimulation protocol during isoproterenol infusion (Olshansky 1987). Finally, right ventricular endomyocardial biopsy should be performed. The latter will be discussed in the next section.

Currently, therapy in sudden death survivors 'without apparent cardiac disease' varies from solitary beta blocker treatment (Brodsky 1986) to

antiarrhythmics (Reeder 1981, Sugrue 1984, Vignola 1984, Belhassen 1987, Martini 1989, Topaz 1989) and implantation of a cardioverter-defibrillator (Dreifus 1991, Meissner 1991b, Siebels 1991, Roelke 1992, Wever 1993). In the absence of randomized trials evaluating different treatment modalities, we advise to individualize therapy (appendix 4). The clinical history often seems neglected, but may provide a clue concerning provoking factors. In case of a clear provocative factor, the patient should be instructed to avoid it. In patients in whom exercise or an increased adrenergic tone was the eliciting factor beta blockade should be given and evaluated with exercise testing. This seems a reasonable approach since adrenergic dependence may be more often present than previously described in consecutive patients. In 7 out of the 10 idiopathic VF patients reported in appendix 4 the event was preceded by exercise (6 patients) or emotional stress (1 patient). If spasm is the likely cause, calcium antagonists can be useful. Serial drug testing should be performed if an arrhythmia related to the event, was identified with programmed stimulation. In the absence of a provocative factor or a parameter for guiding conventional therapy, irrespective of the result of an endomyocardial biopsy, implantation of a cardioverter-defibrillator is the treatment of choice. With this approach none of our idiopathic VF patients had a recurrence of cardiac arrest during follow-up (appendix 3,4), which is in clear contrast to the high recurrence rate of 25-33% reported in the literature (Viskin 1990, Siebels 1991, Meissner 1991b, Wever 1993). Other investigators also found a low recurrence rate (Belhassen 1987, Lemery 1989, Wellens 1992). The favorable prognosis in our study population presumably relates to the frequent association between the event and exercise (appendix 4). In addition, 5 patients responded to antiarrhythmic drug therapy, which reputedly is associated with a low relapse rate (Belhassen 1987, Waller 1987, Viskin 1990). The prognostic value of noninducibility in sudden death survivors without apparent cardiac disease is unknown. However, it may be supposed that the high number of noninducible patients contributed to the observed favorable prognosis, irrespective of antiarrhythmic drug treatment (Swerdlow 1983b, Belhassen 1987, Kron 1987, Freedman 1988, Wilber 1988, Zheutlin 1988, Sager 1990).

The diagnosis 'idiopathic VF' is made by excluding any structural abnormality which may be difficult in retrospective studies. Nevertheless, the results of these retrospective studies (Viskin 1990, Wellens 1992) should not be ignored but used as the starting point for prospective extensive evaluation (appendix 3,4). New techniques should be included in the evaluation. We extended the evaluation of our idiopathic VF patients with noninvasive techniques like heart rate variability and baroreflex sensitivity measurement for evaluation of imbalance of the autonomic nervous system. In addition, our patient group retrospectively underwent positron emission tomography to exclude abnormalities in the myocardial metabolism. No gross abnormalities were found (personal communication). With Nuclear Magnetic

Resonance abnormalities compatible with right ventricular dysplasia were found unexpectedly in 2 of our patients (Ricci 1992). In conclusion, with this extended number of investigations time will reveal subgroups in 'idiopathic VF' patients and hopefully give insight in the arrhythmogenic mechanisms with further directions to optimize treatment.

2.4. Importance of right ventricular endomyocardial biopsy in idiopathic VF patients

One of the causes for conflicting results considering the outcome of idiopathic VF patients may be that in most of the studies endomyocardial biopsies were not performed (Trappe 1988, Lemery 1989, Wever 1993). This may lead to differences in survival, due to unrecognized underlying cardiac disease in patients who seem comparable at first sight. In a subset of idiopathic VF patients an inflammatory cardiac disease may be present (Vignola 1984, Hosenpud 1986, Mason 1989). In these patients, complete recovery either spontaneously or with directed treatment is possible. By contrast, prognosis remains unclear in case of pathoanatomical abnormalities suggesting a cardiomyopathy. In 6 out of 9 idiopathic VF patients we found microscopic pathoanatomical abnormalities compatible with arrhythmogenic right ventricular dysplasia (appendix 3). In view of the fact that right ventricular abnormalities were absent, this represents a relatively high incidence. The high figure we found may relate to the more extensive procedure, i.e. an average of 8 biopsies, with a range 4-14 per procedure (appendix 3). The likelihood to find abnormalities can be enhanced by a targeted approach, aiming at the origin of an induced ventricular tachycardia and the corners of the triangle of dysplasia (Marcus 1982, Manyari 1983, Crijns 1991). In our opinion, standard investigations in sudden cardiac death survivors without apparent cardiac disease, should include endomyocardial biopsy, according to the following clinical guidelines: (a) to perform biopsy early after the event to avoid missing acute inflammatory changes, (b) to biopt in the corners of the triangle of dysplasia, (c) if any wall motion abnormalities visible during echocardiography or angiography to perform biopsies at that site, (d) if possible to perform biopsies targeting at the origin of a monomorphic ventricular tachycardia, and (e) in case of nonspecific abnormalities, biopsy should be repeated after a specified interval.

Difficulties to interpret the biopsy in the early stages of the disease process may be prevented by more accurate definition of an abnormal biopsy (Strain 1983, Caruso 1989, Frustaci 1989, Mehta 1989, Strain 1989). For the diagnosis right ventricular dysplasia fibrolipomatosis is obligatory. However, lipomatosis can also be present in normal hearts (Fontaliran 1991) after viral infections, toxins, alcohol or in the obese (Strain 1989). These factors were ruled out or were not present in

our patients (appendix 3). In how far aspecific fibrosis represents begin stage of a specific cardiomyopathy like arrhythmogenic right ventricular dysplasia is unknown (Frustaci 1989). We only considered the presence of lipomatosis of significance when it was accompanied by an increase in fibrous tissue (appendix 3, Mehta 1989). Possibly, repeated biopsies may clarify this point. Remarkable in this setting is that one of our patients showed at the first biopsy mild lipomatosis and at the second biopsy 3 years later, a clear cut increase in lipomatosis (appendix 3). This suggests that arrhythmogenic right ventricular dysplasia is a progressive disease with a continuum ranging from minor abnormalities without evident right ventricular abnormalities (appendix 3) to a markedly diseased right ventricle (Marcus 1982, Manyari 1983, Thiene 1988).

Brugada and Brugada (1992) presented 8 sudden death survivors without apparent structural heart disease, with right ventricular conduction delay and persistent ST segment elevation in the right precordial leads on the electrocardiogram. These abnormalities might be explained by assuming a localized change from fast to slow response transmembrane action potentials. The latter would produce small and relatively short action potentials, leading to ST segment elevation. It also explains the slowed conduction. The localization of the conduction delay suggests abnormalities primarily in the right ventricular muscle, i.e. the outflow tract. This might be studied with target directed biopsies taken from the ventricular muscle from sites with a short refractory period during programmed stimulation or a short monophasic action potential.

As described in appendix 3, antiarrhythmic therapy was not changed after the pathoanatomical findings, because the clinical value of microscopic abnormalities in idiopathic VF remains to be corroborated. Identification of a specific cause of idiopathic VF may have consequences for diagnosis and prognosis and clinical management. Especially patients with a reversible cause such as inflammatory heart disease, may have a favorable prognosis (Vignola 1984, Mason 1989). On the other hand prognosis may be rather variable in right ventricular dysplasia patients or other cardiomyopathies. This explains the differences in prognosis of sudden death survivors without cardiac disease in studies not using endomyocardial biopsies in the management of these patients. In 8 studies of right ventricular endomyocardial biopsy in sudden death survivors without (major) structural cardiac disease (Table III in appendix 3) limited follow-up results were available in 5 reports (Sugrue 1984, Vignola 1984, Buja 1989, Martini 1989, Topaz 1989), including only 14 patients. None of the 8 patients with a normal biopsy had an arrhythmia recurrence. By contrast, 2 of the 6 patients with an abnormal biopsy died suddenly during follow-up (Martini 1989). It must be noted that these 2 patients had minor right ventricular wall motion abnormalities. Two patients with inflammatory diseases had no arrhythmia recurrence (Vignola 1984). The favorable prognosis in our study population may be due to the fact, that in the 6 patients with right ventricular

dysplasia the diagnosis was made in the very early stages of the disease (appendix 3,4). Although the natural history of patients with arrhythmogenic right ventricular dysplasia is unresolved, prognosis probably depends on the extent and progression of the disease (Marcus 1982, Blomström-Lundqvist 1987, Leclercq 1989, Marcus 1989). One question to resolve is if patients can be identified who show significant progression of microscopic right ventricular abnormalities. A careful follow-up of the patients using repeated biopsy is essential. However, a frequently performed extensive biopsy procedure could implicate a higher complication risk, especially in the more diseased ventricular muscle (Deckers 1992). In the future, Nuclear Magnetic Resonance may be a noninvasive alternative to biopsy procedures for evaluation of progression in idiopathic VF patients with microscopic signs of arrhythmogenic right ventricular dysplasia (Ricci 1992).

Chapter 3

Treatment of sustained ventricular tachycardia and ventricular fibrillation

3.1. Considerations before antiarrhythmic therapy

Antiarrhythmic therapy is indicated in patients with symptomatic or life-threatening arrhythmias. VT/VF patients are at high risk to die suddenly. If treated empirically the sudden death rate may be as high as 30% per year (Roy 1983, Swerdlow 1983a, Wilber 1988). With the use of noninvasive and invasive procedures this may be reduced to 5-10% per year (Waller 1987). To enhance safety of antiarrhythmic therapy, the following considerations must be made before initiating therapy (Table 4).

3.1.1. Risk profile

Antiarrhythmic therapy should be initiated only after careful consideration of the patient's risk profile (Trappe 1988, Brugada 1989b, Wellens 1989). The prognostic importance of structural heart disease, ischemia and left ventricular function was emphasized in the previous chapter. As pointed out, arrhythmia recurrence risk in VT/VF patients without underlying structural heart disease may vary but seems low if the approach mentioned in appendix 4 is used. This is also the case in postinfarct VT/VF patients with marked ischemia, amenable to adequate treatment. Postinfarct patients without coexistent ischemia have a high recurrence risk, which is even higher in those with depressed left ventricular function (appendix 1). Previous studies emphasized the unfavorable prognostic impact of decreased ejection fraction (Swerdlow 1983a, Wilber 1988, Brugada 1989b, Furukawa 1989, Wellens 1989, Leclercq 1991, Kim 1992).

The initial clinical presentation with either VT or VF is also of prognostic importance. VT patients who tolerate the arrhythmia well, can be considered low risk, especially if they have only sporadic attacks. On the other hand sudden death survivors, especially those with low ejection fraction, should be considered at high risk to die suddenly.

Table 4. Considerations before initiating antiarrhythmic therapy in VT/VF patients

1. Indication for antiarrhythmic therapy depends on the risk profile
    - Underlying heart disease
    - Left ventricular function
    - Symptoms
    - Attack rate
2. Identification of provoking factors
    - Ischemia
    - Congestive heart failure
    - High sympathetic tone
    - Electrolyte disturbances
    - Hypoxia
    - Digitalis intoxication
    - Antiarrhythmic drugs
3. Identification of electrophysiologic mechanisms
    - Abnormal automaticity
    - Reentry
    - Triggered activity

3.1.2. Provoking factors

Apart from the risk profile, also provoking factors have to be identified. For this a careful history is mandatory, focusing on the setting preceding the event, for example rest, mental stress or physical exercise. Moreover, specific complaints such as chest pain and dyspnea have to be elaborated. Before prescribing antiarrhythmic therapy these provoking factors have to be treated potentially obviating antiarrhythmic therapy (Wyndham 1991). For example, antiarrhythmic therapy is not indicated in VT/VF patients with significant coronary artery disease amenable to percutaneous transluminal angioplasty or coronary artery bypass surgery (appendix 1). Similarly, patients with heart failure must receive first diuretics, digoxin and angiotensin converting enzyme inhibitors before considering arrhythmia treatment.

Case report: A 53-year old man was resuscitated from ventricular fibrillation 3 weeks after an unrecognized acute anterior wall myocardial infarction. He was referred to our hospital for arrhythmia management. The medication at admission was disopyramide 750 mg daily and acenocoumarol. Disopyramide was stopped for evaluation according to the VT/VF protocol. VF recurred after 6 days. The patient received procainamide. Left ventricular ejection fraction was 22%. Coronary and left ventricular angiography showed an occluded left anterior descending coronary artery and a large anterior wall aneurysm. Left ventricular end-diastolic pressure was elevated suggesting increased level of circulating catecholamines (Bigger 1987, Parmley 1989, Hansen 1990, Podrid 1990b). The latter may lead to shortening of refractoriness as arrhythmogenic factor during ventricular dilatation or stretch (Lab 1982, Calkins 1989, Franz 1992). Subsequently, procainamide was replaced by an angiotensin converting enzyme inhibitor. During follow-up of 4 years there was no arrhythmia recurrence.

High sympathetic tone is the provoking factor in exercise-induced VT/VF (Codini 1981, Sung 1983, Woelfel 1984, Tuininga 1993) as well as in arrhythmias preceded by mental stress. The latter is present in at least 20% of VT/VF patients (Lown 1976, Reich 1981, Brodsky 1987). Beta adrenergic blockade as solitary therapy may be considered in these VT/VF patients (appendix 4,5). As mentioned previously, the favorable prognosis in our idiopathic VF patients presumably relates to the frequent association between the event and exercise (appendix 4). These patients were advised to avoid the provoking factor and were subsequently treated with beta blockade. However, frequently VT/VF is not preceded by a clinically explicit high sympathetic tone. As an alternative, circumstantial evidence for an enhanced sympathetic tone can be looked for which is summed up in appendix 5 (appendix 5, Table I). Obviously, these parameters can be used to identify VT/VF patients who may benefit from solitary or adjuvant beta blockade.

The other provoking factors mentioned in Table 4: electrolyte disturbances, hypoxia and digitalis intoxication can be identified clinically and treated effectively. The role of arrhythmia recurrence during antiarrhythmic drug therapy will be discussed in the sections 3.4 and 3.5.

3.1.3. Arrhythmogenic electrophysiologic mechanisms

In the absence of correctable provoking factors antiarrhythmic therapy has to be considered. Ideally, antiarrhythmic drug therapy focuses at the arrhythmogenic electrophysiologic mechanism. The arrhythmogenic mechanisms in VT/VF patients are abnormal automaticity, reentry and triggered activity. The electrophysiologic

criteria for differentiation between these different mechanisms have not been fully defined (Brugada 1984, Akthar 1988, Cranefield 1988a). In the clinical setting it remains very difficult to distinguish these mechanisms. Programmed stimulation has been used for this purpose, but this method is limited by the fact that VT/VF onset is rather artificial and it does not allow for proper evaluation of neurohumoral modulation of the arrhythmia substrate. Long-term ambulatory monitoring is more suitable to elucidate the role of changes in autonomic tone and rate-dependence of the arrhythmia. Both have enhanced our understanding of electrocardiographic patterns preceding the onset of VT/VF, and relations with specific types of underlying arrhythmogenic mechanisms have been made (Rosen 1981, Brugada 1984, Roden 1986, Zimmerman 1986, Swenne 1987, Van Hemel 1987, Akthar 1988, Cranefield 1988a, 1988b, Jackman 1988, Vos 1990, Moroe 1991). However, it still is not possible to be unequivocally certain about the mechanisms responsible for most clinically occurring arrhythmias. Moreover, initiating and sustaining mechanism of an arrhythmia may differ (Table 5). In the next paragraphs an overview of the arrhythmogenic electrophysiologic mechanisms is given with suggestions to identify the initiating arrhythmogenic mechanism on the 12-lead surface electrocardiogram.

Table 5. Sixteen possible combinations of initiating and sustaining arrhythmia mechanisms for one single tachycardia

Initiating Mechanism	AA	RE	EAD	DAD
Sustaining Mechanism	AA	AA	AA	AA
	RE	RE	RE	RE
	EAD	EAD	EAD	EAD
	DAD	DAD	DAD	DAD

AA: abnormal automaticity; *DAD:* delayed afterdepolarization; *EAD:* early afterdepolarization; *RE:* reentry. Reflection and parasystole were not considered.

A. Abnormal automaticity

Abnormal automaticity is depolarizations of fibers which are partially depolarized. These arrhythmias will occur spontaneously without stimulation, but can be suppressed by overdrive pacing. In contrast to reentry and triggered activity they may reoccur spontaneously after termination. Abnormal automaticity may play a role

in patients in whom VT/VF is the result of autonomic imbalance. Autonomic imbalance may be the result of increased sympathetic stimulation and/or decreased vagal activation. Exercise or emotional stress is a clinical example of changing of the sympathovagal balance. However, not only abnormal automaticity may play an arrhythmogenic role in this setting, but also reentry and triggered activity (Tuininga 1993).

Four of our idiopathic VF patients were not inducible to ventricular tachyarrhythmias and had their arrhythmic event during exercise or emotional stress (appendix 4). This may indicate that abnormal automaticity was the underlying arrhythmogenic electrophysiologic mechanism, but does not rule out triggered activity. In the patient discussed in appendix 6 incessant monomorphic VTs were only present after short-long RR sequences. The tachycardias became incessant during isoproterenol infusion which suggests a role for abnormal automaticity. However, the very first ventricular premature beat, i.e. the first beat of the ventricular tachycardia, follows a pause in the normal rhythm (pause produced by a supraventricular premature beat, presumably caused by abnormal automaticity at the atrial level or due to stretch-induced triggered activity). This strongly suggests early afterdepolarizations as a cause for this beat, but does not tell what the sustaining mechanism is.

B. Reentry

The prerequisites for reentrant tachycardias are slowing of conduction, unidirectional block and an anatomical (Mines 1913, 1914) or functional (Allessie 1977) substrate. An inverse relation can be found between the coupling interval of a normal sinus beat and an initiating premature beat, and the long return interval of the initiating premature beat and first beat of a tachycardia. So, a short coupling interval followed by a long return cycle may suggest reentry as underlying mechanism. By contrast, a positive relationship between the intervals was described by Moroe and colleagues (Moroe 1991).

The majority of our VT/VF patients had an old infarct allegedly representing an anatomical substrate for reentry (appendix 1). To support this, most of these patients were reproducibly inducible to VT/VF using the extrastimulus technique.

C. Triggered activity

The following definitions are according to Cranefield and Aronson (Cranefield 1988a). Triggered activity is activity in which nondriven action potentials arise from afterpotentials that follow and are caused by the previous action potential.

Delayed afterdepolarization is defined as a depolarizing afterpotential that begins after normal repolarization (phase 3) or its continuation into an early afterhyperpolarization is completed. During programmed stimulation shortening of the pacing cycle length and/or increase of the number of stimuli increases

inducibility and increases also the number of induced beats in case of arrhythmias due to delayed afterdepolarizations. There is no inverse relation between the coupling interval and the return cycle. The return cycle will shorten with shortening of the coupling interval and with increase of the number of stimuli. However, it must be kept in mind that induction by extrastimuli will be more likely in case of a reentrant tachycardia than a tachycardia due to delayed afterdepolarizations. Overdrive pacing is more likely to accelerate the tachycardia but incidentally the tachycardia may terminate (Vos 1989).

On the electrocardiogram initiation and sustaining of a ventricular tachycardia due to delayed afterdepolarizations may show a direct relation between the rate of the basic sinus cycle length and the coupling interval of the initiating beat.

Early afterdepolarization begins prior to the completion of repolarization and causes an interruption or retardation of normal repolarization during phase 2 or 3, or both. Generally, early afterdepolarizations are preceded by pauses. During programmed stimulation shortening of the pacing cycle length and/or increase of the number of stimuli reduces inducibility and reduces also the number of induced beats in case of arrhythmia due to early afterdepolarizations. Overdrive may suppress spontaneous activity due to early afterdepolarizations (Cranefield 1988a).

On the electrocardiogram arrhythmias due to early afterdepolarizations may present with preceding short-long-short RR sequences associated with TU wave changes (Roden 1986, Cranefield 1988b, Jackman 1988, El-Sherif 1989). Therefore, triggered activity due to early afterdepolarizations was considered the electrophysiologic mechanism in the patient discussed in appendix 6. Other studies have reported on similar bradycardia-dependent onset of monomorphic ventricular tachycardia or ventricular fibrillation using 24-hour Holter recordings or Holter facilities in the implantable defibrillator (Zimmerman 1986, Coumel 1987). Also in one of the patients in appendix 8 with prolongation of the coupling interval during intravenously almokalant triggered activity as arrhythmogenic mechanism is suggested since apparently the premature beat is coupled to the repolarization of the normal complex. In appendix 9 the pause-dependent changes of the TU wave possibly representing early afterdepolarizations preceding the onset of torsades de pointes during infusion of almokalant are clearly illustrated. To our knowledge these recordings are one of the first 12-lead electrocardiographic registration of the onset of torsades de pointes in a patient. These and other observations led to the construction of a TU-morphology scoring system as presented in appendix 10 (Edvardsson -Sahlgrenska Hospital, Göteborg, Sweden-, and Svernhage -Astra Hässle, Mölndal, Sweden-, personal communications). The background for this morphology scoring system is that it allows the study of the prediction of torsades de pointes from preceding repolarization changes as reflected in TU-morphology changes.

3.2. Antiarrhythmic therapy

The antiarrhythmic therapeutic options are mentioned in Table 6. In some patients antiarrhythmic treatment can be avoided. The typical profile is that of a patient with monomorphic ventricular tachycardia and good left ventricular function having sporadic attacks (i.e. less than once per year) which are well tolerated. In the other VT/VF patients the pharmacological approach remains the cornerstone of therapy because it is noninvasive, convenient and widely available. Also in our hospital antiarrhythmic drug therapy is the therapy of first choice. As pointed out in the previous section it is not always possible to identify the electrophysiologic mechanism in VT/VF patients. As a consequence, antiarrhythmic drug therapy directed at the arrhythmogenic mechanism is not always feasible.

Initially, antiarrhythmic drugs were classified according to the Vaughan Williams classification (Vaughan Williams 1984). The major drawback of the Vaughan Williams classification is that it does not link arrhythmia mechanisms with antiarrhythmic actions and efficacy of therapy. Hence, this classification is less satisfactory to choose the optimal antiarrhythmic drug treatment. Although this classification is useful in educating physicians, current insights necessitated an update. This resulted in the Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: 'The Sicilian Gambit' (1991). The goal of the Task Force was: 'to reconsider the actions of antiarrhythmic drugs and to develop a rational and useful construct whereby basic and clinical investigators and clinicians might communicate and design research more effectively in order to further drug development, evaluation, and administration' (The Sicilian Gambit 1991). The Sicilian Gambit continues at the point of identification of the electrophysiologic mechanism in Table 4, point 3. It must be kept in mind that the Sicilian Gambit has its starting-point in the electrophysiology. The considerations noted in 3.1.1. and 3.1.2 should not be omitted. The approach of the Sicilian Gambit may be helpful to find the most appropriate drug by using 5 steps which are mentioned in Table 7 (The Sicilian Gambit 1991, Janse 1992, Schwartz 1992).

Table 6. Treatment of sustained ventricular tachycardia and ventricular fibrillation

1. No treatment
2. Pharmacological treatment
3. Nonpharmacological treatment
    - Ablation
        - Radiofrequency ablation
        - Transcoronary ablation
        - Direct current ablation
    - Arrhythmia surgery
        - Endocardial resection
        - Cryoablation
        - Aneurysm resection
    - Implantation of a cardioverter-defibrillator

Table 7. Approach according to 'The Sicilian Gambit'

1. Define the mechanisms of the arrhythmia,
2. Identify the 'vulnerable parameter', i.e. the electrophysiologic parameter which is most susceptible for modification. Modification will suppress or prevent the arrhythmia,
3. Consider the theurapeutic choices,
4. Identify the ionic current or receptor most likely to modify the vulnerable parameter (target),
5. Choose the drug.

Identification of an antiarrhythmic drug with the most appropriate profile to attack the most vulnerable parameter of the arrhythmogenic mechanism may improve long-term outcome of VT/VF patients. The approach of the Sicilian Gambit is an important step forward, however using it in VT/VF patients in clinical practice is quite optimistic. It may be difficult to identify the electrophysiologic mechanism in VT/VF patients. Generally it will be reentry, however reentry may depend on different ion channels. Moreover, Na^+-dependent reentry may be accompanied by either a long or a short excitable gap. In case of a long excitable gap the vulnerable parameter is excitability and conduction and Na^+ channel blockade is the treatment of choice. In case of a short excitable gap the vulnerable parameter is the effective refractory period and the K^+ channel is the target of therapy (Colatsky 1990, Janse 1992). These examples show that choosing antiarrhythmic drug therapy based on the principles of the Sicilian Gambit may eventually lead to empiric rather than rational choices. As a consequence, one may, apart from targeting therapy at the electrophysiologic mechanism, focus primarily on clinical predictors of efficacy, underlying heart disease or left ventricular funtion. Clinical predictors of response of antiarrhythmic drug therapy are absence of structural heart disease, absence of coronary heart disease including myocardial infarction, well preserved left ventricular function (Spielman 1983, Hohnloser 1987, Kuchar 1988, Meissner 1988, Gilles 1991, ESVEM 1993), low age (Spielman 1983), female gender or fewer episodes of ventricular tachycardia (Swerdlow 1983b). So, the choice of the antiarrhythmic drug may be guided by the underlying heart disease. Frequently VT/VF patients have a depressed left ventricular function. In these patients the choice of the antiarrhythmic drugs will be influenced by their hemodynamic effects (Block 1983, Schlepper 1989). Negative inotropism is the unfavorable characteristic of class 1a and 1c antiarrhythmic drugs (Gottlieb 1990, Hammermeister 1990, Tuininga 1994). Class 3 drugs exert less negative inotropic effects (Josephson 1988, Seipel 1989).

Recent data from studies with sotalol and amiodarone suggest that these drugs are more effective than class 1 agents in controlling life-threatening arrhythmias (Yusuf 1991). In favor of sotalol are the results of the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) comparing electrophysiologic testing with Holter monitoring to predict antiarrhythmic drug efficacy for ventricular tachyarrhythmias (ESVEM 1989). The actuarial probability of arrhythmia recurrence was significantly lower in the patients treated with sotalol compared to those treated with class 1 drugs. Moreover, sotalol was better tolerated (Mason 1993a). In the Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation study, empiric amiodarone in survivors of cardiac arrest was superior to class 1 antiarrhythmic drug therapy (CASCADE 1991, 1993). The survival free of cardiac death and sustained ventricular arrhythmias at 2 years was 78% in the patients treated empirically with amiodarone versus 52% in those treated conventionally with

class 1 drugs. In addition, there were fewer discharges of implantable cardioverter-defibrillators in patients given amiodarone than those treated with class 1 agents (CASCADE 1993).

Although the designs of the ESVEM and CASCADE study have their limitations, class 3 drugs seem to have a lot of potential which is encouraging for the development of new 'pure' class 3 drugs. The main difference between the new class 3 antiarrhythmic drugs and sotalol or amiodarone is that the latter compounds possess beta adrenergic blockade properties. Moreover, amiodarone combines several antiarrhythmic actions. In the suppression of ventricular premature beats amiodarone is superior to class 1c agents (Salerno 1990, Singh 1993a, 1993b). High efficacy rates of class 3 agents are found in suppression of inducible VT/VF, especially for sotalol (Nademanee 1990, Singh 1993a). Sager and colleagues found complete suppression of inducible VT in 26% of patients treated with sematilide (a new class 3 drug)(Sager 1993), which is comparable to that reported in a review of the literature for quinidine (mean$\pm$SD, 22$\pm$9%) as well as for procainamide (23$\pm$9%)(Nattel 1991). Efficacy of other new class 3 drugs is under investigation. In appendix 8 we investigated the electropharmacologic effects and pharmacokinetics of almokalant, a new class 3 antiarrhythmic drug, in postinfarct patients. We found that almokalant suppressed isolated ventricular premature beats significantly without having negative inotropic effects. Other favorable characteristics of class 3 drugs are their marked antifibrillatory effects (Lynch 1985, Lynch 1990, Dorian 1993, Lucchesi 1993, Roden 1993) and less negative inotropic effects (Katritsis 1993).

An unfavorable characteristic of class 3 drugs is their differential effect on Purkinje fibers and ventricular muscle (Singh 1993b, appendix 8,9). This may be accompanied by a higher incidence of proarrhythmia. Amiodarone is devoid of this effect which may be one of the reasons of the lower incidence of proarrhythmia with this drug. Furthermore, the therapeutic potential of class 3 antiarrhythmics is limited by a diminished ability to prolong repolarization at fast heart rates, i.e. reverse use-dependence (Hondeghem 1990), which reduces their effectiveness in preventing or terminating tachycardias. Moreover, a tendency to produce excessive prolongation at slow heart rates might lead to a higher incidence of proarrhythmia. Again, amiodarone shows no reverse use-dependency. In appendix 7 the use-dependent effects of almokalant were investigated in the porcine heart. Prolongation of refractoriness was maintained at short pacing cycle lengths, especially at the atrial level, indicating absence of reverse-use dependence of almokalant in the porcine heart.

In the VT/VF protocol serial antiarrhythmic drug testing was performed using class 1 and 3 agents. Initially, we instituted class 1a or 1c antiarrhythmic drugs as first therapy. After failure of these agents, class 3 antiarrhythmic drugs were tested. More recently, sotalol was used as first choice drug. Amiodarone was considered as last resort therapy, i.e. in patients not responding to conventional

therapy or those with severely depressed left ventricular function. Although recent studies are in favor of class 3 antiarrhythmic drug treatment in VT/VF patients, it is premature to condemn class 1 drugs: 'class 1 is not necessarily bad, and class 3 is not necessarily better' (Mason 1993b). The currently available class 3 antiarrhythmic drugs sotalol and amiodarone certainly have their limitations. Sotalol cannot be given to patients with chronic obstructive pulmonary disease on the basis of its beta-2 blocking properties and amiodarone frequently causes side effects of prolonged duration, due to its extremely long half-life.

3.3. Evaluation of antiarrhythmic therapy according to the VT/VF protocol

Several methods that can be used to evaluate antiarrhythmic therapy in VT/VF patients are summarized in Table 8, and discussed in the next paragraphs.

Initiation of antiarrhythmic drug treatment in VT/VF patients should be monitored in-hospital. First, because arrhythmias may recur easily before reaching a stable plasma level of the antiarrhythmic drug. For amiodarone hospitalization for at least 2 weeks seems appropriate. Secondly, in-hospital monitoring is done to detect possible proarrhythmic effects or progression of heart failure.

The 12-lead electrocardiogram at rest gives information about antiarrhythmic drug effects, which is not equal to antiarrhythmic drug efficacy. The prolongation of the QRS duration during class Ic antiarrhythmic drugs or prolongation of the QT interval during class Ia or 3 antiarrhythmic drugs are signs of electrophysiologic effects without any relationship with drug efficacy. However, the electrocardiogram can be used to reveal a large widening of the QRS interval (>50% prolongation), conduction disturbances, or a too pronounced prolongation of the QT interval (QTc>500 ms accompanied by (potentially) arrhythmogenic TU wave changes). Therefore, it is useful to record a 12-lead electrocardiogram at regular intervals after drug initiation.

Table 8. Evaluation of antiarrhythmic therapy in the VT/VF protocol

1.	Clinical observation
2.	12-lead electrocardiogram
3.	Signal-averaged electrocardiography
4.	Antiarrhythmic drug plasma level
5.	Exercise testing
6.	Holter monitoring
7.	Programmed electrical stimulation

In addition to the standard 12-lead electrocardiogram, signal-averaged electrocardiography can be used to evaluate drug effects. Previous studies have shown changes in the signal-averaged electrocardiogram during treatment with antiarrhythmic drugs, which depress conduction velocity (Simson 1987a, 1987b). In the evaluation of new antiarrhythmic drugs signal-averaged electrocardiography can be used to evaluate electrocardiographic changes more accurately. Using signal-averaged electrocardiography in appendix 7 and 8 neither the healthy pigs nor postinfarct patients showed changes in intraventricular conduction during intravenous almokalant. By contrast, the QT interval increased dose-dependently in both studies (appendix 7,8). Limited information is available about the value of signal-averaged electrocardiography in predicting antiarrhythmic drug efficacy (Freedman 1991, Hopson 1993, Kulakowski 1993). Signal-averaged electrocardiography can be used to evaluate antiarrhythmic surgery after which a late potential can disappear (Breithardt 1982, Marcus 1984, Denniss 1987).

The value of plasma level determination is limited in the assessment of antiarrhythmic efficacy. Interindividual drug kinetics may differ to a large extent, for instance protein binding. As a result the free drug concentrations may vary accordingly. Moreover, some drugs make active metabolites and their concentrations may differ between individuals. All these factors lead to substantially wide 'therapeutic windows' for most antiarrhythmic drugs. The plasma level should be determined after the antiarrhythmic drug has been used for at least 5 half-lifes and before the next dose because the trough plasma level should be effective. Although there is no absolute relation between plasma level and antiarrhythmic or proarrhythmic effect, it still can be helpful to distinguish between these clinical entities. In case of a breakthrough arrhythmia during a too high plasma level, obviously there is inefficacy or proarrhythmia. In case of a low plasma level inefficacy or facilitation of the arrhythmia can be present (class 1c antiarrhythmic drugs) or there is an idiosyncratic response (class la or 3 antiarrhythmic drugs) (appendix 9). Furthermore, the determination of plasma levels may be used to evaluate patient compliance. Finally, determination of the plasma level can be useful in patients with compromised clearance, for example congestive heart failure or renal insufficiency to prevent toxicicity (Woosley 1986, 1987).

Exercise testing should be performed in each patient before hospital discharge, although this test has a low sensitivity and specificity considering the occurrence of arrhythmias in ventricular tachyarrhythmia patients. Arrhythmia aggravation may be found in up to one third of the patiens (Slater 1988). In addition, despite optimal treatment ischemia may be present. Ischemia may cause dispersion of refractoriness and differences in conduction velocity, the prerequisites for reentry. Ischemia may also change the electrophysiologic effects of antiarrhythmic drugs. Furthermore, catecholamines may abolish antiarrhythmic efficacy (Morady 1988, Jazayeri 1989). Finally, exercise testing may unmask use-

dependent effects during class 1 antiarrhythmic treatment (Anastasiou-Nana 1987, Ranger 1989). With class 3 drugs complete reversal of antiarrhythmic effect may occur because of reverse use-dependence (Hondeghem 1990, Sager 1992).

Holter monitoring and programmed electrical stimulation are both used to evaluate the efficacy of antiarrhythmic therapy in VT/VF patients. However, Holter efficacy criteria are considered too lenient (low sensitivity) and programmed stimulation criteria are considered too strict (low specificity) (Kim 1988). The results of the Electrophysiologic Study Versus Electrocardiographic Monitoring did not resolve the dilemma to use either Holter monitoring or programmed stimulation for evaluation of antiarrhythmic drug efficacy (ESVEM 1989, Mason 1993c). The two approaches can be considered complementary rather than competitive. Evaluation of drug efficacy with Holter monitoring is hampered by spontaneous variability of the incidence of ventricular arrhythmias (Winkle 1981a, Pratt 1985, Toivonen 1987). In addition, up to 50% of VT/VF patients do not have sufficient ventricular premature beats to evaluate drug efficacy (Marchlinski 1985, Swerdlow 1985). Moreover, for occurrence of VT/VF the number of premature beats is not the only important factor. Just one critical-timed ventricular or even supraventricular premature beat may initiate VT/VF. In 'The VT/VF protocol' Holter monitoring was used to uncover inefficacy of antiarrhythmic drug therapy, use-dependence and proarrhythmic effects.

Noninducibility during antiarrhythmic drug treatment using programmed electrical stimulation is associated with favorable outcome (Swerdlow 1983a, Belhassen 1987, Kron 1987, Freedman 1988, Wilber 1988) and changes in inducibility have been associated with acceptable outcome (Waller 1987). During the VT/VF protocol serial drug testing using programmed stimulation (Wellens 1986) was performed. Patients were considered responders if they were not inducible (complete responders) or only to nonsustained ventricular tachycardias of less than 30 seconds duration without hemodynamic consequences. Partial responders were those patients in whom a hemodynamically stable ventricular tachycardia could be induced which was more 'difficult' to induce (i.e. at a shorter pacing cycle length or using more extrastimuli) and that showed an increase of tachycardia cycle length. During serial testing the number of antiarrhythmic drugs can be 'unlimited'. However, the significance of performing more than 3 tests is questionable (Kavanagh 1991, Kudenchuk 1993). After ≥ 2 tests, we considered amiodarone or nonpharmacological alternatives. It has been suggested that if the first drug trial is ineffective, the likelihood that subsequent drugs will be effective is very low. In such instances VT/VF patients are perhaps better treated by nonpharmacological approaches (Kudenchuk 1993).

3.4. Proarrhythmia during antiarrhythmic drug therapy

The incidence of proarrhythmia during antiarrhythmic drug therapy in VT/VF patients depends on the criteria used but may be as high as 10-15% (Poser 1985, Rae 1988, Slater 1988, Stanton 1989). Proarrhythmia is defined as aggravation and provocation of brady- or tachyarrhythmias. The clinician should be alert on this phenomenon, because the patient taking antiarrhythmic drugs remains always at risk. In other words patients can develop these side effects late after initiation of drug therapy. It is not possible to eliminate the risk of proarrhythmia, but appropriate use of antiarrhythmic drugs, selection of patients and extensive evaluation of drug efficacy may reduce the incidence. Due to the results of the Cardiac Arrhythmia Suppression Trial (CAST 1989) much attention has been paid to proarrhythmia with antiarrhythmic drugs that slow conduction. However, drugs delaying repolarization have also their proarrhythmic capacity. With the higher prescription rate of class 3 drugs more patients will present with the typical proarrhythmia torsades de pointes. In the 'Retrospective case-control study on drug-induced long QT-related arrhythmias' only 8 patients with torsades de pointes during class 1a drugs versus 23 patients during sotalol were included (appendix 10) which may reflect the changing prescription attitude in the last decade. The other 9 cases were treated with an investigational new class 3 drug. All events in these patients occurred between 1975 and 1993. In 87% of the patients using sotalol the drug was started between 1989-1993. The risk of torsades de pointes with the new class 3 antiarrhythmic drugs may be higher than with sotalol or amiodarone. The relative proarrhythmia incidence probably is: new class 3 antiarrhythmic drugs > sotalol > amiodarone (Katritsis 1993, Singh 1993b, personal observations). This brings into question if selective potassium channel blockade is desirable.

The main proarrhythmic effects are (a) increase of the incidence of arrhythmia, (b) awakening of a dormant arrhythmia, (c) change of characteristics of the arrhythmia, (d) new onset sustained VT or VF, (e) induction of bradyarrhythmias, and (f) combinations of these.

An increase of the incidence of ventricular premature beats, couplets or nonsustained VT is difficult to define because of day-to-day intrapatient variability. Frequently used criteria are of Velebit and colleagues (Velebit 1982) or Morganroth and Horowitz (Morganroth 1984).

Awakening of a dormant arrhythmia can occur e.g. in a postinfarct patient with asymptomatic isolated ventricular premature beats or nonsustained ventricular tachycardia treated with a class 1 antiarrhythmic drug. Such a patient may present with life-threatening arrhythmias. Several studies have proven the inefficacy of these agents (Furberg 1983, CAST 1989, Hine 1989b, Teo 1993). In postinfarct patients only beta blockers have proven to be effective in reducing death rate (Yusuf 1985). The role of class 3 drugs in these patients remains to be established. The results of

studies using amiodarone in postinfarct patients seems promising (Burkart 1990, Cairns 1991, Ceremuzynski 1992, Nademanee 1993, Pfisterer 1993). We studied postinfarct patients by giving a single infusion of almokalant and evaluated the electropharmacologic effects, pharmacokinetics, and efficacy in the suppression of spontaneous ventricular arrhythmias (appendix 8). Almokalant effectively suppressed ventricular premature beats. Further studies may reveal whether the new class 3 drugs can prolong life after myocardial infarction.

A change of the characteristics of a ventricular tachycardia includes either decrease of cycle length, or a higher incidence or longer duration of the attacks. In addition, the ventricular tachycardia can become incessant and difficult to terminate.

> ***Case report***: A 24-year old male patient presented with cardiac arrest. He was inducible during programmed stimulation to a sustained monomorphic ventricular tachycardia with left bundle branch block. Subsequently flecainide 200 mg daily was prescribed. After 7 days he had a spontaneous sustained ventricular tachycardia identical to the induced ventricular tachycardia. Inefficacy due to low flecainide plasma level was supposed and the dose was increased to 300 mg daily (flecainide plasma level was 480 ng/L). Within 2 days he had identical incessant monomorphic ventricular tachycardias during therapeutic flecainide plasma levels (845 ng/L). The electrocardiogram of this arrhythmia is presented (Figure 1). This was considered to be a proarrhythmic response. Flecainide was discontinued and disopyramide 500 mg daily was given. During subsequent programmed stimulation he was noninducible.

New onset sustained VT or VF may occur in patients treated for ventricular premature beats or nonsustained VT and even in patients suffering from supraventricular arrhythmias (Crijns 1988, 1993a, Marcus 1990). The typical presentation with class 1c antiarrhythmic drugs is incessant sinusoidal VT and with class 1a or 3 drugs it is torsades de pointes (appendix 10). Change of ventricular tachycardia morphology from monomorphic to polymorphic or even to ventricular fibrillation should also be considered as a proarrhythmic response.

The main problem of proarrhythmia is that the same electrophysiologic mechanisms which are antiarrhythmic can also be proarrhythmic (Rosen 1987, Levine 1989). Using class 1c antiarrhythmic drugs depression of excitability and conduction may induce unidirectional block setting the stage for reentry, i.e. proarrhythmia. However, a further impairment of excitability and conduction may result in a zone of bidirectional block and reentry cannot be initiated anymore, which would be antiarrhythmic. It has been suggested that proarrhythmia during class 1c agents occurs particularly during exercise, because of the use-dependent effects of class 1c agents (Falk 1989).

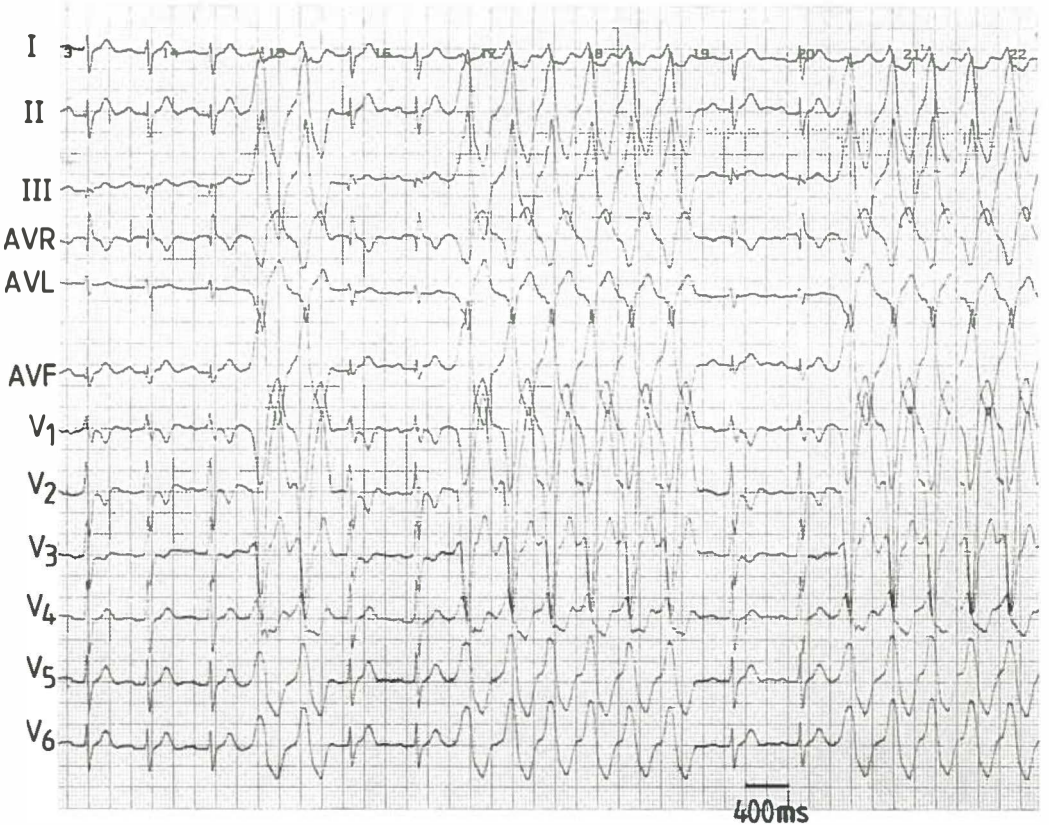

Figure 1. Proarrhythmia during flecainide. See text for details.

The arrhythmogenic mechanism of torsades de pointes during class 1a or 3 antiarrhythmic drug therapy is far from clear. Torsades de pointes is a ventricular tachyarrhythmia with undulating peaks of sequential QRS complexes and T waves, occurring in the setting of QT interval prolongation and preceded by short-long RR sequences and pause-dependent TU wave changes. Discussion is ongoing whether early afterdepolarizations inducing triggered activity or increased dispersion of refractoriness is the underlying arrhythmogenic mechanism (Surawicz 1989, Sasyniuk 1989, Habbab 1990). The origin of early afterdepolarizations is more likely in Purkinje fibers than in ventricular muscle (El-Sherif 1988). In in vivo experiments early afterdepolarizations and triggered activity could be registrated from the ventricular muscle, but not in in vitro experiments. A subgroup of cells was suggested in the human ventricle and also identified: the M cells (Drouin 1993). These M cells have electrophysiologic characteristics in between the ventricular and Purkinje tissue. In the canine ventricular myocardium they are located in the deep subepicardial to midmyocardial regions and in the deep subendocardial tissues of endocardial structures formed by invagination of the free wall (papillary muscles, trabeculae and septum) (Sicouri 1991a, 1991b). In these M cells action potential duration prolongs dramatically with slowing of stimulation rate. Furthermore, it is possible to provoke early afterdepolarizations and triggered activity in M cells, which is not possible in the ventricular endocardium or epicardium. It has been suggested that the prolongation of the action potential duration of the M cells may be seen as an early afterdepolarization-like deflection on the monophasic action potential. The U wave on the electrocardiogram may reflect triggered activity or prolongation of action potential duration in M cells and/or triggered activity in Purkinje fibers (Antzelevitch 1994). Hence, M cells and Purkinje fibers may be responsible for early afterdepolarizations. Additionally dispersion of repolarization and refractoriness may be found either between the Purkinje fibers and ventricular myocardium, because lengthening of the action potential duration will be more pronounced in Purkinje fibers, or between the M cells and the rest of the myocardium. It has been suggested that the M cells may function as an area of functional refractoriness setting the stage for a reentrant mechanism (Antzelevitch 1994).

In Table 9 clinical and electrocardiographic factors associated with proarrhythmia are summarized (Ejvinsson 1980, Morganroth 1984, 1985, Roden 1986, Morganroth 1987, Jackman 1988, Slater 1988, Herre 1990, Hashiba 1992). The clinical parameters are rather well described. Although cerebrovascular diseases may be accompanied by a prolonged QT interval (Davis 1993), it is unknown if they are associated with an increased risk for proarrhythmia during antiarrhythmic drugs delaying repolarization. Patients with Morbus Steinert (or other muscle diseases) or using concomitantly phenothiazines or tri/tetracyclic antidepressants may be at increased risk. Proarrhythmia with class 1c drugs occurs more often during high

dosages or rapid dose increase. By contrast, with class 1a and 3 drugs torsades de pointes may occur at low dose, even after the first dose. Dose-dependency seems to play a role with sotalol and the new class 3 drugs (Hohnloser 1992, appendix 9,10).

Table 9. Clinical and electrocardiographic signs associated with proarrhythmia

AAD delaying conduction Class 1c AAD	AAD prolonging repolarization Class 1a or 3 AAD
Clinical parameters	
structural heart disease	female gender
depressed LV function	depressed LV function
sustained VT/VF	intercurrent bradycardia
too high dose	conversion of AF to SR
rapid dose increase	SSS
	ectopy with short-long RR sequences
	change of dose/ preparation of AAD
	reinitiation after short discontinuation
	hypopotassemia, hypomagnesemia
	prolonged QT
ECG at rest with AAD	
QRS prolongation > 150%	prolonged QT
or	increased QT dispersion
excessive prolongation	pause-dependent TU wave changes
during exercise	
Exercise ECG without AAD	
	paradoxical increase of QT

AAD: antiarrhythmic drug; *AF:* atrial fibrillation; *AV block:* atrioventricular block; *ECG:* electrocardiogram; *LV:* left ventricle; *SR:* sinus rhythm; *SSS:* Sick Sinus Syndrome; *VF:* ventricular fibrillation; *VT:* ventricular tachycardia.

Controversy exists about the predictive value of electrocardiographic parameters either at rest or during exercise *and* either with or without antiarrhythmic drug. Marked QRS prolongation on the electrocardiogram at rest during treatment with class Ic agents, i.e. excessive intraventricular conduction slowing, has been suggested as an increased risk for the occurrence of proarrhythmia (Winkle 1981b, Nathan 1984, Anastasiou-Nana 1987, Crijns 1987, Ranger 1989, Wellens 1989), but has not been confirmed yet. Considering the use-dependent effects of class Ic agents excessive QRS prolongation may be unmasked during exercise testing (Crijns 1987, Ranger 1989, Wellens 1989) and used as noninvasive tool for identification of patients at high risk for proarrhythmia (Falk 1989, Crijns 1993a, 1993b).

During class Ia or 3 antiarrhythmic therapy, the predrug QT interval on the electrocardiogram at rest has a questionable predictive value for torsades de pointes. Torsades de pointes can occur in patients with either a normal or a prolonged predrug QT interval. Conversely, a prolonged QT interval on the electrocardiogram at rest during treatment with class Ia or 3 agents is associated with a higher incidence of proarrhythmia. However, there is no direct relationship between the degree of QT lengthening and onset of proarrhythmia. The discussion on the predictive value of QT prolongation is hampered by the different methods used for measuring the QT interval (Garson 1993). The morphology of the QT complex may be of greater predictive value than the duration of the QT interval per se. The onset of torsades de pointes is accompanied by a prolonged QT interval and pause-dependent TU wave changes. In the patient with torsades de pointes during intravenous almokalant these pause-dependent TU wave changes were also present on the predrug electrocardiogram (appendix 9). So, it may be that patients at increased risk for proarrhythmia show predrug pause-dependent TU wave changes on the electrocardiogram. Furthermore, if these pause-dependent TU wave changes are present on an electrocardiogram during chronic treatment the patient may also be at increased risk. In appendix 10 a classification of QT morphology is introduced, which may be helpful to identify a 'malignant' type and to select the patients at high risk (appendix 9, 10).

Bradycardia facilitates the reverse use-dependent effects of class Ia and 3 antiarrhythmic drugs. In fact, the pause-dependent TU wave changes are induced by a relative bradycardia. A ventricular premature beat is followed by a postextrasystolic pause which represents a decrease in heart rate. In patients with (paroxysmal) atrial fibrillation conversion to sinus rhythm is comparable with a sudden decrease in heart rate. After conversion supraventricular ectopic beats may induce short-long-short RR sequences. In atrial fibrillation patients using class Ia or 3 agents conversion to sinus rhythm has been associated with proarrhythmia (Roden 1986).

QT dispersion as measured on the 12-lead electrocardiogram is a new parameter. The group of Campbell found a decreased dispersion of the QT interval

in postinfarct patients treated with sotalol (Day 1991). Hii and colleagues (1992) treated patients with torsades de pointes during quinidine subsequently with amiodarone. During amiodarone treatment less QT dispersion was measured on the 12-lead electrocardiogram suggesting a more homogeneous prolongation of repolarization, which may be one of the factors for a lower incidence of torsades de pointes in patients treated with amiodarone. The importance of QT dispersion was underscored by the findings of Hohnloser et al. (1993). QT dispersion decreased in 19 VT/VF patients responding to sotalol treatment and remained unchanged in 20 nonresponders. By contrast, QT dispersion increased in 11 patients with torsades de pointes. Prospective studies are necessary to evaluate the clinical predictive value of predrug QT dispersion and the response of QT dispersion on antiarrhythmic drug treatment. Increase of QT dispersion was seen in the 9 postinfarct patients treated with intravenous almokalant from 72 ± 29 ms before almokalant to 137 ± 45 ms during almokalant ($p=0.005$). For the QT dispersion corrected for heart rate these figures were 72 ± 29 and 132 ± 39 ms ($p=0.007$), respectively. However, none of these 9 patients had torsades de pointes during or after the short-lasting infusion (appendix 8).

The clinical predictive value of an abnormal response of the QT interval during exercise is controversial. Kadish et al. (1990) found a paradoxical increase of the QT interval during exercise without antiarrhythmic drug treatment in patients with polymorphic ventricular tachycardia during class 1a agents. However, this could not be confirmed by Hii and colleagues (1990). Our torsades de pointes case (appendix 9) had an abnormal prolongation of the predrug QT interval during exercise testing. Unfortunately, very few data are available in the retrospective study because of the retrospective design (appendix 10). Using this point in the future, some considerations should be taken into account. First, Bazett's formula may not be appropriate at the fast heart rates during exercise (Bazett 1920, Funck-Brentano 1993). It may be more useful to make RR-QT scattergrams (Tobé 1992b). Secondly, recovery of the QT interval should also be considered, which includes measurement of the QT interval in the recovery phase of exercise testing.

Therapy of a proarrhythmic response during either 1c or 1a and 3 antiarrhythmic drugs is summarized in Table 10. Most important is to stop the antiarrhythmic drug and to take a blood sample for plasma concentration determination. In case of (sinusoidal) VT during class 1c agents cardioversion is the safest option. It should be noted that higher stored energy levels can be necessary and the VT can recur easily. In case of too high drug concentrations of flecainide, sodium lactate or hypertonic sodium bicarbonate intravenously may be helpful (Chouty 1989, Salerno 1991). Beta blockade has also shown to be effective in the reversal of a proarrhythmic response during class 1c antiarrhythmic drug treatment. Myerburg et al. (1989) described 4 VT/VF patients who developed an increase of premature ventricular ectopic beats or new ventricular tachycardia during treatment

with flecainide or encainide. Propranolol effectively suppressed these proarrhythmic responses.

Table 10. Therapy of ventricular proarrhythmia during class 1 or 3 antiarrhythmic drug treatment

AAD delaying conduction Class 1c AAD	AAD prolonging repolarization Class 1a or 3 AAD
Classical proarrhythmia	
monomorphic/sinusoidal VT	Torsades de pointes
Tachycardia termination	
STOP THE DRUG + determine plasma concentration	STOP THE DRUG + determine plasma concentration
	correction of potassium, magnesium i.v., isoproterenol i.v., transvenous pacing with a rate above underlying heart rate, AV block: atropin i.v.
cardioversion Note: higher threshold	in case of hemodynamic collapse due to VT/VF: defibrillation
beta blockade ?	

AAD: antiarrhythmic drug; *AV block:* atrioventricular block; *i.v.:* intravenously; *VF:* ventricular fibrillation; *VT:* ventricular tachycardia.

In case of torsades de pointes during 1a or 3 agents prevention of pauses (either using isoproterenol infusion or transvenous pacing) is the main goal, concomitantly with correction of hypopotassemia and with administration of magnesium intravenously. Magnesium can be given always, even in the absence of a hypomagnesemia. In a hemodynamically stable patient magnesium intravenously may be the first choice. The role of potassium channel openers in rhythm abnormalities

related to delayed repolarization is under investigation (Carlsson 1992).

To minimize the risk of torsades de pointes as much as possible, 10 considerations before prescribing antiarrhythmic drugs delaying repolarization are given in Table 11.

Table 11. Ten considerations to minimize the risk of drug-induced torsades de pointes

1.	Is treatment indicated ?
2.	Correct congestive heart failure, hypopotassemia and hypomagnesemia
3.	Predrug electrocardiogram at rest: Spontaneous bradycardia? Prolonged QT interval? Are there pause-dependent TU wave changes? Reevaluation of these parameters is mandatory while on treatment
4.	Sick sinus syndrome or atrioventricular conduction disturbances ?
5.	Depressed renal or hepatic function ?
6.	Concomitant disease ? (for example Morbus Steinert, cerebrovascular disease)
7.	Concomitant medication ?
8.	Use an antiarrhythmic drug which you are familiar with, especially its pharmacokinetics
9.	Start treatment in-hospital and monitor the electrocardiogram
10.	Perform exercise testing before and during antiarrhythmic drug therapy

3.5. Considerations in case of arrhythmia recurrence during antiarrhythmic therapy

In case of arrhythmia recurrence during antiarrhythmic drug treatment it is important to review the indication for antiarrhythmic therapy (Table 12). Proarrhythmia should be the first concern. This is extensively discussed in the previous section. Another possibility is progression of underlying structural heart disease which may be treated effectively with targeted therapy instead of changing antiarrhythmic treatment. The presence of new developed ischemia or overt heart failure may change the efficacy of an antiarrhythmic drug. The latter may also be caused by new adjuvant therapy, like diuretics inducing hypopotassemia. The clinician should carefully evaluate the

consequences of initiating additional therapy in patients treated with antiarrhythmics. Additional beta blockade is associated with higher efficacy of antiarrhythmic drugs (appendix 5). However, it has been suggested that bradycardia may promote torsades de pointes in patients using drugs delaying repolarization (appendix 8,9,10). Finally, a real failure of the antiarrhythmic therapy may be the case.

Table 12. Considerations in case of arrhythmia recurrence

1. Indication antiarrhythmic therapy
2. Proarrhythmia
3. Progression of underlying cardiac disease
4. Changed adjuvant therapy
5. Real failure of the antiarrhythmic therapy

3.6. Nonpharmacological antiarrhythmic therapy

The nonpharmacological modalities are included in Table 6. In the future, it may be possible that nonpharmacological therapy will be used just as frequently as pharmacological therapy in VT/VF patients or even more frequently. In a subset of ventricular tachyarrhythmia patients antiarrhythmic drug treatment is ineffective and nonpharmacological treatment has to be considered. In case of a monomorphic ventricular tachycardia one of the options is ablation of the site of origin after a careful mapping procedure. Radiofrequency ablation seems to be the most promising ablation procedure. Transcoronary ablation is hampered by the difficult identification of the coronary artery supplying the site of origin. Direct current ablation has been largely abandoned.

Arrhythmia surgery can be considered in VT/VF patients with monomorphic ventricular tachycardias and ≥ 4 normokinetic segments on the left ventricular angiogram. Endocard resection or cryoablation can be combined with coronary artery bypass surgery or aneurysm resection.

In the VT/VF protocol implantation of a cardioverter-defibrillator was considered after antiarrhythmic drug failure and no other nonpharmacological options. Logistic reasons limited implantation to these difficult-to-treat patients. Implantation of a cardioverter-defibrillator as first choice therapy was performed in the setting of a Dutch randomized multicenter trial (Wever 1992) and in a subset of the idiopathic VF patients (appendix 4). Extremely-high risk patients, i.e. sudden

death survivors with low ejection fraction but low attack rate and longer life expectancy (e.g. >2 years) may be considered for primary cardioverter-defibrillator implantation.

The role of the implantable cardioverter-defibrillator is increasing. Ongoing trials will give more insight in antiarrhythmic therapy of high risk patients using either antiarrhythmic drugs or implantation of a cardioverter-defibrillator (Moss 1993).

Summary

Sustained ventricular tachycardia and ventricular fibrillation (VT/VF) are life-threatening arrhythmias. Pharmacological and nonpharmacological therapy of VT/VF patients are important. In the last decade the role of antiarrhythmic drugs has changed tremendously. In addition, more selective antiarrhythmic drugs became available and nonpharmacological therapy is developing rapidly. As a consequence, reorientation in the evaluation and treatment of VT/VF patients seems appropriate. Therefore, in the University Hospital Groningen a standardized approach of patients with sustained ventricular tachycardia or ventricular fibrillation was started in January 1989 *'The Groningen VT/VF protocol'*. This approach focused on identification of underlying heart disease, the risk stratification of VT/VF patients and identification of arrhythmogenic factors. Antiarrhythmic therapy was only initiated in the absence of an evident arrhythmogenic provoking factor. As a rule drug therapy was the first line approach.

The role of underlying heart disease in VT/VF patients was reevaluated. The most frequent cause of VT/VF is an old myocardial infarct. The clinical significance of coronary anatomy in postinfarct VT/VF patients was evaluated (**appendix 1**). Eighty-two postinfarct VT/VF patients underwent coronary angiography to define 3 groups concerning the arrhythmogenic role of ischemia. Ischemia was considered the definite cause (Group A, 17%) or a coexistent factor of the event (Group B, 16%). In Group C (67%) ischemia did not play a significant role. Using life-table analysis group A had an excellent long-term outcome considering arrhythmia recurrence. Prognosis in group B and C was unfavorable. The 2-year arrhythmia-free rates were 100%, 56%, 52% for group A, B and C, respectively. In the absence of major ischemia (group B and C) prognosis depended on ejection fraction and a long time between the last infarct and the arrhythmic event (>5 years). The present approach helps to identify postinfarct VT/VF patients, who may benefit from single antiischemic therapy. The importance of depressed left ventricular function was confirmed in a study evaluating left ventricular function parameters (**appendix 2**). Sixty-nine VT/VF patients were followed up to evaluate the predictive value of functional capacity (i.e. New York Heart Association class and peak oxygen consumption) and resting left ventricular function (i.e. radionuclide left ventricular ejection fraction, angiographic left ventricular wall motion score and echocardiographic dimensions) with respect to arrhythmia recurrence. During a mean follow-up of 19 months 18 patients (26%) had a recurrence of their arrhythmia. Parameters of functional capacity and echocardiographic dimensions were not related to recurrence of arrhythmia. Left ventricular ejection fraction and wall motion score were worse in patients with a recurrence compared to the arrhythmia-free patients. The most powerful predictive parameter was left

ventricular wall motion score.

A small subgroup of VF patients was identified without underlying heart disease, i.e. idiopathic VF (**appendix 3**). However, right ventricular endomyocardial biopsy revealed right ventricular dysplasia in 6 out of 9 patients. The need for a more accurate definition of these 'idiopathic VF patients' is emphasized. Identification of a specific cause of idiopathic VF may have consequences for diagnosis and prognosis.

Before initiating antiarrhythmic therapy in VT/VF patients a careful search for provoking factors was performed. Identification of provoking factors and subsequent correction or modification can obviate antiarrhythmic therapy. This was confirmed by the finding that antiischemic therapy in a subset of postinfarct patients was related with good outcome (appendix 1). Idiopathic VF patients with a high sympathetic tone preceding the event were treated effectively with beta adrenergic blockade (**appendix 4**).

Appendix 5 summarizes the role of beta blockade in VT/VF patients. Beta blockade is the treatment of choice in patients with VT/VF preceded by high sympathetic tone, but also in patients without clear enhancement of sympathetic tone beta blockade can be effective. This may be especially the case in the setting of congestive heart failure because of neurohumoral activation. Beta blockers can also be used to enhance efficacy of class 1 and 3 antiarrhythmic drugs or as an adjuvans to cardioverter-defibrillator therapy to prevent too frequent discharges. Hence, if tolerated, beta blockers are an important alternative to conventional drugs in the management of VT/VF patients.

In the absence of provoking factors antiarrhythmic therapy was considered. In VT/VF patients antiarrhythmic drugs remain the cornerstone of therapy. The reproducibly inducible VT/VF patients underwent serial antiarrhythmic drug testing using programmed electrical stimulation (appendix 1,2,4). In selected cases, it was attempted to identify an arrhythmogenic electrophysiologic mechanism using noninvasive and invasive procedures in order to prescribe individualized antiarrhythmic drug therapy. In the postinfarct VT patient presented in **appendix 6**, tachycardias were only inducible after short-long RR sequences. After isoprenaline tachycardias became incessant, and all were preceded by short-long RR sequences. This strongly suggested early afterdepolarizations enhanced by increased sympathetic tone as arrhythmogenic electrophysiologic mechanism. Beta adrenergic blockade was succesful. The characteristics of almokalant, a new class 3 antiarrhythmic drug, were investigated in an animal experiment (**appendix 7**) with emphasis on the rate dependency of the drug's action on refractoriness. Prolongation of refractoriness by almokalant was more pronounced at the atrial than the ventricular level. Prolongation of refractoriness maintained at short pacing cycle lengths especially in the atrium, indicating absence of reverse use-dependence of almokalant in the porcine heart. In **appendix 8**, the electropharmacologic effects and pharmacokinetics

of almokalant were investigated in a randomized, placebo-controlled, double-blind study of 10 postinfarct patients with complex ventricular arrhythmias. This gave us the opportunity to evaluate antiarrhythmic effects of a new class 3 drug on ventricular arrhythmias. The electrocardiographic changes during administration of almokalant are pointed out.

The major drawback of antiarrhythmic drug therapy is the ever present risk of proarrhythmia. One patient of appendix 8 received almokalant infusion at a higher rate and developed self-terminating torsades de pointes (**appendix 9**). It has been suggested that proarrhythmia with the newer class 3 drugs is dose-dependent. In addition, the incidence with these drugs seems to be higher than with sotalol or amiodarone. Therefore, it is of utmost importance to identify patients at increased risk. The typical electrocardiographic changes preceding torsades de pointes in the presented case are illustrative (appendix 9). In retrospect, the presented patient may have been prone to drug-related torsades de pointes as suggested by preexisting electrocardiographic characteristics also found in the acquired long-QT syndrome: pause-dependent TU complex changes and an abnormal response of the QT interval during exercise. Also, comparable to torsades de pointes during quinidine treatment, the proarrhythmia occurred soon after the first almokalant administration. Although the predictive value of predrug electrocardiographic abnormalities remains to be established, it is emphasized that attention should be given to electrocardiographic characteristics associated with proarrhythmia. In addition, it may be of value to look for these electrocardiographic signs during chronic treatment. The 'Retrospective case-control multicenter study on drug-induced long QT-related arrhythmias' was performed to identify a profile of the patient at risk (**appendix 10**). In addition, special attention is given to electrocardiographic characteristics associated with proarrhythmia. The identification of markers of high risk may result in greater safety of antiarrhythmic drugs delaying repolarization. In appendix 10 the protocol of this retrospective study is described and a preliminary report of the 40 patients with torsades de pointes is given.

A lot is moving in 'Arrhythmia Land' with respect to identification of patients at increased risk for sudden cardiac death, pharmacological and nonpharmacological therapy. This thesis emphasizes that VT/VF patients should be evaluated more accurately before initiating antiarrhythmic therapy. The differences in long-term outcome between VT/VF patients with different underlying heart disease stresses the need for prospective studies in homogeneous patient populations. Moreover, discussion should focus on the endpoint of studies. Mortality seems more appropriate than arrhythmia recurrence in sight of the more frequently used implantable cardioverter-defibrillator. Furthermore, adequate treatment of provoking factors may obviate antiarrhythmic therapy thereby precluding the always present risk of proarrhythmia. Finally, treatment should always be directed to an arrhythmogenic electrophysiologic mechanism, whenever possible.

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Appendix 1

The clinical significance of coronary anatomy in postinfarct patients with late sustained ventricular tachycardia or ventricular fibrillation

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Abstract

Eighty-two postinfarct patients with sustained ventricular tachyarrhythmias underwent coronary angiography to define 3 groups concerning the arrhythmogenic role of ischemia. Ischemia was considered the *definite* cause of the event in the presence of a ≥90% stenosis in a coronary artery supplying viable myocardium or when this area only received collateral blood flow (Group A, 17%). Ischemia was defined a *coexistent* factor if there was an area of viable myocardium supplied by a coronary artery with a 70-90% narrowing (Group B, 16%). In Group C (67%) ischemia did *not* play a significant role. It included the patients without significant stenoses and those with a <90% stenosis but without demonstrable ischemia on exercise thallium-201 scintigraphy.

Using life-table analysis group A had an excellent long-term outcome considering arrhythmia recurrence. Prognosis in group B and C was unfavorable. The 1- and 2-year arrhythmia-free rates were 100%, 75%, 68% and 100%, 56%, 52% for group A, B and C respectively. In a univariate analysis arrhythmia recurrence was determined by the severity of coronary abnormalities, i.e. the potential arrhythmogenic role of ischemia, left ventricular ejection fraction and the time from the old infarct to the index arrhythmia. Multivariate analysis of group B and C identified depressed ejection fraction (RR 0.69, CI 0.49-0.98) and very long time to the index infarct (>5 years, RR 2.53, CI 1.12-5.75) as independent predictors for arrhythmia recurrence.

The present approach helps to identify postinfarct patients with ventricular tachycardia or fibrillation, who may benefit from stand-alone antiischemic therapy, i.e. the group A patients with severe coronary stenoses. In all other patients prognosis depends on left ventricular ejection fraction but also on the age of the previous infarct. Despite adequate antiischemic therapy prognosis remains poor in these patients if ejection fraction is below 40% or if the infarct is older than 5 years.

Introduction

The most important risk factors for the development of late ventricular tachycardia or fibrillation after a myocardial infarction are low left ventricular ejection fraction, a high incidence of ventricular premature beats, and ischemia. The contributive role of ischemia in causing sustained ventricular tachycardia or fibrillation in these patients is, however, not completely established[1]. On one hand, ischemia may be the primary cause of the event. On the other hand, it may be a coexistent factor and merely facilitate arrhythmia onset. Finally, postinfarct ventricular tachyarrhythmia may occur without ischemia[1,2]. Obviously, the clinical consequences differ markedly among these 3 groups.

Previous studies emphasized the role of ischemia in sudden death survivors. Those studies concerned mixed groups and included also patients with acute myocardial infarction[3-5]. The favorable prognosis of ventricular fibrillation in the initial stages of *acute infarction* is beyond any doubt[6]. However, in patients with an *old infarct*, prognosis may be poor due to recurrent ventricular tachycardia or ventricular fibrillation. Reentry is thought to underly these arrhythmias and hemodynamic, autonomic and ischemic events all have been implicated as a trigger[7]. The role of ischemia remains however controversial since in most documented cases of spontaneous ventricular tachycardia or fibrillation there are no ischemic ST changes before the event. Up till now it is unknown whether ischemia adversely affects prognosis in patients with ventricular tachyarrhythmias late after myocardial infarction[1,2].

Coronary angiography can be used to identify patients with *potential* ischemia[8,9]. Although coronary angiography is performed frequently in ventricular tachyarrhythmia patients, it has not been systematically used to classify the arrhythmogenic role of potential ischemia. Using coronary angiography, we studied prospectively the incidence and clinical significance of potential ischemia in 82 postinfarct patients presenting with sustained ventricular tachycardia or ventricular fibrillation.

Methods

Patients. Between January 1989 and January 1992 136 consecutive patients with sustained ventricular tachycardia or fibrillation were admitted to the Groningen University Hospital. Eighty-two patients (60%) had sustained a previous myocardial infarction, defined as a history of an infarct with typical changes of the cardiac enzymes and development of pathologic Q waves. These postinfarct patients form the study group. Excluded were patients with an acute myocardial infarct within 48 hours prior to the tachyarrhythmic event. Also were excluded patients with cardiomyopathy, significant obstructive valvular heart disease, congenital heart disease, long QT syndrome, inflammatory heart disease or electrolyte disturbances, i.e. hypopotassemia or hypomagnesemia. Finally, patients with a proarrhythmic response to antiarrhythmic drugs were excluded from this study[10]. All patients had given informed consent and the study was approved by the Institutional Review Board.

Evaluation program. All patients underwent a standard evaluation program, which included physical examination, serial 12-lead electrocardiograms, standard blood tests to exclude an acute myocardial infarct and electrolyte abnormalities, and symptom-limited exercise testing. Left ventricular function was assessed with multigated blood pool scintigraphy and transthoracic echocardiography, which

included measurement of the cardiac dimensions. Finally, coronary angiography and a left ventricular angiogram were performed.

Coronary angiography. Patients were scored as having 1, 2 or 3-vessel disease on the basis of the presence of a $\geq 70\%$ visual cross-sectional stenosis in any angiographic view, in any of the major coronary arteries. Left main stem disease was considered significant if there was a $>50\%$ stenosis. Normally moving or hypokinetic myocardium was considered as viable, whereas akinetic, dyskinetic or aneurysmatic segments were defined as nonviable. An aneurysm was scored as present or absent. Coronary angiograms were evaluated by two cardiologists, who were unaware of the clinical course and diagnosis of the patient. In case of an interobserver difference, a final decision was reached by consensus.

The results of coronary angiography were used to define 3 groups, grossly reflecting the role of ischemia in causing the tachyarrhythmic event. *Group A* included the patients in whom ischemia might be considered the *definite* cause of the event. Patients were included in this group in the presence of a $\geq 90\%$ stenosis in a coronary artery supplying viable myocardium or when this area only received collateral blood flow. *Group B* included the patients with less severe coronary artery stenoses in whom ischemia might have acted as a *coexistent* factor. These patients had at least one area of viable myocardium supplied by a coronary artery with a 70-90% narrowing. In addition, ischemia was either demonstrated by >0.1 mV ST segment depression in 2 adjacent leads on the 12-lead electrocardiogram during bicycle exercise testing, or by a reversible perfusion defect at exercise thallium-201 scintigraphy. *Group C* were the patients in whom ischemia as a cause of the tachycardia was extremely unlikely. It included the patients without significant coronary artery stenoses in other than the infarct-related vessel(s). In addition, the patients with a $<90\%$ stenosis but without demonstrable ischemia were included in this group.

Treatment. Treatment was directed to the primary cause of the tachyarrhythmic event, i.e. it was antiischemic, antiarrhythmic or both. Patients in group A received antiischemic therapy only, including medication, percutaneous transluminal coronary angioplasty or coronary artery bypass surgery. In group B patients antiischemic *and* antiarrhythmic therapeutic strategies were followed. In group C patients antiarrhythmic treatment was the primary goal. Efficacy of antiischemic therapy was assessed with a repeated exercise test. To guide antiarrhythmic drug treatment serial electrophysiologic testing was done[11,12]. Additionally, patients underwent exercise testing and ambulatory monitoring to assess efficacy and safety of drug therapy. In case of inefficacy of antiarrhythmic drugs[12] patients underwent catheter ablation or arrhythmia surgery or received a cardioverter-defibrillator (Cardiac Pacemakers, Inc., St. Paul, Minnesota). In a subset of sudden death survivors from group C, a cardioverter-defibrillator was implanted as first choice therapy, as part of a randomized Dutch multicenter study[13].

Follow-up and end-points. Follow-up was assessed from the initial event. Arrhythmic events were the end-point of the present study. Arrhythmic events were defined as sustained ventricular tachycardia or sudden cardiac death. Sustained ventricular tachycardia was defined as a ventricular tachycardia with a rate above 100 beats per minute and lasting for more than 30 seconds or requiring an intervention within 30 seconds, because of a hemodynamic collapse. Sudden cardiac death was defined as death within 1 hour after onset of symptoms or during sleep, in the absence of increasing angina or overt heart failure. Patients with appropriate discharges of the cardioverter-defibrillator were considered to represent recurrent cardiac arrest, because implantation was done for documented ventricular fibrillation[13]. Cardioverter-defibrillator discharges were considered appropriate only if they were preceded by syncope or presyncope.

Statistical analyses. The statistical tests used included Student's *t* test, the Mann-Whitney U test, the Chi-square test with Yates' correction and Fisher's exact test. Kaplan-Meier survival curves were used to illustrate the 1- and 2-year pattern of arrhythmia recurrence according to the 3 subgroups concerning the arrhythmogenic role of ischemia. Differences were tested by the Mantel-Haenszel log-rank test. To assess the relative value of variables in predicting arrhythmia recurrence 2 years in advance, either as independent variables or in combination with others, Cox proportional-hazard regression analysis was performed. All prognostic determinants of arrhythmia recurrence, that were identified by univariate analysis, were tested in the multivariance model if they were associated with improvement in the composite index ($p < 0.20$). The relative risks and 95 per cent confidence intervals were based on the Cox proportional hazard model, which incorporates the duration of follow up. Data are presented as mean $\pm$ 1 standard deviation unless indicated otherwise. All the statistical calculations were conducted with standardized biomedical programs (SPSS/PC+, SPSS, Chicago, and EGRET, Statistics and Epidemiology Research Cooperation, Seattle).

Results

Patients. The characteristics of the study patients are described in Table I. Forty-four per cent of the total group presented with ventricular fibrillation. Patients of group A presented predominantly with ventricular fibrillation, whereas only 4 of them had a monomorphic tachycardia. The incidence of ventricular fibrillation was lowest in group C. For the total group the time interval between the last infarct and the arrhythmic event was approximately 3 years (median value). Twenty-four per cent of the total group had their last infarct within 2 months before the tachyarrhythmic event. In 32% of the patients the event was more than 5 years after the last infarct. Twenty-eight per cent of the total group had sustained more than 1

Table I. Clinical characteristics of the total group and stratified to the arrhythmogenic role of ischemia.

	Total	Group A	Group B	Group C
Number of patients	82	14	13	55
Age (yrs)	64±10	64±10	69±7	63±11
Sex (male/female)	65/17 (79/21%)	11/3 (79/21%)	10/3 (78/23%)	44/11 (80/20%)
Reason of admission: VF	36 (44%)	10 (71%)	7 (54%)	19 (35%)
VT	46 (56%)	4 (29%)	6 (46%)	36 (65%)
VT rate at admission (bpm)	175±34	169±36	164±14	177±35
Anterior infarct	46 (56%)	5 (36%)	6 (46%)	35 (64%)
Inferior(posterior) infarct	36 (44%)	9 (64%)	7 (54%)	20 (36%)
More than one infarct (pts)	23 (28%)	3 (21%)	3 (23%)	17 (31%)
Time from last infarct (days, median)	1078	403	1921	1012
< 2 months	24%	36%	27%	21%
> 5 years	32%	36%	55%	27%
NHYA (dyspnea) ≥III	16 (20%)	2 (14%)	3 (23%)	11 (20%)
Echocardiographic dimensions				
LVEDD (mm)	61±9	57±7	61±11	62±8
LVESD (mm)	48±10	44±11	47±11	49±9
LA long axis (mm)	42±6	39±3	42±7	42±7
LVEF (%)	31±15	46±17	35±14	27±12
2-vessel / 3-vessel disease	29% / 30%	27% / 45%	17% / 75%	32% / 22%
Left ventricular aneurysm	21%	9%	17%	28%

Bpm: beats per minute; *NYHA:* New York Heart Association class for dyspnea; *LA:* left atrium; *LV:* left ventricle; *LVEDD:* left ventricular end-diastolic diameter; *LVEF:* left ventricular ejection fraction; *LVESD:* left ventricular end-systolic diameter, *VT:* ventricular tachycardia; *VF:* ventricular fibrillation.

infarct. The highest incidence of multiple infarcts was noted in group C. The numbers of anterior and inferior infarcts were the same in the total group. However, group C had predominantly old anterior infarcts, while in group A and B there were more inferior infarcts. As a consequence, left ventricular function was depressed most in group C.

Treatment. The majority of group A patients (8 patients) underwent percutaneous transluminal coronary angioplasty. The other patients underwent coronary artery bypass grafting (3 patients) or received antiischemic medication (3 patients).

Five patients of group B underwent coronary artery bypass grafting. Three of these patients also had cryoablation of the ventricular tachycardia origin. The other 2 patients received antiarrhythmics after surgery. Three patients underwent percutaneous transluminal coronary angioplasty and received thereafter amiodarone. In 5 patients neither coronary artery bypass grafting nor percutaneous transluminal coronary angioplasty was feasible. Therefore, antiischemic medication in combination with amiodarone was given.

Six patients of group C underwent antiarrhythmic surgery. One patient underwent catheter ablation of the ventricular tachycardia origin. In 6 patients a cardioverter-defibrillator was implanted. The other patients received antiarrhythmics.

At discharge 50% of the group A patients used beta blockers, which were prescribed in only 23% of group B and 18% of group C patients. By contrast, 62% of group B and 47% of group C patients received angiotensin converting enzyme inhibitors versus only 14% of group A.

Follow-up. During a mean follow-up of 21 ± 11 months, 11 patients died suddenly: 2 in group B and 9 in group C. Four patients from group C had appropriate discharges of the cardioverter-defibrillator. In addition, 5 patients died in-hospital because of progressive congestive heart failure: 1 in group A and 4 in group C. One noncardiac death occurred in group C. Finally, 13 patients had recurrent sustained ventricular tachycardia: 2 patients in group B and 11 patients in group C. All patients with sudden death or discharge of the cardioverter-defibrillator had left ventricular ejection fractions below 40%. None of the patients sustained a new infarct during follow-up.

Only 11% of the patients with an old infarct within 2 months of the event had an arrhythmia recurrence. The incidence of arrhythmia recurrence was higher, the longer the time window between the old infarct and the event: 20%, 37% and 54% for the patients with 2-6 months, 6 months to 5 years and more than 5 years between the old infarct and the arrhythmic event, respectively.

Using life-table analysis, patients in group A had the most favorable long-term outcome considering arrhythmia recurrence, i.e. recurrent ventricular tachycardia and sudden death (Figure 1). Outcomes of group B and C were comparable. The arrhythmia-free rate at 1 year was 100%, 75%, 68%, at 2 years

100%, 56%, 52%, and at 3 years 100%, 56%, 34% for group A, B and C respectively.

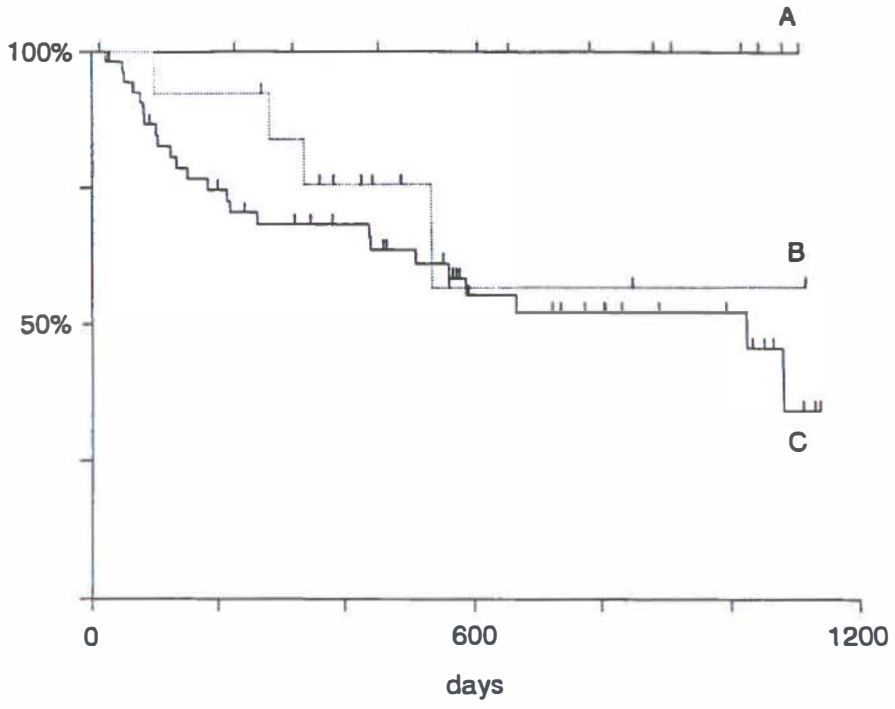

Figure 1. Kaplan-Meier arrhythmia-free survival curves of group A, B and C.

Univariate analysis of the total group indicated that patients with arrhythmia recurrence had lower left ventricular ejection fractions. Further, the time from the old infarct to the index arrhythmia was significantly longer. Conversely, severe coronary artery narrowing at the baseline investigation (i.e. group A), related to absence of arrhythmia recurrence (Table II). Multivariate analysis of the total group could not be performed, because none of the patients in group A had an arrhythmia recurrence. Therefore, multivariate analysis of the pooled data of group B and C was performed. Univariate analysis of group B and C showed that patients with arrhythmia recurrence had a lower left ventricular ejection fraction than those without arrhythmia recurrence: $25\pm11\%$ and $32\pm13\%$, respectively ($p=0.04$). In addition, they had a longer time interval between the last infarct and the index arrhythmia: 1546 (10-7856) and 295 (7-6187) days (median,range), respectively ($p=0.01$). These 2 parameters remained statistically significant in the multivariate analysis (Table III).

Table II. Comparison of the total group considering patients with and without arrhythmia recurrence during follow-up. Results of univariate analysis.

	No arrhythmia recurrence	Arrhythmia recurrence	p-value
Number of patients	54	28	
Group A	14 (26%)	0	┐
Group B	9 (17%)	4 (14%)	0.0085
Group C	31 (57%)	24 (86%)	┘
Time from last infarct (days, median)	349	1546	0.0108
< 2 months	33%	8%	
> 5 years	23%	50%	
LVESD (mm)	46±10	51±10	0.079
LVEF (%)	35±16	25±11	0.002
Percentage of patients with 1,2,3-vessel disease	45/25/30%	23/35/42%	0.186

All data mean±standard deviation. *LVEF:* left ventricular ejection fraction; *LVESD:* left ventricular end-systolic diameter.

Table III. Relative risk and confidence intervals of univariate analysis and multivariate analysis of the patients from group B and C considering arrhythmia recurrence. Ejection fraction was considered with 10% intervals. * The time interval between the infarct and the arrhythmic event was stratified: < or > 5 years between the last infarct and the arrhythmic event leading to inclusion into the study. The relative risk for arrhythmia recurrence using left ventricular ejection fraction was 0.69. This indicates that for every increase of 10% of ejection fraction, the risk of arrhythmia recurrence decreases with 31%. If the time interval between the last infarct and the event was longer than 5 years, the relative risk of arrhythmia recurrence was 2.5 times higher compared to the patients with a shorter time interval.

Parameter	Univariate analysis		Multivariate analysis	
	RR	CI	RR	CI
Time between last infarct and VT/VF	2.73	1.26-5.92	2.53	1.12-5.75
LVESD	1.03	0.99-1.07	-	-
LVEF	0.70	0.51-0.96	0.69	0.49-0.98
Vessel Disease				
2 compared to 1	2.20	0.78-6.24	-	-
3 compared to 1	2.30	0.85-6.28	-	-

CI: confidence interval; *LVEF:* left ventricular ejection fraction; *LVESD:* left ventricular end-systolic diameter; *RR:* relative risk; *VF:* ventricular fibrillation; *VT:* ventricular tachycardia.

Discussion

The incidence of significant coronary artery disease potentially producing ischemia in postinfarct patients with ventricular tachycardia or fibrillation (i.e. group A and B), was 33% in our study. This result compares favorably with the findings of Sellers et al.[14], who performed thallium-201 scintigraphy in 38 ventricular tachyarrhythmia patients. They found redistribution and persistent perfusion defects suggesting ischemia in 9 of 32 postinfarct patients (28%). Jordaens et al.[15] also using

thallium scintigraphy found an incidence of 45%. These findings support not only the validity of the present findings but also the feasibility of the present approach in the assessment of the role of ischemia in postinfarct ventricular tachycardia patients.

Clinically significant ischemia may be less often present than previous studies have suggested. In a study by Goldstein et al. 27 of 49 (55%) resuscitated postinfarct patients had presumed superimposed ischemia[3]. However, those investigators classified also patients with elevated cardiac enzymes as ischemic events. It may be supposed that many of these patients had an acute nontransmural infarction. Adhar et al.[16], using similar angiographic criteria, found potentially ischemic segments in as many as 61% of their ventricular tachyarrhythmia patients. Unfortunately, it is not possible to recover from the report if all their patients had an old infarct, making a comparison with the present study hazardous. In addition, those investigators did not perform thallium-201 scintigraphy or exercise testing in an attempt to subclassify patients with less severe stenoses. Coronary angiography was also used to detect potential ischemia in the study by Stevenson et al.[17]. They included only patients with ventricular tachycardia or fibrillation associated with a healed infarct. Applying similar angiographic definitions, they found that 20 of 36 patients (56%) had an area with potential ischemia. However, it is reasonable to assume that if tests for demonstrating ischemia were performed the incidence of clinically significant ischemia would be much less.

In patients with severe coronary artery disease in whom ischemia was considered the primary cause (group A), prognosis concerning arrhythmia recurrence was extremely favorable. This is in accordance with the clinical observation that ventricular fibrillation in the setting of an *acute* infarct does not have adverse prognostic implications[6]. The present study supports the contention that these patients may be successfully treated simply by preventing recurrence of ischemia[18,19]. On the other hand the group with less severe stenoses (group B) had a similar prognosis as found in postinfarct patients without additional significant stenoses or demonstrable ischemia (group C). In these patients multivariate analysis identified depressed left ventricular ejection fraction and a very long interval between the old infarct and ventricular tachyarrhythmia as the only parameters for arrhythmia recurrence. This implies that adequate antiischemic therapy in patients with coexistent ischemia does not improve prognosis compared to postinfarct patients without additional ischemia. Supposing that in a substantial number of these patients ischemia was an important arrhythmogenic trigger, abolishing this trigger could have been sufficient to prevent further arrhythmias. However, the present study shows that this was not the case. One explanation is that the prognostic impact of low left ventricular ejection fraction, completely independent of other factors, was large[20-22]. This was confirmed by the fact that all patients with sudden death had a left ventricular ejection fraction below 40%. In addition, severely depressed left ventricular function precluded institution of beta blocker therapy in many patients,

which might have improved outcome[23,24]. Another explanation relates to the mode of treatment. In patients with triple vessel disease and poor left ventricular function, surgical treatment of ischemia is associated with better outcome compared to medical treatment[5,25]. Since in most group B patients coronary artery bypass surgery or percutaneous transluminal coronary angioplasty was not feasible this may have had an additional negative influence on outcome. Finally, it cannot be excluded that antiarrhythmic drug therapy produced proarrhythmic effects in some of these patients[26,27], outweighing the beneficial effects of the antiischemic interventions.

Multivariate analysis indicated that patients with very old infarcts (i.e. > 5 years between the last infarct and the arrhythmic event) had a significantly increased risk for arrhythmia recurrence compared to patients with relatively recent infarcts. It must be noted that this was found irrespective of ejection fraction. By contrast, other studies found an unfavorable outcome in patients having their first arrhythmic event *early*, i.e. within 2 months, after the last infarct[28-30]. This discrepancy may be explained by differences in study population. In the present study only a small portion had rather recent infarcts. On the other hand, in the studies by the group of Wellens[28-30] the arrhythmogenic role of ischemia was not specified and only limited coronary angiographic results were presented[28,30]. We can only speculate why the patients with the very old infarcts were intractable. It may be that they had more advanced stages of the disease associated with differences in arrhythmia substrates compared to patients with more recent infarcts.

Experimental data showed that in the presence of acute ischemia the presenting arrhythmia will be ventricular fibrillation rather than ventricular tachycardia[31,32]. This applies to the patients in group A, who had a definite ischemia related event. By contrast, more than half of the patients in group B had a monomorphic ventricular tachycardia, This indicates that postinfarct patients with *coexistent* ischemia present frequently with monomorphic ventricular tachycardia rather than ventricular fibrillation. The discrepancy between experimental and clinical data may be due to differences in coronary anatomy. In animal experiments there is no generalized atherosclerotic heart disease and for the purpose of the experiment only one single infarction is provoked. Patients often have multivessel disease, sustained more infarcts and probably developed collaterals. The latter permit more moderate types of ischemia, e.g. occurring only subendocardially. This may be important for the genesis of monomorphic tachycardias. It has been suggested that in the setting of an old infarct a subtle area of ischemia may be the final (conduction slowing) part to complete the partially present reentrant circuit[1].

Study limitations. Several studies have shown that occurrence of ischemia is related to the extent and the severity of coronary artery disease[8,9]. However, the severity of a stenosis may not directly reflect the potential for developing ischemia since more dynamic factors such as coronary artery spasm, transient intraluminal thrombus[33,34] and myocardial oxygen demand are also important. This limitation

holds especially in the patients with the less severe stenoses and may have led to underestimation of the role of ischemia with too many patients included in group C. To prevent this as much as possible exercise testing with or without thallium-201 scintigraphy was done. However, spasm provocation was not a part of the study protocol. Acute coronary lesions or intraluminal thrombi were not found on coronary angiography.

Although the present study was prospective, patients were not randomized to antiischemic or antiarrhythmic treatment. In the absence of cardioverter-defibrillator back-up randomization was considered unethical. Randomization after implantation of a cardioverter-defibrillator might have given insight into the relative effects of antiischemic and antiarrhythmic drugs in the treatment of postinfarct ventricular tachycardia and fibrillation.

Clinical implications. Coronary angiography is performed routinely in ventricular tachyarrhythmia postinfarct patients. This study indicates that angiographic results are important in determining the arrhythmogenic role of ischemia and its prognostic implications in these patients. Postinfarct ventricular tachyarrhythmia patients with severe coronary artery stenoses and ischemia as the *main* arrhythmogenic factor (group A) have a very low risk of recurrence after adequate antiischemic treatment. In these patients implantation of a cardioverter-defibrillator is not indicated. By contrast, postinfarct patients with less severe coronary artery stenoses in whom ischemia is a *coexistent* arrhythmogenic factor (group B) prognosis is similar to that in patients without ischemia (group C). Considering the high recurrence rates despite therapy, group B and C patients are candidates for implantation of a cardioverter-defibrillator. This holds especially in patients with ejection fractions below 40% but also for those with a very old infarct. In how far additional antiischemic therapy prevents further arrhythmias in patients with coexistent ischemia (group B) is unclear at present. It is however tempting to hypothesize that a subset of these patients with hemodynamically tolerated monomorphic ventricular tachycardia might benefit from stand-alone antiischemic treatment in stead of adding potentially hazardous antiarrhythmic drugs. Further studies are needed to confirm these concepts.

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Appendix 2

Importance of angiographic left ventricular wall motion score in predicting arrhythmia recurrence in patients with sustained ventricular tachycardia or ventricular fibrillation

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Abstract

Sixty-nine patients with sustained ventricular tachyarrhythmias were followed up to evaluate the predictive value of functional capacity (i.e. New York Heart Association class and peak oxygen consumption) and resting left ventricular function (i.e. radionuclide left ventricular ejection fraction, angiographic left ventricular wall motion score and echocardiographic dimensions) with respect to arrhythmia recurrence.

During a mean follow-up of 19 months 18 patients (26%) had an arrhythmia recurrence. Parameters of functional capacity and echocardiographic dimensions were not related to arrhythmia recurrence. Left ventricular ejection fraction and wall motion score were worse in patients with a recurrence compared to the arrhythmia-free patients: $30\pm16\%$ versus $40\pm19\%$ (mean$\pm$SD, $p=0.035$) and 25 ± 5 versus 20 ± 7 ($p=0.01$) respectively. Multivariately the most powerful parameter was left ventricular wall motion score (Odds ratio 1.12, 95% confidence intervals 1.02-1.23).

Arrhythmia recurrence in ventricular tachyarrhythmia patients relates to resting left ventricular function and not to functional capacity. Since angiographic left ventricular wall motion score is prognostically more important than ejection fraction this parameter should be considered for risk stratification in these patients.

Introduction

Impaired left ventricular function is prognostically unfavorable in patients with sustained ventricular tachycardia or ventricular fibrillation. The most frequently used parameter for ventricular function is left ventricular ejection fraction. However, this parameter gives only an impression of global left ventricular function[1]. A left ventricular wall motion score incorporating local differences in contractility may be superior to left ventricular ejection fraction as predictor for arrhythmia recurrence. In the Collaborative Study in Coronary Artery Surgery angiographically determined left ventricular wall motion score was superior to ejection fraction in predicting operative mortality[2]. Left ventricular wall motion score was also of value to stratify postinfarction patients with ventricular tachycardia eligible for either surgery or medical therapy[3]. In addition, it is a powerful predictor of outcome in ventricular tachycardia or fibrillation patients treated with cardioverter-defibrillator or subendocardial resection[4,5].

Left ventricular ejection fraction and left ventricular wall motion score give only an index of resting left ventricular function. By contrast, the classification for exercise tolerance of the New York Heart Association and measurement of peak oxygen consumption reflect the functional capacity of the patient[6,7]. As such the latter dynamic parameters might have an additional value in predicting long-term

prognosis.

The present prospective study compares parameters of functional capacity and resting left ventricular function in patients with sustained ventricular tachycardia or ventricular fibrillation. The aim was to evaluate the additional value of left ventricular wall motion score and peak oxygen consumption in identifying patients prone to arrhythmia recurrence.

Methods

Patients. The present study included survivors of cardiac arrest or patients with sustained ventricular tachycardia admitted to the arrhythmia service of our hospital. Patients with cardiac arrest had documented ventricular fibrillation and were defibrillated during their resuscitation. Patients with an acute myocardial infarction within 48 hours prior to the event and those with obstructive valvular heart disease, electrolyte disturbances or a proarrhythmic response to antiarrhythmic drug therapy were not included. Finally, patients with New York Heart Association class IV for exercise tolerance were not included, because in these patients measurement of peak oxygen consumption was not feasible.

After clinical stabilization and individualized treatment for heart failure if indicated, patients underwent evaluation of their exercise capacity and left ventricular function. This included: (a) application of the New York Heart Association classification for exercise tolerance, (b) measurement of peak oxygen consumption, (c) echocardiographic evaluation of left ventricular dimensions, (d) radionuclide left ventricular ejection fraction and (e) left ventricular angiography to determine the left ventricular wall motion score.

Antiarrhythmic treatment was individualized. Patients with sporadic attacks (i.e. less than once per year), or hemodynamically tolerable ventricular tachycardia did not receive any antiarrhythmic drug treatment. Patients with a higher incidence of attacks or ventricular fibrillation underwent serial drug treatment or implantation of a cardioverter-defibrillator (Cardiac Pacemakers, Inc., St. Paul, Minnesota). Efficacy of antiarrhythmic drug treatment was evaluated with programmed electrical stimulation[8], 24-hour Holter monitoring and exercise testing.

Cardiopulmonary exercise testing. Treadmill exercise testing with respiratory gas exchange measurements was performed using a modified Naughton protocol[9]. Oxygen consumption, carbon dioxide production, and respiratory exchange ratios were measured continuously during exercise using an automated gas exchange measuring system (Sensormedics system 2900, SensorMedics Corp, Anaheim, California). Blood pressure was measured noninvasively and the electrocardiogram was monitored continuously. All patients terminated the test because of dyspnea or fatigue. In all patients the gas exchange anaerobic threshold

and a respiratory exchange ratio > 1.0 were reached. Peak oxygen consumption (peak VO2) was defined as oxygen consumption (ml/kg/min) at peak exercise calculated as the mean of values during the last minute of exercise[10].

Left ventricular wall motion score. The left ventricular wall motion score was determined from the biplane left ventriculogram. The left ventricle was divided in 10 segments[11]. Five segments (anterobasal, anterolateral, apical, diaphragmatic, posterobasal) were evaluated from the right anterior oblique ventriculogram and 5 segments (basal septal, apical septal, posterolateral, inferior lateral, superior lateral) from the left anterior oblique ventriculogram. Each segment was scored for contractility: normal (1 point), moderately hypokinetic (2 points), severely hypokinetic (3 points), akinetic (4 points) and dyskinetic (5 points). The left ventricular wall motion score is the summation of the score of the 10 segments. As a consequence, the higher the score the worse the overall left ventricular function. All ventriculograms were evaluated by two cardiologists, who were unaware of the clinical course and diagnosis of the patient.

Follow-up and end-points. Arrhythmic events, i.e. sustained ventricular tachycardia or sudden cardiac death, were the end-point of the present study. Sustained ventricular tachycardia was defined as a ventricular tachycardia with a rate above 100 beats per minute and lasting for more than 30 seconds or requiring an intervention within 30 seconds, because of a hemodynamic collapse. Sudden cardiac death was defined as death within 1 hour of symptoms or during sleep, in the absence of increasing angina or overt heart failure. Patients with appropriate discharges of the cardioverter-defibrillator were considered to represent recurrent cardiac arrest, because implantation was done for documented ventricular fibrillation. Discharges were considered appropriate only if they were preceded by syncope or presyncope.

Statistical analysis. Data are presented as mean $\pm$ 1 SD or median (range). Comparison of the clinical characteristics between the subgroups were made by Student's unpaired *t* test for continuous variables and Wilcoxon Mann-Whitney U test for nonuniformly distributed variables and Chi-square with continuity correction or Fisher exact test if appropriate. Logistic regression analysis was used to determine Odds ratios with confidence intervals for arrhythmia recurrence. Risk factors were evaluated by univariate and multivariate logistic regression analysis, calculated by EGRET (Statistics and Epidemiology Research Cooperation, Seattle). Each variable was considered for multivariate analysis if it achieved a significance of $p < 0.10$ in the univariate analysis. Actuarial analysis of arrhythmia recurrence (sustained ventricular tachycardia and sudden death) were performed by the life-table analysis method and compared using the log-rank test. A two-tailed probability value of < 0.05 was considered significant.

Results

Patients. Between January 1989 and June 1992 135 consecutive patients with sustained ventricular tachycardia or cardiac arrest were evaluated. The following patients were excluded from the present study: 10 patients already known with ventricular tachyarrhythmias and admitted to the hospital because of an arrhythmia recurrence, 6 patients admitted because of amiodarone side effects and 1 patient with proarrhythmia during disopyramide treatment. Peak oxygen consumption was not determined in 41 patients. Finally, 7 patients did not reached their anaerobic threshold during cardiopulmonary exercise testing and 1 patient developed a sustained ventricular tachycardia during the test. Therefore, the final study population was 69 patients. The clinical characteristics of the study population are summarized in Table I. Figure 1 shows the relation between left ventricular ejection fraction and left ventricular wall motion score in the study. There was a significant correlation with correlation coefficient $r=0.77$ ($p=0.000$) for all values. Visual interpretation suggests that with left ventricular ejection fraction $\leq 40\%$ the relation with left ventricular wall motion score is rather scattered ($r=0.17$, $p=0.30$), whereas a significant correlation exists with ejection fraction $>40\%$ or wall motion score <15 ($r=0.73$, $p=0.000$).

Treatment. At discharge 32% of the patients received beta adrenergic blockade, 43% angiotensin converting enzyme inhibitors, 35% diuretics and 18% digoxin.

Seven patients (10%) did not need any specific antiarrhythmic treatment. Forty-two patients (61%) received antiarrhythmic drug treatment. In 6 patients (9%) a cardioverter-defibrillator was implanted. Seven patients (10%) underwent percutaneous transluminal coronary angioplasty. Three of these patients received also antiarrhythmic drug treatment. Coronary artery bypass grafting was performed in 4 patients (6%) with arrhythmia surgery in 1 patient and postoperative antiarrhythmic drug treatment in 1 patient. Three patients (4%) underwent arrhythmia surgery.

Follow-up. During a mean follow-up of 19 ± 11 months 18 patients (26%) had an arrhythmia recurrence: 4 died suddenly and 4 received appropriate cardioverter-defibrillator discharges. In addition, 10 patients experienced recurrent sustained ventricular tachycardias. The patients with an arrhythmia recurrence received less often beta blockade ($p<0.05$) and more often angiotensin converting enzyme inhibitors ($p>0.05$) compared to the arrhythmia-free patients, 11% versus 37% and 50% versus 37%, respectively. Other treatment modalities were not different. Death was noncardiac in 1 patient and due to progressive heart failure in 4 patients. None of the patients had a recurrent acute myocardial infarction.

Table I. Clinical characteristics of the total group and comparison of the patients with and without arrhythmia recurrence during follow-up. Results of univariate analysis.

	Total group	Arrhythmia free	Arrhythmia recurrence	p
Number of patients	69	51 (74%)	18 (26%)	-
Male (n)	57 (83%)	41 (80%)	16 (89%)	ns
Age (years)	59±12	66±8	58±13	ns
Underlying disease (n)				
Coronary artery disease	51 (74%)	36 (71%)	14 (78%)	ns
Cardiomyopathy	12 (17%)	8 (16%)	4 (22%)	ns
No structural heart disease	6 (9%)	6 (12%)	0	ns
Presenting arrhythmia (n)				
Sustained VT	32 (46%)	23 (45%)	9 (50%)	ns
VF	37 (54%)	28 (55%)	9 (50%)	ns
NYHA I/II/III	43/17/9	32/11/9	11/6/1	
	62/25/13%	63/21/16%	61/33/6%	ns
Peak oxygen consumption (ml/kg/min)	19±7	19±7	17±6	ns
Echocardiographic dimensions				
LVEDD (mm)	60±9	60±9	60±10	ns
LVESD (mm)	46±10	46±10	47±9	ns
LA long axis (mm)	41±7	41±6	41±9	ns
Fractional shortening(%)	24±8	24±8	23±6	ns
LV ejection fraction (%)	37±19	40±19	30±16	0.035
Angiographic LV wall motion score	21±7	20±7	25±5	0.01

Data are presented as mean±1 SD. *p:* p-value of univariate analysis of the patients with and without arrhythmia recurrence is given. *LA:* left atrium; *LV:* left ventricular; *LVEDD:* left ventricular end-diastolic diameter; *LVESD:* left ventricular end-systolic diameter; *n:* number of patients; *NYHA:* New York Heart Association classification; *VF:* ventricular fibrillation; *VT:* ventricular tachycardia.

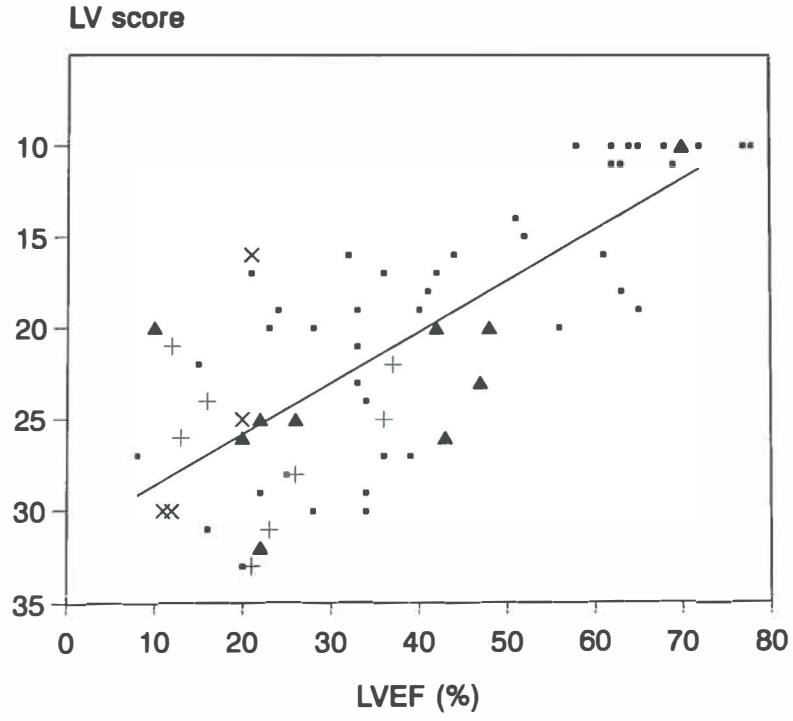

Figure 1. Significant correlation between left ventricular wall motion score and ejection fraction (correlation coefficient = 0.77, p=0.000). Note that in patients with ejection fractions below 40% left ventricular wall motion score may vary widely (correlation coefficient = 0.17, p=0.30). By contrast, a significant correlation exist in patients with ejection fractions above 40% (correlation coefficient 0.73, p=0.000). Due to overlap the results of 5 patients without cardiac event during follow-up are not visible. Filled squares = no arrhythmia recurrence; filled triangles = recurrence of ventricular tachycardia; + = sudden death and appropriate cardioverter-defibrillator discharges during follow-up; x = death due to congestive heart failure.

Parameters associated with arrhythmia recurrence. Comparison of the patients with and without arrhythmia recurrence is presented in Table I. New York Heart Class for exercise tolerance and peak oxygen consumption were comparable. However, in the patients with an arrhythmia recurrence left ventricular ejection fraction was significantly lower and left ventricular wall motion score was

significantly higher. Sensitivity, specificity and positive predictive value of left ventricular ejection fraction < 30% for arrhythmia recurrence were 61%, 63% and 37%, respectively. Similar values were found for left ventricular wall motion score above 21 (median value of the total group): 76%, 64% and 43%, respectively. Using multivariate logistic regression analysis left ventricular ejection fraction was not significantly different between the groups (p=0.058, Odds ratio 0.97, 95% confidence intervals 0.94-1.00). By contrast, left ventricular wall motion score was significantly higher, i.e. worse, in the patients with arrhythmia recurrence (p=0.017, Odds ratio 1.12, 95% confidence intervals 1.02-1.23).

The actuarial 1- and 2-year arrhythmia-free rates for patients with LVEF<30% were 70% and 45%, and for LVEF≥30% 85% and 77%, respectively (Figure 2A). For patients with left ventricular wall motion score >21 these figures were 65% and 36%, and for a score ≤21 90% and 83%, respectively (Figure 2B). The actuarial 1- and 2-year survival rates for patients with LVEF<30% were 79% and 55%, and for LVEF≥30% 94% and 94%, respectively (Figure 3A). For patients with left ventricular wall motion score >21 the 1- and 2-year survival rates were 75% and 56%, and for ≤21 97% and 94%, respectively (Figure 3B).

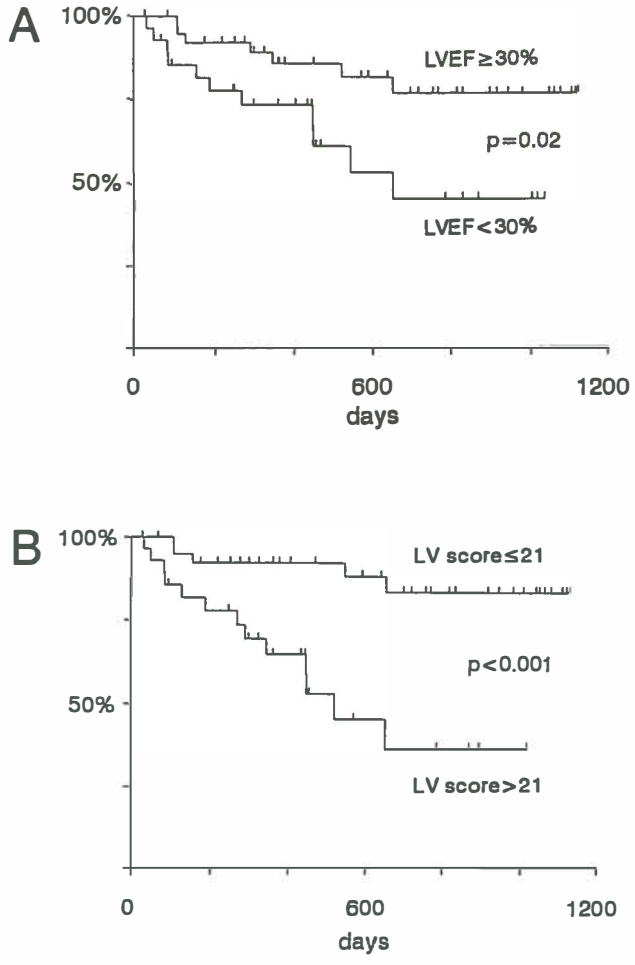

Figure 2. Kaplan-Meier arrhythmia-free survival curves according to LVEF< or ≥30% (panel A) or LV wall motion score > or ≤21 (panel B). Comparison of the arrhythmia-free curves for 2 years in patients with LVEF<30% and LVEF≥30% showed a statistically significant difference (p=0.02). This was also found for patients with LV wall motion score >21 and ≤21 (p<0.001). *LVEF:* left ventricular ejection fraction; *LV score:* left ventricular wall motion score.

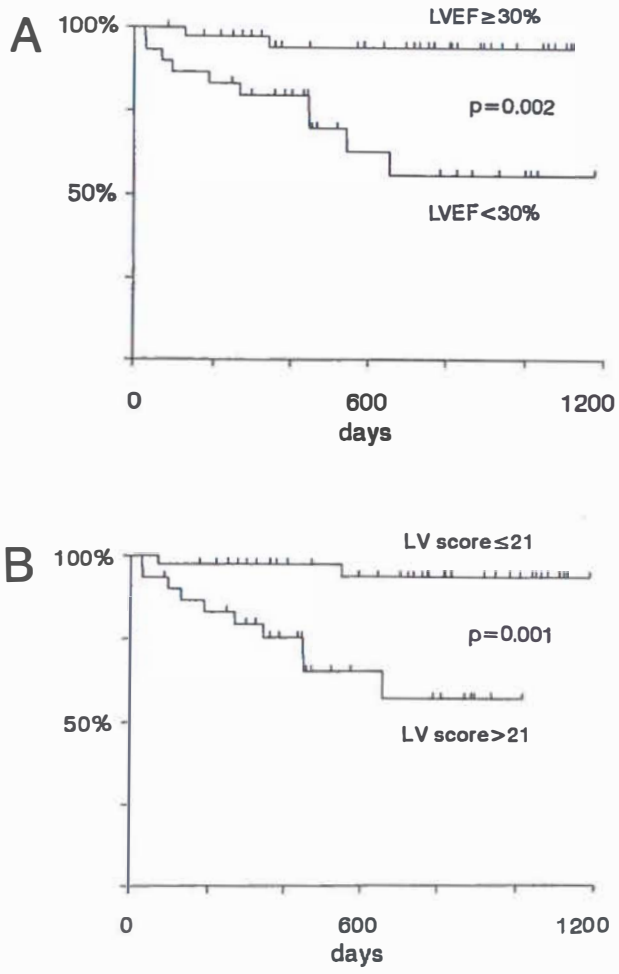

Figure 3. Kaplan-Meier survival curves according to LVEF< or ≥30% (panel A) or LV wall motion score > or ≤21 (panel B). Comparison of the survival curves for 2 years in patients with LVEF<30% and LVEF≥30% showed a statistically significant difference (p=0.002). This was also found for patients with LV wall motion score >21 and ≤21 (p=0.001). *LVEF:* left ventricular ejection fraction; *LV score:* left ventricular wall motion score.

Discussion

In the present study arrhythmia recurrence was related to parameters of resting left ventricular function rather than functional capacity. In addition, left ventricular wall motion score predicted arrhythmia recurrence better than left ventricular ejection fraction, which is in agreement with previous studies[4,5]. Most ventricular tachycardia recurrences or sudden death occurred with low left ventricular ejection fraction or high left ventricular wall motion score. Surprisingly, Figure 1 shows that this was the area where the largest discrepancies existed between these parameters. Considering exclusively the patients with arrhythmia recurrence, even there was a large variation between these 2 parameters. This suggests that apart from left ventricular function as represented by left ventricular ejection fraction or left ventricular wall motion score, other factors possibly related to left ventricular geometry determine sudden death or arrhythmia recurrence in these patients.

The finding that, at least in patients with left ventricular dysfunction, left ventricular wall motion score might be better than ejection fraction in predicting arrhythmia recurrence may be due to the fact that ejection fraction provides only information on global left ventricular function[1,12]. Consequently, left ventricular ejection fraction may be the same in patients with a localized infarct or a left ventricular aneurysm compared to patients with a diffusely depressed wall motion. It may be conjectured that, irrespective of the left ventricular ejection fraction, patients with a local wall motion abnormality may have a better prognosis than those with a diffusely depressed left ventricle. A diffusely hypokinetic left ventricle is more extensively damaged, thereby harbouring more arrhythmia triggers and more reentry substrates than a locally damaged left ventricle. In addition, higher peaks in sympathetic activation at minor exercise may be expected in patients with diffuse hypokinesis, while patients with a locally damaged left ventricle may have sufficient residual left ventricle with normal contractility precluding potentially arrhythmogenic rises in sympathetic tone[13].

Angiographically determined left ventricular wall motion score is not routinely considered as prognostic parameter in ventricular tachyarrhythmia patients. One reason may be that it is an invasive parameter, relatively difficult to obtain. Another reason is the absence of a standardized method of its assessment[3,11,14]. We considered biplane ventriculograms, while the Collaborative Study in Coronary Artery Surgery evaluated monoplane right anterior oblique ventriculograms[11]. Schwartz et al.[2] demonstrated in a subset of these patients that biplane ventriculographic wall motion score was associated with improved survival prediction after bypass surgery compared to monoplane assessments and it was superior to left ventricular ejection fraction. Despite the problem of feasibility and lack of standardization we feel that due to its clinical implications left ventricular angiography with assessment of left ventricular wall motion is an important tool in

the clinical work-up of patients with these life-threathening arrhythmias.

Echocardiographic left ventricular dimensions and fractional shortening were not of prognostic importance. This may be explained by the fact that these parameters reflect only the contractility at one place in the ventricle, neglecting contractility of the total left ventricle. However, due to advanced techniques echocardiographic determination of left ventricular wall motion score has become feasible and probably will have the same value as the angiographically determined score.

In the present study arrhythmia recurrence was not related to parameters of functional capacity. The lack of prognostic value of New York Heart Class in contrast to other studies[15] can be explained by the high number of patients with class I for exercise tolerance. This may have resulted in a different study population with relatively preserved functional capacity. Further, class IV patients were excluded. Since New York Heart Association class may be a too subjective parameter[16], we considered also peak oxygen consumption as an objective parameter of functional capacity[6,7]. In patients with congestive heart failure peak oxygen consumption was one of the strongest predictors for cardiac mortality[10,17]. However, similar to New York Heart Association classification, this parameter was also not able to predict arrhythmia recurrence.

The arrhythmia-free patients used more frequently beta adrenergic blockade and less frequently angiotensin converting enzyme inhibitors than the patients with arrhythmia recurrence. This reflects the more preserved left ventricular pump function in the arrhythmia-free patients. The role of angiotensin converting enzyme inhibitors in patients with sustained ventricular tachyarrhythmias is unresolved. However, independent of left ventricular function beta blockade reduces cardiac mortality, including sudden cardiac death[18]. In addition, favorable effects are observed in patients with sustained ventricular tachyarrhythmias[19-21]. Trials concerning angiotensin converting enzyme inhibitors in patients with depressed left ventricular function are less conclusive in this respect.

Implication of the study. Left ventricular wall motion score should be considered for risk stratification in patients with sustained ventricular tachycardia and ventricular fibrillation. The need for an invasive angiographic study may be obviated by using echocardiography, which is a widely available technique. In combination with noninvasive methods for the detection of ischemia, these techniques may provide a rapid assessment of risk for arrhythmia recurrence in patients with sustained ventricular tachycardia or fibrillation.

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Appendix 3

Potential role for endomyocardial biopsy in the clinical characterization of patients with idiopathic ventricular fibrillation

Arrhythmogenic right ventricular dysplasia, an undervalued cause

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Job D. Elema, Ype S. Tuininga, Kong I. Lie

Neth J Cardiol 1992;5:298 (abstr)
PACE 1993;16:883 (abstr)
Am Heart J 1994;127:1421-1424

Introduction

Controversy exists about the risk for arrhythmia recurrence in idiopathic ventricular fibrillation. One of the causes for conflicting results may be that in most studies endomyocardial biopsies were not performed. This may lead to differences in survival, because of unrecognized underlying cardiac disease in patients who seem comparable at first sight. In a subset of patients with idiopathic ventricular fibrillation, a cardiomyopathy may be present, for example arrhythmogenic right ventricular dysplasia. Obviously, in the absence of macroscopic abnormalities, subclinical cardiomyopathy can only be diagnosed by biopsy. The present report describes the pathoanatomic findings in nine consecutive survivors of idiopathic ventricular fibrillation, in an attempt to subclassify this clinical entity and to bring into question the concept of idiopathic ventricular fibrillation.

Methods and results

Nine patients (Table I) without a history of cardiac disease or acute myocardial infarction were admitted to our department after successful resuscitation for a cardiac arrest. All were defibrillated during their resuscitation. History and physical examination were unremarkable and the family history was negative for sudden cardiac death. None of the patients used cardioactive drugs. In six patients the arrest was exercise related. In patients No. 3 and 4, who were both competetive athletes, arrhythmia occurred during vigorous exercise. Patient No. 7 had prolonged emotional stress before the event and had not slept for 3 days. The corrected QT interval was normal in all patients. During exercise testing, there were neither signs of ischemia nor ventricular tachyarrhythmias. The incidence of ventricular arrhythmias during ambulatory monitoring was low. Nonsustained ventricular tachycardias were noted only in two patients. Mean radionuclide left ventricular ejection fraction was $61 \pm 3\%$. Echocardiography, including right ventricular evaluation, revealed neither wall motion nor valve abnormalities. Coronary and left ventricular angiography were normal. Careful evaluation of the right ventricular angiogram revealed no wall motion disturbances or other abnormalities. Provocation tests for coronary spasm were normal. After the baseline investigations and after we had obtained informed consent, patients underwent programmed electrical stimulation. including isoproterenol administration if indicated. Finally they underwent right ventricular endomyocardial biopsy. A minimum of four standard right ventricular septal biopsies were obtained with a Cordis bioptome (Cordis Corp., Miami Lakes, Fla).

Table I. Patient characteristics.

Patient Age(yr)/Sex	Premonitory symptoms	Activity at arrest	ECG abnormalities	Holter VPC	Baseline PES
1. 47 F	exercise-related chest pain	jogging	no	1	VF
2. 21 M	dizziness during cycling	cycling	no	n.a.	AVNT
3. 24 M	none	playing soccer	persistent negative T lead V2,V3.	341	LBBB-VT
4. 26 M	dizziness during jogging	cycling	no	752	LBBB-VT
5. 37 M	chest pain	rest	no	1	noninducible
6. 56 F	none	swimming	transient ST and T wave abnormalities	180	noninducible
7. 36 M	palpitations emotional stress	rest	transient ST abnormalities, incomplete RBBB	5	AF/AFL
8. 39 M	none	carrying boxes upstairs	LAFB	0	noninducible
9. 48 M	aspecific complaints	rest	incomplete RBBB	15	VF

AF/AFL: atrial fibrillation/atrial flutter; *AVNT:* atrioventricular nodal tachycardia; *LAFB:* left anterior fascicular block; *LBBB-VT:* left bundle branch block ventricular tachycardia; *n.a.*: not available; *PES:* programmed electrical stimulation; *RBBB:* right bundle branch block; *VF:* ventricular fibrillation; *VPC:* number of ventricular premature complexes during 24-hour Holter monitoring.

Table II. Results of right ventricular endomyocardial biopsy.

Patient number	1	2		3	4	5	6	7	8	9
Number of RV biopsies	6	4 in 1985	4 in 1988	12	11	4	4	14	8	11
Subendocardial fibrosis	0	0	+	++	0	0	0	0	0	+
Interstitial fibrosis	+	+	+	++	+	+	+	+	+	+
Patchy fibrosis	+	++	++	++	0	+	+	+	0	+
Nuclear polymorphy	0	0	0	+	+	+	+	+	0	0
Cellular polymorphy	0	+	0	++	+	0	0	+	0	0
Hypertrophy	0	0	0	+	+	0	0	+	0	0
Mononuclear infiltrate	0	0	0	0	0	0	0	0	+	0
Polynuclear infiltrate	0	0	0	0	0	0	0	0	0	0
Lipomatous replacement	+	+	++	++	0	+	0	+	0	+
Thickening of vessel walls	0	0	+	0	0	+	+	0	0	0
Diagnosis	RVD	RVD		RVD	N	RVD	N	RVD	N	RVD

Score for histologic abnormality of the right ventricular endomyocardial biopsy: 0, absent; +, mild; ++, marked.
RVD: right ventricular dysplasia; *RV:* right ventricle; *N:* normal (i.e. normal biopsy).

If the electrocardiogram suggested arrhythmogenic right ventricular dysplasia (negative T waves in the right precordial leads or (in)complete right bundle branch block[1]) a more extensive procedure was followed, with biopsies being taken from the corners of the 'triangle of dysplasia'[1] (patients No. 3, 4, 7, and 9). In addition, in patients with inducible arrhythmias a more extensive biopsy procedure was also performed. This is reflected in the number of biopsies taken in each patient (Table II). All biopsy specimens were reviewed by one pathologist (C.S.), who was unaware of the clinical diagnosis. Biopsy specimens were fixed in 4% formaldehyde and were embedded in paraffin or plastic and stained with hematoxyline-eosine and trichrome-azan. Light microscopic histologic examination focused on the items listed in Table II. A semiquantitative score was used to evaluate the extent of abnormalities. It was scored as absent, mild or marked (a score of 0, + or ++ respectively). Mild lipomatosis with at least two different types of mild fibrosis was the minimum requirement for the diagnosis of arrhythmogenic right ventricular dysplasia. Table II shows that pathoanatomic abnormalities compatible with arrhythmogenic right ventricular dysplasia were present in six patients. In one of these patients (patient No. 2) repeated biopsy showed progression of the disease, with more extensive fibrosis and lipomatosis (Figure 1A and 1B).

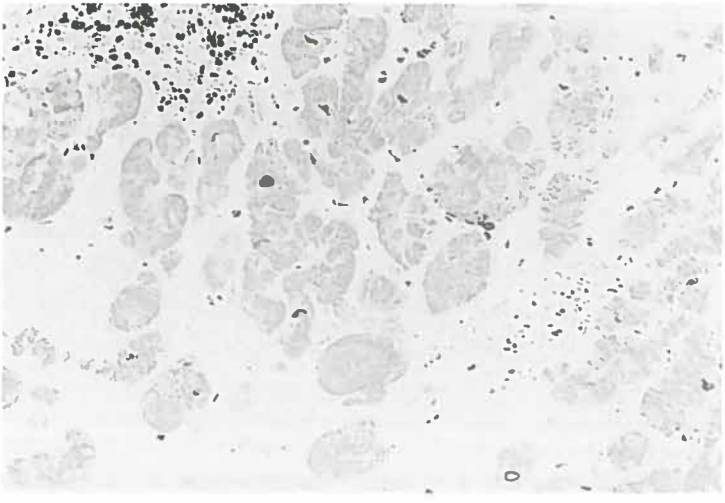

Figure 1. A. Photomicrograph of right ventricular endomyocardial biopsy specimen from patient No. 2. Lipomatosis is noted in the upper right corner and interstitial fibrosis is seen in the middle (original magnification x224).

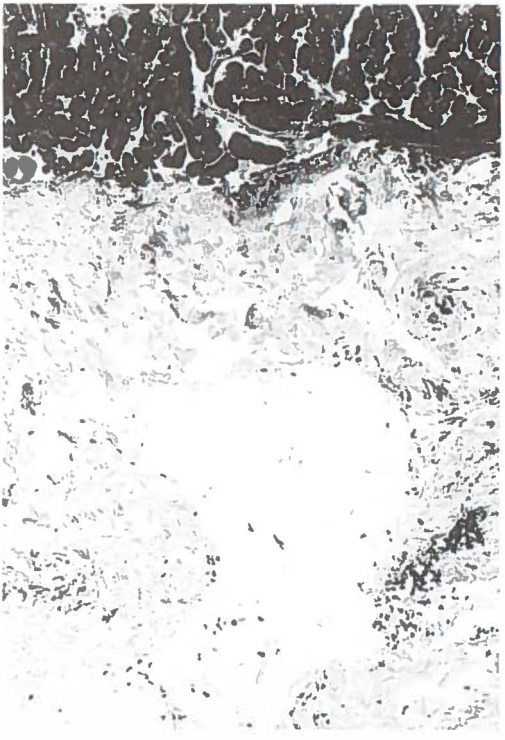

Figure 1. B. Photomicrograph of a biopsy specimen from the same patient a few years later, showing myocardium in the top and under it extensive fibrosis, with marked lipomatosis in the middle (original magnification x140).

Discussion

In the present study all patients were classified as sudden death survivors 'without apparent heart disease' according to the generally accepted definition[2]. However, right ventricular endomyocardial biopsy revealed right ventricular dysplasia in six of nine patients.

There is a striking lack of pathoanatomic data in *survivors* of idiopathic ventricular fibrillation. Most pathoanatomic studies evaluated heterogenous populations by including a variety of arrhythmias, among which ventricular fibrillation. From all the biopsy studies reported in the literature we could identify 22 cardiac arrest survivors without a (major) cardiac abnormality[3-10] (Table III). Abnormalities were found in a high percentage of patients (64%). Six of the 22 patients (27%) had an inflammatory heart disease. The other patients showed normal histology (eight patients, 36%) or increased fibrosis (seven patients, 32%), which was accompanied by pathologic lipomatosis in only three patients (14%). In the present study, we often found significant fibrolipomatosis (66%), leading to the diagnosis of arrhythmogenic right ventricular dysplasia. This high incidence of right ventricular dysplasia may relate to the more extensive procedure used, which obviously may increase the likelihood to find clinically significant microscopic abnormalities. It may be objected that the high incidence may have been the result of less strict pathoanatomic criteria, compared to those used by other investigators[3]. In addition, lipomatosis may be considered a normal observation in endomyocardial right ventricular biopsies. However, in accordance with the report by Mehta et al.[11], we considered the presence of adipose tissue only significant when it was accompanied by an increase in fibrous tissue.

Identification of a specific cause of idiopathic ventricular fibrillation has consequences for diagnosis and prognosis. Patients with a reversible cause, such as inflammatory heart disease, may especially have a favorable prognosis[6]. On the other hand, the prognosis may be rather variable in patients with right ventricular dysplasia or other cardiomyopathies. This explains the differences in prognosis of survivors of sudden death who have no cardiac disease in studies that did not use endomyocardial biopsies.

The clinical value and feasibility of extensive right ventricular endomyocardial biopsy procedures in idiopathic ventricular fibrillation remain to be established in a larger cohort of patients. An extensive biopsy procedure could implicate a higher complication risk than a standard procedure, especially in case of diseased right ventricles. During the biopsy procedures, care was taken to prevent deep transmural biopsies. The absence of complications in the present report may relate to the fact that biopsies were taken from patients in the early stages of the disease whose ventricular tissue was still relatively well preserved.

Table III. Overview of right ventricular endomyocardial biopsy studies considering only sudden death survivors without (major) structural cardiac disease.

First author (reference)	Age/sex (yrs)	Patho-anatomical abnormalities	Remarks
Strain[3]	56/F	small vessel disease	MVP (Echo)
	50/M	myopathy	
	9/M	myocarditis	
Hosenpud[4]	28/M	small vessel vasculitis	
	35/M	granulomatous myocarditis	
	64/M	chronic lymphocytic myocarditis	
	19/F	fibrosis and hypertrophy	
Iesaka[5]	54/M	fibrolipomatosis	ECG:T wave inversion V1-V4.
Vignola[6]	-	myocarditis	
	-	myocarditis	
	-	fibrosis and hypertrophy	
	-	normal	
Sugrue[7]	21/F	normal	
Topaz[8]	28/M	normal	Forme fruste LQTS ?
	25/M	normal	hypertension
	30/M	normal	
	33/M	normal	
Martini[9]	35/M	fibrosis	RV wall motion abnormalities, MVP, TVP.
	14/F	fibrolipomatosis	RV and LV wall motion abnormalities, MVP, TVP.
	24/M	fibrolipomatosis	RV wall motion abnormalities.
	18/M	normal	
Buja[10]	19/M	normal	

ECG: electrocardiogram; *F:* female; *LQTS:* long QT syndrome; *M:* male; *MVP:* mitral valve prolaps; *TVP:* tricuspid valve prolaps; *RV:* right ventricle; *LV:* left ventricle.

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Appendix 4

Favorable outcome in idiopathic ventricular fibrillation with treatment aiming at prevention of high sympathetic tone and suppression of inducible arrhythmias

Harry J.G.M. Crijns, Ans C.P. Wiesfeld, Jan L. Posma, Kong I. Lie

Abstract

Objective: In the absence of an obvious cause for cardiac arrest, idiopathic ventricular fibrillation patients are difficult to manage. A subset of patients has inducible arrhythmias. In others sympatho-excitation plays a role in the onset of the cardiac arrest. This study evaluates a prospective stepped care approach in the management of idiopathic ventricular fibrillation, with therapy first directed at induced arrhythmias and secondly at adrenergic trigger events.

Setting: University Hospital.

Patients: Ten consecutive patients successfully resuscitated from idiopathic ventricular fibrillation.

Interventions: Programmed electrical stimulation to determine inducibility, followed by serial drug treatment. Assessment of pre-arrest physical activity and mental stress status by interview, followed by beta blockade. Cardioverter-defibrillator implantation in noninducible patients not exhibiting significant arrest-related sympatho-excitation.

Main Outcome Measure: Recurrent cardiac arrest or ventricular tachycardia.

Results: Five patients were managed with serial drug treatment and 4 with beta blockade. In 1 patient a defibrillator was implanted. During a median follow-up of 2.8 years (range 6 to 112 months) no patient died or experienced defibrillator shocks. One patient had a recurrence of a well tolerated ventricular tachycardia on disopyramide.

Conclusion: Idiopathic ventricular fibrillation may relate to enhanced sympathetic activation. With the present approach most idiopathic ventricular fibrillation patients can be treated effectively and safely with serial antiarrhythmic drug testing or beta blockade. It may help to avoid potentially hazardous antiarrhythmic drugs or obviate the need for implantation of cardioverter-defibrillators.

Introduction

In idiopathic ventricular fibrillation controversy exists about the risks for arrhythmia recurrence[1-5]. One cause for conflicting data may be differences in therapy between studies. It has been suggested that if stress or exercise triggered the event, this might be a useful target of treatment and counseling of the patient[6,7]. Similarly, Viskin and Belhassen reported that if a monomorphic tachycardia (induced at programmed electrical stimulation) can be suppressed by class I agents, prognosis may be favorable[3,8]. Other investigators have advocated implantation of an automatic defibrillator, irrespective of presumed trigger events or inducible ventricular arrhythmias[4,5]. Up till now, these different strategies have not been studied

sequentially. In the present study we evaluated a stepped care approach in the management of idiopathic ventricular fibrillation, combining these treatment strategies. As a first step, therapy aimed at suppression of induced arrhythmias and secondly at prevention of adrenergic trigger events or both. The automatic implantable cardioverter-defibrillator was used in the third stage in patients not manageable within the previous 2 stages.

Methods

Patients. Between January 1985 and May 1993 ten consecutive patients with idiopathic ventricular fibrillation were evaluated at our department after being resuscitated. Idiopathic ventricular fibrillation was defined as previously reported[2,3,5,9,10], i.e. ventricular fibrillation in the absence of demonstrable cardiac abnormalities. In the present study this included no family history of unexpected sudden death and no abnormalities on physical examination, 12-lead electrocardiogram, ambulatory monitoring and exercise testing. In addition, echocardiography with Doppler measurements and coronary angiography, including ergonovine provocation and right and left ventriculography were normal. Spasm provocation with ergonovine maleate was performed as described by Heupler et al.[11]. The baseline characteristics of the first eight patients and patient 10 (Table 1) in the present study have been described previously[12].

Premonitory symptoms and pre-arrest physical and mental stress status. After resuscitation all patient had regained normal consciousness and had adequate cognitive functions. After stabilization of their clinical condition patients were carefully questioned for premonitory symptoms preceding the event. Symptoms asked for were chest pain, exertional dyspnea, palpitations, presyncope and syncope. Also, the patient's activities immediately preceding the cardiac arrest were noted. The physical activity status was semiquantitatively scored as resting, moderately active or heavily exercising. If the patient was unable to recall the immediately preceding events, bystanders were questioned concerning the circumstances of arrest. Finally, to assess mental stress preceding the event a separate interview was held, focusing on remarkable psychological experiences.

QT dispersion on the 12-lead electrocardiogram. To estimate dispersion of refractoriness the QT intervals of all 12 leads of the standard electrocardiogram were measured by an independent observer, unaware of the patients diagnosis (JP). QT dispersion was measured as previously reported[13]. QT was measured in all 12 leads separately and dispersion was expressed as the difference between the shortest and the longest QT duration. Rate correction of the QT interval (QTc) was done using Bazett's formula[14]. The reference values for QT and QTc dispersion at our institution are 32 ± 12 ms (range 10-50 ms) and 36 ± 13 ms (range 12-60 ms),

respectively. These were determined in 31 control patients (22 men), referred for minor surgical procedures. The mean age of the control group was 47±15 years (range 19-70 years). On the basis of these data and those found previously[15-17], we defined QT dispersion >50 ms as abnormal.

Programmed electrical stimulation. Programmed electrical stimulation was conducted in the absence of antiarrhythmic medication. During the study, arterial blood pressure was recorded from the right femoral artery. If applicable, programmed stimulation was repeated during antiarrhythmic drug treatment after at least 5 half-lifes of the drug. Stimulation in the right atrium was done with one or 2 extrastimuli during sinus rhythm and basic drive cycle lengths 600, 500 and 430 ms. Ventricular stimulation from the right ventricular apex was performed using up to 3 extrastimuli at sinus rhythm and 3 basic drive cycle lengths: 600, 500 and 430 ms. If by then no arrhythmias were induced, a similar stimulation protocol was continued from the right ventricular outflow tract. Subsequently, isoproterenol was given to noninducible patients, aiming at a heart rate increase of 25% or more. Programmed stimulation was repeated during isoproterenol administration. The study was terminated if refractoriness was reached or a sustained ventricular tachyarrhythmia was induced. Sustained ventricular tachycardia was defined as repetitive ventricular beats with a frequency above 100 beats per minute, either longer than 30 seconds duration or requiring an intervention before that time. Patients with repetitive ventricular responses of less than 6 beats were considered noninducible. A complete response to drug treatment was defined as noninducibility.

Treatment. The following clinical decision algorithm containing 3 separate steps was used (Figure 1). First, serial antiarrhythmic drug testing was performed if an arrhythmia related to the event was induced at programmed stimulation. Initially class I drugs (flecainide, disopyramide) were tested first, followed by class III agents (sotalol and amiodarone). More recently, sotalol was used as first line agent. Secondly, if the patient was not inducible but exercise or emotional stress was the eliciting clinical factor, beta blocker therapy was initiated. The dose was increased guided by maximal heart rate at exercise testing (peak heart rate < 130 bpm). In addition, the patient was instructed to avoid strenuous exercise. As a third step, i.e. in the absence of a trigger or a parameter for guiding antiarrhythmic drug therapy, a cardioverter-defibrillator was implanted. Also if arrhythmias could not be suppressed at programmed electrical stimulation, the protocol required the implantation of a defibrillator and cessation of antiarrhythmic drugs.

Follow-up. All patients were followed with regular intervals in the outpatient department by one cardiologist (HC). The length of follow-up was assessed from the cardiac arrest. Among others, patients were checked for therapy compliance and their daily activities.

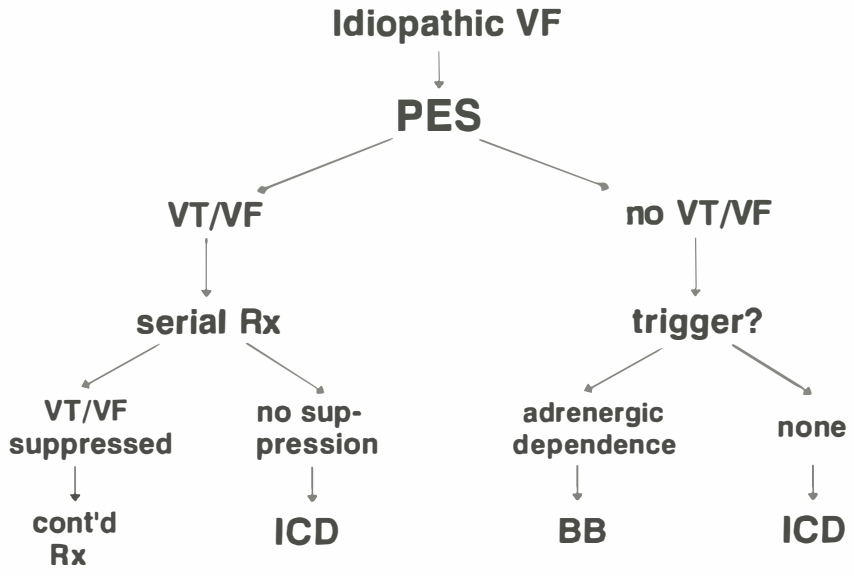

Figure 1. Decision algorithm for management of idiopathic ventricular fibrillation (VF). During programmed electrical stimulation (PES) 3 patients were inducible to ventricular tachycardia (VT) and 2 had VF. These 5 patients were successfully managed by serial drug testing (serial Rx) and continued on antiarrhythmic drug treatment (cont'd Rx). In 4 out of 5 noninducible patients the event was considered adrenergic-dependent and these patients received beta blockade (BB). Only one patient did not have an inducible arrhythmia or a clear trigger and was given an implantable cardioverter-defibrillator (ICD).

Table 1. Baseline characteristics and outcome of the 10 study patients. Patients are listed according to physical activity and mental stress status before the arrest.

Pt/Age/Sex	Premonitory symptoms	Physical activity/ Mental stress at event	PES	Treatment	FU (mth)
1. 24/M	X-related presyncope	vigorous exercise	sust VT at BCL 500 ms + 3 ES	serial R_X: flec → diso	59
2. 26/M	X-related syncope	vigorous exercise	sust VT at BCL 430 ms + 2 ES	serial R_X:flec →sotalol→ ß-blocker →ß-blocker + amio	47
3. 47/F	X-related chest pain	moderate exercise	VF at BCL 600 ms + 2 ES	serial R_X: flec	112
4. 21/M	X-related (pre)syncope	moderate exercise	noninducible AVNT	ß-blocker	96
5. 36/M	stress-related palpitations	extreme anxiety*	noninducible AF/AFL	ß-blocker	25
6. 56/F	none	moderate exercise	noninducible	ß-blocker	36
7. 39/M	none	moderate exercise	noninducible	ß-blocker	24
8. 48/M	none	rest	VF at BCL 430 ms + 2 ES	serial R_X:flec →sotalol	18
9. 38/M	none	rest	sust VT at BCL 600 ms + 2 ES	serial R_X:sotalol	6
10. 37/M	none	rest	noninducible	defibrillator	44

* at the time of the episode of ventricular fibrillation this patient had not slept for 72 hours: see text for details.
Amio: amiodarone; *BCL:* basic drive cycle length; *diso:* disopyramide; *ES:* number of extrastimuli used after the BCL when inducing the arrhythmia; *F:* Female; *flec:* flecainide; *FU:* follow-up; *PES:* programmed electrical stimulation; *Pt:* patient; *M:* Male; *serial* R_X: serial antiarrhythmic drug testing using programmed electrical stimulation; *sust VT:* sustained ventricular tachycardia; *VF:* ventricular fibrillation; *X-related:* exercise related.

Results

Table 1 summarizes the premonitory symptoms, arrest-related activity status and results of programmed stimulation. Furthermore, it shows the treatment instituted and duration of follow-up. In the present study there were 8 males and 2 females and the mean age was 37±11 years (range 21 to 56 years). One of the patients (nr. 8) had electrocardiographic abnormalities at admission, with an incomplete right bundle branch block (QRS duration 120 ms) and ST segment elevation in the right precordial leads[18]. In one other patient (nr. 5) incomplete right bundle branch block without ST segment elevation was seen and two patients had persistent negative T waves in the right precordial leads (numbers 1 and 9). Two patients (numbers 4 and 8) had positive late potentials, defined as all 3 parameters (filtered QRS duration, D40 and V40) abnormal[19]. One and two abnormal parameters on the signal-averaged electrocardiogram were seen in patients 9 and 5, respectively. The mean filtered QRS was 100±13 ms, D40 34±10 ms and V40 32±20 μV. The mean left ventricular ejection fraction was 0.63±0.03.

Premonitory symptoms. From all patients a detailed description of premonitory symptoms could be obtained (Table 1). In 5 patients the attack of ventricular fibrillation was completely unexpected, whereas 3 had suffered a collapse or near collapse several times previously during exertion. One patient had chest pain on a few occasions during moderate exercise. Patient 5 had had emotion-related palpitations previously (see below).

Activity status immediately before the cardiac arrest. In all patients the activity status at the time of the event could be evaluated. In the patients 1 and 2 the arrest occurred during vigorous exercise. Both were competetive athletes. The first of these 2 patients had a presyncope during playing soccer immediately before the cardiac arrest. Both the presyncope and the arrest occurred in connection with acute strenuous exercise (sudden onset running). The other patient, a semi-professional boxer, nominated champion of the 3 northern provinces of the Netherlands, experienced recurrent syncope at his training sessions, i.e. during prolonged running. His collapses occurred only with near exhaustion. The same occurred at the time of the arrest leading to inclusion in the present study. Patient 3 performed fitness training on a regular basis. Apart from the above mentioned chest pain during exercise, she never had had other premonitory symptoms. Before her ventricular fibrillation she was exercising moderately, but had not felt chest pain. Patient 4 was cycling rapidly in cold wheather, trying to catch a train. In the months before the arrest, he had experienced several bouts of dizziness under similar circumstances. Patient 6, a regular swimmer, collapsed after swimming. She had been doing well until the arrest and did not have chest discomfort or exaggerated dyspnea before the arrest. Case nr. 7, a 39 year old librarian, had been carrying heavy boxes upstairs before the arrest. For this physically rather inactive man it was an unusual activity.

In the last 3 patients no premonitory symptoms were found and the event occurred at rest.

Mental stress status. Only 1 patient (nr. 5) appeared to have excessive mental stress preceding the cardiac arrest. This patient had palpitations in connection with emotional stress during several weeks before the arrest. The stress was due to problems at work and reached a climax in an acute anxiety state. Deliberately, the patient did not sleep for more than 72 hours, which was followed by the cardiac arrest.

Exercise testing. Of all patients with adrenergic drive dependent ventricular fibrillation only patient 2 had the cardiac arrest reproduced during exercise testing at baseline. He developed an extremely rapid ventricular tachycardia causing instantaneous unconsciousness. The tachycardia had a left bundle branch block QRS morphology with a vertical axis and its cycle length was 205 ms. It started at a sinus rate of 163 beats per minute, at an exercise level of 240 Watts. Degeneration into ventricular fibrillation was not recorded since the arrhythmia was rapidly cardioverted. In all other patients baseline exercise testing was unremarkable. Surprisingly, 1 patient (nr. 8) in whom the arrest was not considered to be exercise-related, developed nonsustained polymorphic ventricular tachycardias during treadmill exercise while treated with flecainide 200 mg daily (see below).

QT dispersion. The mean QT and QTc dispersion were 56 ± 34 ms (range 20-140 ms) and 67 ± 35 ms (range 31-149 ms), respectively. Five patients had QTc dispersion larger than 50 ms (patients 1, 3, 4, 6 and 7).

Programmed stimulation. Three patients were inducible to ventricular tachycardia and 2 had ventricular fibrillation. The ventricular tachycardias showed a cycle length of 215, 200 and 210 ms (patients 1, 2 and 9, respectively) and caused cardiovascular collapse instantaneously. Due to prompt cardioversion within 15 to 20 seconds, degeneration to ventricular fibrillation was not seen. In all these cases the QRS complex during tachycardia showed a left bundle branch block morphology with either a vertical axis, an intermediate axis or a left axis (patients 1, 2 and 9, respectively). In the noninducible patients programmed stimulation was repeated during the administration of isoproterenol. However, no further arrhythmias were found.

The right ventricular effective refractory periods after applying one extrastimulus at basic drive cycle lengths 600, 500 and 430 ms were in the normal range and amounted 228 ± 16, 220 ± 15 and 201 ± 14 ms, respectively. None of the patients had latent preexcitation or circus movement tachycardia using a concealed bypass tract. Atrioventricular nodal reentrant tachycardia without hemodynamic consequences was induced in one patient and sustained atrial fibrillation and flutter with 2:1 atrioventricular block (RR interval 370 ms) in another patient (Table 1).

Treatment. Four of the 5 patients with inducible arrhythmias underwent serial treatment using programmed stimulation (Table 1). Patient 1 was given 300

mg flecainide daily. However, during telemetric monitoring he showed incessant monomorphic ventricular tachycardias with the same morphology but at a slower rate as found during programmed stimulation at baseline. The flecainide plasma concentration during tachycardias was 845 ng/L (nontoxic). Flecainide was changed to disopyramide 500 mg daily which was found to successfully prevent tachycardia reinduction during subsequent programmed stimulation. Patient 2 failed flecainide, sotalol and metoprolol, but became noninducible on amiodarone. After initiation of flecainide, patient 8 developed nonsustained ventricular tachycardias during exercise testing. Flecainide was considered ineffective and was changed to sotalol 320 mg daily. No further arrhythmias occurred neither during exercise testing nor at programmed stimulation. In patient 3, flecainide was given guided by repeated Holter monitoring.

In 4 out of the 5 noninducible patients there was a clear adrenergic-dependence of the cardiac arrest and these were treated with beta blockade. The other noninducible patient (nr. 10) did not have an evident trigger for the event and received an implantable cardioverter-defibrillator. All patients with an exercise or mental stress related arrest were advised to avoid vigorous exercise or stressful situations. Counseling of patient 5 included to maintain a normal day-night pattern.

Follow-up. None of the patients died or experienced a recurrence of fatal ventricular tachycardia or fibrillation during a median follow-up of 2.8 years (range 6 to 112 months). There were no defibrillator discharges. Patient 1 had a recurrence of sustained monomorphic ventricular tachycardia after he had lowered disopyramide dosage. The tachycardia was well tolerated due to the fact that it was relatively slow as a result of residual action of disopyramide. He remained free of arrhythmias after reinstitution of the original dose.

Discussion

Sudden cardiac death survivors without overt heart disease are difficult to manage, especially since in most cases the underlying arrhythmogenic mechanism is not well understood[3,9]. Outcome remains uncertain in individual patients[1-5] and therefore implantation of a defibrillator is often advocated[4,5]. The present study indicates however, that outcome may be excellent if trigger events and results of programmed electrical stimulation are considered in the management of these patients.

Viskin and Belhassen have stressed that suppression of tachycardia inducibility on class 1a drugs portends an excellent prognosis[3,8]. Other investigators have indicated the importance of mental stress in idiopathic ventricular fibrillation[6,7] and showed a favorable outcome on beta blockade[7]. This study is the first to combine suppression of inducible tachycardia and treatment with beta blocker targeted at pre-arrest sympatho-excitation in the management of idiopathic

ventricular fibrillation. In patients with inducible arrhythmias serial drug testing appeared successful and in those with adrenergic-dependent arrhythmias beta blockade prevented new cardiac arrests.

The importance of preventing sympatho-excitation seems obvious, at least in patients with a clear relation between vigorous exercise or extreme psychological disturbances and the fatal arrest. In their review of the literature on idiopathic fibrillation Viskin and Belhassen[3] noted that in 40 patients the circumstances immediately preceding the arrest were known. Physical and mental stress were present in 6 (15%) and 9 (22%) of 40 cases, respectively. In the study by Reich et al.[6], mental stress was present in 6 out of 9 patients (67%) representing a subgroup with idiopathic ventricular fibrillation in that study. We found a higher incidence of physical stress (50%) and a lower incidence of mental stress (10%) as a trigger, which may relate to different methodology in identifying the subtypes of clinical sympatho-excitation. In most of the studies reviewed by the Tel Aviv group trigger events were not considered primary targets for patient management. The present study lends further support for the notion that these items are important in management, with counseling concerning stress on one hand, and medical treatment consisting of beta blockade on the other.

In approximately 50% of patients surviving idiopathic ventricular fibrillation sustained arrhythmias can be induced with programmed electrical stimulation[3,5,9,20].This indicates that the approach adopted herein is feasible since many patients may be amenable to treatment guided by serial drug testing using programmed electrical stimulation. Recently sotalol appeared useful in the management of sustained arrhythmias[21,22]. It seems therefore justified to institute sotalol as a first line treatment in those patients showing inducible ventricular arrhythmias and we advocate assessment of efficacy with programmed stimulation.

In agreement with previous studies[5,9] we found that ventricular fibrillation in the apparently normal heart can be caused by a monomorphic ventricular arrhythmia with an extremely short cycle length. Obviously, very rapid ventricular tachycardias may deteriorate into ventricular fibrillation, especially in the setting of a too large dispersion of refractoriness, as reflected in the abnormally large QT dispersion found in 5 of our patients. As has been suggested previously[9], the presence of a monomorphic tachycardia supports the view that a reentrant pathway as a substrate for the arrhythmia is present. In this respect it is noteworthy that in 2 patients spontaneous or exercise-induced tachycardias were present only after the initiation of flecainide, which may have provided sufficient conduction slowing to set the stage for reentry. As such, flecainide or other 1c agents might appear useful as a test to uncover the presence of such reentrant substrates.

Idiopathic ventricular fibrillation has been associated with a recurrence risk between 25 and 37%, depending on the duration of follow-up[3-5]. Viskin and Belhassen[3], reviewing the world literature, found an 11% annual sudden death rate.

Other reports have indicated a more benign course[2,8,9]. The present study also suggests a favorable prognosis with none of the patients dying suddenly or having defibrillator shocks, and only one suffering a recurrence of a well tolerated ventricular tachycardia during disopyramide. The following may explain the favorable prognosis in our study group. First, there was a relatively frequent association between the event and physical or emotional stress, providing a target for treatment. All these patients were advised to avoid vigorous exercise or significant mental stress and almost all of them received beta blockade. Secondly, our patients were either noninducible at baseline or became noninducible on drug treatment. The prognostic value of noninducibility in sudden death survivors without apparent cardiac disease is unknown. However, many previous studies have indicated a favorable prognosis in patients who were noninducible, either with[8,23-26] or without antiarrhythmic treatment[27,28]. Thirdly, previous studies reported fewer patients with inducible monomorphic ventricular tachycardias[5,9,20]. Obviously, monomorphic tachycardias may be better amenable to serial drug treatment than polymorphic arrhythmias or ventricular fibrillation. Fourthly, previous studies using defibrillators may have overestimated the recurrence risk, since in a few instances defibrillator shocks may have been spurious or given for nonsustained arrhythmias. Finally, it must be noted that differences between studies concerning the recurrence risk also relate to the definition of idiopathic fibrillation used, i.e. the number and type of investigations performed to uncover an underlying cardiac diagnosis[12].

The tachyarrhythmia associated with the arrest was reproduced with bicycle exercise in only 1 patient. In our view this does not argue against adrenergic-dependence of the cardiac arrest in the other patients. It is well known that reproducibility of ventricular arrhythmias in patients with proven exercise-induced tachycardias is low[29]. In addition, despite absence of a clear sympatho-excitation, many patients show a circadian variation in onset of ventricular tachyarrhythmia, suggesting adrenergic-dependence[30]. Meredith et al. showed that ventricular tachycardia or fibrillation patients without clearly evident sympathetic stimulation, may have elevated norepinephrine plasma levels, potentially enhancing tachycardias[31]. This is further supported by the fact that beta blockade may effectively prevent sustained arrhythmias even in patients without overt sympatho-excitation at the onset of tachycardias[32].

In conclusion, this study lends further support to the notion that idiopathic ventricular fibrillation may relate to an enhanced sympathetic activation. Using the approach presented herein, most patients can be treated effectively and safely with beta blockade or serial drug testing. This approach may help to avoid potentially hazardous antiarrhythmic treatment. In addition, it may obviate the need for implantation of costly cardioverter-defibrillators.

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Appendix 5

Beta adrenergic blockade in the treatment of sustained ventricular tachycardia or ventricular fibrillation

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Abstract

The value of beta blockers as antiarrhythmic drugs in patients with sustained ventricular tachycardia or ventricular fibrillation has received only little attention. This review summarizes the current state of knowledge regarding the identification of patients with sustained ventricular tachycardia or fibrillation with the highest benefit of beta blockade. The antiarrhythmic mechanisms of beta adrenergic blockade and its efficacy as single or adjuvant therapy in patients with sustained ventricular tachycardia or fibrillation are reviewed. Current insights into the effects of beta blockade in patients suffering from ventricular tachycardia, in particular in the setting of heart failure, are discussed and future directions are considered.

Introduction

Postinfarct patients with sustained ventricular tachycardia or ventricular fibrillation (VT/VF) are at increased risk for sudden cardiac death. Antiarrhythmic strategies vary from medical treatment to implantation of an automatic cardioverter-defibrillator. The use of conventional antiarrhythmic drugs is however limited due to potential induction of proarrhythmia and heart failure. In this respect, beta blockers seem safe but their efficacy has not been tested in larger randomized studies of VT/VF patients. On the other hand, it is well known that beta blockers can suppress adrenergic-dependent arrhythmias and have proven efficacy in reducing the incidence of sudden death in the general postinfarct population[1].

Sudden death risk is highest in postinfarct patients with a depressed left ventricular function[2]. Especially in these patients beta blockers are most effective[3,4]. However, the depressed left ventricular function often is the very reason that there is some reluctance in prescribing these agents. Postinfarct sudden death survivors and those suffering from sustained ventricular tachycardia often have a depressed left ventricular function[5,6]. Considering the above, it may be hypothesized that especially in these VT/VF patients beta blockers can be very useful as an antiarrhythmic drug. In addition, these drugs do not provoke proarrhythmia like conventional antiarrhythmics. The recently reported Electrophysiologic Study Versus Electrocardiographic Monitoring shows that sotalol, combining beta blockade with class 3 activity, was more effective in suppressing sustained arrhythmias and preventing sudden death than class 1 agents[7]. Other recently published studies have shown that metoprolol or nadolol can effectively prevent recurrent sustained ventricular tachycardia or fibrillation[8,9], even in patients with significant left ventricular dysfunction[8]. The present report reviews (1) the antiarrhythmic mechanisms of beta adrenergic blockade, (2) the clinical characteristics of patients with the highest benefit from beta blockade, and (3) the effects of beta blockers as

adjuvant therapy in patients with sustained ventricular tachycardia or fibrillation.

(1) Antiarrhythmic mechanisms of beta adrenergic blockade

Beta adrenergic blockade prevents the adverse electrophysiologic effects of catecholamines. Catecholamines increase the spontaneous depolarization (phase 4) in the sinus node cells, induce a more negative diastolic transmembrane potential and increase the amplitude of the action potential. In the atrioventricular node conduction is enhanced and refractory period is shortened. In *normal* atrial and ventricular tissue there is little effect of catecholamines[10-13]. Conversely, in *diseased* myocardium the increase of catecholamines may exert a direct toxic effect. In addition, catecholamines provoke an increase in cyclic adenosine monophosphate, which results in increased cytosolic calcium. This may induce delayed afterdepolarizations, intercellular uncoupling and augmentation of intracellular resistance. In response to high catecholamine levels an increase of extracellular potassium concentration will lower the membrane potential: 'depressed fast response' [14,15]. These effects all may cause conduction slowing and hence promote reentry.

Beta adrenergic blockade antagonizes the effects of catecholamines. Therefore, beta blockers suppress spontaneous depolarization, decrease atrioventricular node conduction and prolong its refractory period. In addition, they limit the formation of cyclic adenosine monophosphate[16] and by reducing sinus tachycardia they can lessen cytosolic calcium overload precluding the above mentioned arrhythmogenic mechanisms. Furthermore, beta blockade preserves normal serum potassium levels and diminishes vulnerability to ventricular fibrillation[17].

The beneficial effects of beta adrenergic blockade are most marked during ischemia. In postinfarct patients with VT/VF, ischemia may play a facilitating role in the induction of the arrhythmia. It has been suggested that in the setting of an old infarct a subtle area of ischemia may be the final (conduction slowing) part to complete the partially present reentrant circuit[18]. By preventing ischemia beta blockade may help to prevent these arrhythmias.

(2) Clinical characteristics of patients who may benefit from beta adrenergic blockade (Table I)

A - VT/VF associated with a high sympathetic tone

Obviously, beta blockade can be effective in VT/VF provoked by a high sympathetic tone. This is the case in arrhythmias preceded by mental stress, which is evident in at least 20% of VT/VF patients[19-21].

Table I. Parameters for identifying patients with sustained ventricular tachycardia or ventricular fibrillation who may benefit from beta adrenergic blockade.

1.	Clinical parameters
	* sinus tachycardia
	* exercise or mental stress precedes sustained ventricular tachycardia or ventricular fibrillation
	* concomitant ischemia
	* congestive heart failure
2.	Increased catecholamine plasma level
3.	Characteristics of ventricular tachycardia
	* short cycle length
	* polymorphic
	* facilitated by isoproterenol

Also in exercise-induced VT/VF[22-26] and sustained arrhythmias provoked by isoproterenol infusion beta blockers are treatment of choice. Isoproterenol may be used during programmed stimulation. Olshansky et al.[27] followed 9 patients who were not inducible during standard programmed stimulation, but became inducible during isoproterenol infusion. Propranolol prevented arrhythmia recurrence in 8 patients and reduced the incidence in 1 patient during a mean follow-up of 39 months. Isoproterenol may also provoke spontaneous ventricular tachyarrhythmias[28]. These arrhythmias also respond to beta blockade[29].

B - VT/VF in the absence of evident high sympathetic tone

Most ventricular tachycardias are *not* preceded by a clinically evident high sympathetic tone. Nevertheless, Meredith et al.[30] showed that in VT/VF patients without clearly evident sympathetic stimulation, increased plasma levels of norepinephrine still may be present. In clinical practice plasma concentrations of catecholamines are not always available. As an alternative, circumstantial evidence for an enhanced sympathetic tone can be used, for example sinus tachycardia or polymorphic ventricular tachycardia with a relatively short cycle length[8,31] (Table I). Huikuri et al.[31] tested propranolol in 24 patients with coronary artery disease and sustained VT, who failed at least 1 membrane active antiarrhythmic drug. Propranolol dose aimed at at least a 15% reduction of basal heart rate. Seven patients (29%) became noninducible during programmed stimulation. These patients

had a faster basal heart rate, a greater heart rate reduction on propranolol and a shorter cycle length of the induced VT at baseline. Duff et al.[32] performed programmed stimulation before and after infusion of propranolol in 28 patients with sustained VT. The majority of the patients had coronary artery disease (75%). All patients had failed several antiarrhythmic drugs. In 10 patients (36%) propranolol was effective. The only parameter predicting success was the presence of sinus tachycardia at baseline reflecting enhanced sympathetic drive. Leclercq et al.[8] evaluated the role of programmed stimulation using the parallel approach in 36 VT patients treated with nadolol (40-80 mg daily dose). The mean left ventricular ejection fraction was 40%. Sixteen patients (44%) were noninducible after nadolol. Arrhythmia recurrence rate was 13% in the noninducible patients versus 60% in those who remained inducible after nadolol. Overall, 14 of the total 36 patients (39%) had an arrhythmia recurrence. Arrhythmia recurrence rate was lower in the patients with a ventricular tachycardia cycle length below 400 ms, again indicating the importance of a shorter cycle length as a predictor of efficacy of beta blockade. Steinbeck et al.[9] studied prospectively the antiarrhythmic efficacy of metoprolol in VT/VF patients. Inducible patients were randomized to metoprolol given empirically as stand alone antiarrhythmic therapy (54 patients), or to serial drug testing (61 patients) using metoprolol combined with a class 1 antiarrhythmic drug as the first step. Sotalol and amiodarone were used later. During a mean follow-up of 23 months the arrhythmia recurrence rate was 52% in the patients treated empirically with metoprolol versus 60% in those undergoing serial drug testing.

These studies suggest that in VT/VF patients without a clearly evident high sympathetic tone, stand alone beta adrenergic blockade may still be effective in 29%[31] to 39%[32] of cases when tested with programmed stimulation and 48%[9] to 61%[8] when given empirically. Potential responders seem characterized by sinus tachycardia and fast polymorphic ventricular tachycardia at baseline. Finally, if patients remain inducible during conventional antiarrhythmic drug therapy, treatment with metoprolol alone is a reasonable alternative. Nevertheless, nonmedical treatment modalities should be considered because of the high recurrence rate.

C - Beta adrenergic blockade in patients with congestive heart failure

Congestive heart failure is associated with neurohumoral activation[33,34]. The elevation of catecholamine plasma levels is an important arrhythmogenic factor[35]. The Beta Blocker Heart Attack Trial showed that propranolol decreased the incidence of sudden death most in the postinfarct patients with congestive heart failure, i.e. 47% versus 13% in those with versus those without heart failure, respectively[3]. Recently, the benefit and safety of beta adrenergic blockade in postinfarct patients with a history of congestive heart failure was confirmed by data from the Cardiac Arrhythmia Suppression Trial[4]. These observations support the notion that beta adrenergic blockade might be especially effective in sustained ventricular tachycardia

associated with congestive heart failure. This is confirmed by the findings of Brodsky et al.[36] who prescribed beta blocker treatment in 32 VT/VF patients (81% with coronary artery disease) with left ventricular dysfunction (mean left ventricular ejection fraction 29%). The arrhythmia recurrence rate was 17% in the patients who received beta blockade versus 40% in the other patients. A drawback of this retrospective study was that beta blockade was frequently combined with conventional antiarrhythmic drugs. Furthermore, evaluation of drug efficacy was not standardized. In a study of Leclercq and colleagues[37] beta blockade was superior to class 1 antiarrhythmic drugs in 156 coronary artery disease patients with sustained ventricular tachycardia and left ventricular ejection fraction below 30%. Unfortunately, these data are rather difficult to interpret. In the absence of a placebo group (absent for obvious reasons) it cannot be excluded that the class 1 agents were deleterious rather than beta blockade effective[38]. Nevertheless, these studies strongly support the use of beta blockade in the treatment of sustained VT or VF in the setting of left ventricular dysfunction.

Patients with an impaired left ventricular function often fail conventional antiarrhythmic drug treatment[39]. In those cases implantation of a cardioverter-defibrillator is warranted. However, concomitant antiarrhythmic drug treatment is sometimes necessary because of frequent discharges. In these patients beta adrenergic blockade should be considered[40,41]. Levine and colleagues[42] followed 197 VT/VF patients after implantation of a cardioverter-defibrillator with or without cardiac surgery. In the majority of the patients the best antiarrhythmic drug selected by serial testing was continued. The investigators analyzed the time to the first discharge of the cardioverter-defibrillator and survival after the shock. Appropriate discharges of the cardioverter-defibrillator occurred in 105 patients. Severe left ventricular dysfunction (left ventricular ejection fraction $<25\%$) was associated with an earlier discharge of the cardioverter-defibrillator and shortened survival after the shock. Beta blocker treatment and coronary bypass surgery were associated with a later discharge of the cardioverter-defibrillator, however only surgery was associated with more prolonged survival.

Considering the above, beta blockade may enhance survival and lower the attack rate in VT/VF in the setting of left ventricular dysfunction. Obviously, this holds only in patients tolerating beta blockade. Progression to severe congestive heart failure during beta blocker treatment was reported in 11 to 36% of VT/VF patients[8,36,40]. However, the majority of the investigators[9,31,32,37] does not report progression of congestive heart failure. This stresses the fact that beta blocker therapy can be given safely in appropriately selected patients. Nevertheless, beta blocker therapy should be titrated, starting in-hospital with a low dose under close monitoring for heart failure symptoms.

(3) Beta adrenergic blockade as adjuvant therapy in sustained ventricular tachycardia and fibrillation (Table II)

The advantage of combining antiarrhythmic drugs with different electrophysiologic mechanisms is enhanced antiarrhythmic efficacy and reduced toxicity. The latter relates to lower dosing schemes. In this respect, beta blockade is potentially useful as adjuvant therapy in VT/VF patients, especially when the effects of conventional agents are reversed by sympathetic stimulation. Unfortunately, randomized studies on the long-term efficacy of adjuvant beta blockade are not available.

The electrophysiologic effects of class 1 antiarrhythmic drugs can be reduced or reversed by increased sympathetic adrenergic tone. Jazayeri et al.[43] infused isoproterenol in 17 VT/VF patients who were noninducible on class 1 antiarrhythmic drugs. Seven patients remained noninducible and had no arrhythmia recurrence during follow-up. By contrast, 3 of the 10 patients who became inducible had an arrhythmia recurrence. Morady et al.[44] investigated the effect of isoproterenol infusion in 21 VT patients with coronary artery disease. During quinidine treatment 12 patients were noninducible and 9 patients were inducible to nonsustained VT. After isoproterenol 2 of the former and 8 of the latter group became inducible to sustained VT. This clearly illustrates the permissive role of catecholamines in the induction of significant ventricular arrhythmias in patients who seem protected by conventional antiarrhythmics.

The beneficial effect of adjuvant beta blockade in patients with VT/VF is supported by a small scale study of Friehling and colleagues[45]. They administered propranolol intravenously to 23 postinfarct patients who were inducible despite treatment with a class 1 antiarrhythmic drug. The ventricular effective refractory period and the cycle length of the VT, which were prolonged by the class 1 drug, was further increased by propranolol. Seven patients (30%) became noninducible and in 10 patients (43%) the VT cycle length increased ≥ 100 ms. Brodsky and colleagues[46] treated 19 VT/VF patients with adjuvant beta blockade because of persistent inducibility during class 1 antiarrhythmic drug treatment: 8 patients (42%) became noninducible and 8 patients (42%) were more difficult to induce. Sixty-two per cent of the patients with a ventricular tachycardia cycle length ≤ 300 ms at baseline became noninducible during adjuvant beta blocker therapy versus none of the patients with a ventricular tachycardia cycle length > 300 ms.

Besides enhancement of antiarrhythmic efficacy, beta blockade may also be effective in the prevention of a proarrhythmic response during class 1c antiarrhythmic drug treatment. Myerburg et al.[47] described 4 VT/VF patients who developed an increase of premature ventricular ectopic beats or new ventricular tachycardia during treatment with flecainide or encainide. Propranolol effectively suppressed these proarrhythmic responses probably by preventing use-dependent conduction slowing[48,49], thereby precluding ventricular reentry.

Table II. Results of programmed stimulation in sustained ventricular tachycardia or fibrillation patients during adjuvant beta blocker therapy after *failure* of conventional antiarrhythmic drugs.

First author	n	CAD(%)	Failure to AAD	Result of PES after adjuvant BB	
				Complete responders (%)	Overall responders (%) *
Friehling[45]	23	100%	class 1	30%	74%
Brodsky[46]	19	95%	class 1	42%	84%
Tonet[52]	15	67%	amiodarone	27%	87%
Leclercq[8]	24	-	amiodarone	17%	-
Dorian[53] #	50	88%	class 1	42%	76%

AAD: antiarrhythmic drug; *BB:* beta blocker therapy; *CAD(%):* percentage of patient population with coronary artery disease; *n:* number of patients; *PES:* programmed electrical stimulation. * Including both complete and partial responders during programmed electrical stimulation. # This study combined class 1 antiarrhythmic drugs with sotalol.

Recently, in vitro investigations[50] supported the findings of Myerburg and colleagues. Propranolol reduced flecainide-induced dispersion of refractoriness.

The class 3 antiarrhythmic drugs amiodarone and sotalol have beta adrenergic blocking properties. Hence, the reversal of electrophysiologic effects during increased sympathetic tone may be less pronounced with these agents. Calkins et al.[51] investigated the effect of epinephrine in 29 VT/VF patients treated with quinidine or amiodarone. Epinephrine completely reversed the electrophysiologic effects of quinidine but only partially those of amiodarone. Five patients were noninducible during amiodarone and remained noninducible during epinephrine infusion. Unfortunately, the long-term effect of concomitant beta adrenergic blockade was not investigated. Tonet et al.[52] evaluated the effect of low dose beta blockade in 20 patients with refractory VT during amiodarone treatment (65% coronary artery disease, 10 patients with left ventricular ejection fraction $<30\%$). In 15 patients programmed stimulation was performed during adjuvant beta blocker treatment: 4 patients became noninducible (27%), 9 patients had hemodynamically stable ventricular tachycardia (60%), and in 2 patients the result was unchanged (13%). In the other 5 patients antiarrhythmic drug treatment was successful according to noninvasive evaluation. During a mean follow-up period of 14 months only 1 patient had recurrence of VT. Leclerq et al.[8] treated 24 VT/VF patients with amiodarone for at least 6 months and added nadolol orally because of persistent inducibility. The mean left ventricular ejection fraction was 30% in this subset of patients from that study. Only 4 patients (17%) became noninducible, which probably relates to the severely depressed left ventricular function. None of these patients had an arrhythmia recurrence versus 35% of the patients who remained inducible. Recently, Dorian et al.[53] reported on low dose sotalol combined with quinidine or procainamide in 50 patients with sustained ventricular tachycardia (88% with coronary artery disease). All patients had at least one antiarrhythmic drug failure previously. Twenty-one patients (42%) became noninducible and in 17 patients (34%) a partial response was reached. Forty-two patients were discharged on the drug combination and the actuarial arrhythmia recurrence rate at 3 years was 11%.

The above mentioned studies suggest that in VT/VF patients beta adrenergic blockade can be combined safely with class 1 and 3 antiarrhythmic drugs and that the combination may be more effective than the conventional drug alone (Table II). Although it may be expected that beta adrenergic blockade is useful when antiarrhythmic efficacy is reversed by isoproterenol, there are no randomized studies to confirm this hypothesis.

Conclusions and future directions

Beta blockers reduce sudden death in postinfarct patients especially in those with impaired left ventricular function. Although this seems in part due to an antiarrhythmic action, efficacy of beta blockade in suppressing sustained VT/VF has not been studied extensively. Obviously, beta blockade is the treatment of choice in patients with VT/VF preceded by high sympathetic tone. On the other hand, studies performed in patients without clear enhancement of sympathetic tone indicate that beta blockade can be as effective as serial drug treatment in preventing VT/VF recurrences. This should be viewed against the background that catecholamines play a permissive role in the induction of sustained arrhythmias. Of note, such an adrenergic mechanism may become increasingly important in patients with a depressed left ventricular function since the latter often is associated with neurohumoral activation. Therefore, beta blockers are an important alternative to conventional antiarrhythmics in the suppression of VT/VF in the setting of congestive heart failure. This holds even more since these agents lack any proarrhythmic effect. Beta blockers can also be used to enhance efficacy of class 1 and 3 antiarrhythmic drugs or as an adjuvants to cardioverter-defibrillator therapy to prevent too frequent discharges.

Future studies should evaluate in a randomized fashion the effects of beta blockade in patients with sustained VT/VF. These studies might focus on the effects in patients with heart failure in particular on improvement of neurohumoral status and left ventricular function in relation to the incidence of recurrent VT/VF. In this respect, third generation beta blockers deserve special attention since these agents combine favorable neurohumoral and peripheral vascular effects with specific antiarrhythmic actions related to beta blockade. Finally, more data are needed for adequate identification of VT/VF patients who may benefit from stand alone beta blocker treatment. Obviously, since recurrence rates are high, most of these studies can be done only in patients with an implantable cardioverter-defibrillator.

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Appendix 6

Triggered activity as arrhythmogenic mechanism after myocardial infarction

Clinical and electrophysiologic study of one case

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Abstract

In a woman with an old infarction and sustained ventricular tachycardia, tachycardias were only inducible after short-long RR sequences. After isoprenaline tachycardias became incessant, and all were preceded by short-long RR sequences. This strongly suggests that triggered activity plays a role in initiation of ventricular tachycardias in postinfarct patients.

Introduction

After myocardial infarction reentry is the main mechanism of sustained ventricular tachycardia. In a subset of patients triggered activity may play an arrhythmogenic role. Electrophysiological criteria to differentiate between both mechanisms have not been completely elucidated[1]. We describe a postinfarct patient with cycle length dependent TU wave changes associated with monomorphic ventricular tachycardia, probably induced by triggered activity.

Case report

A 67-year-old woman with an inferolateral myocardial infarction 3 months previously, was admitted to our hospital with recent onset exertional dyspnea. At physical examination no signs of congestive heart failure were found. The electrocardiogram showed ventricular tachycardia with right bundle branch block and left axis morphology (Figure 1). Intravenous procainamide and correction of the potassium plasmalevel (3.0 mmol/L, normal value 3.6-4.8 mmol/L) restored sinus rhythm. Left ventricular ejection fraction was depressed (33 %) and coronary angiography did not show significant stenoses except in the infarct related vessels, which were occluded.

During exercise testing monomorphic nonsustained and sustained ventricular tachycardias were seen, initiated by short-long-short RR sequences accompanied by changes of the TU wave. Atrial premature beats set the stage for the short-long-short sequences, which consisted invariably of an atrial premature beat followed by a sinus beat with normal intraventricular conduction (Figure 2). All ventricular tachycardias were identical to the clinical tachycardia.

After giving informed consent the patient underwent an electrophysiological study without antiarrhythmic drug treatment. First, we determined ventricular refractoriness (range 210 to 290 ms) and inducibility at the right ventricular apex using a standard protocol[2]. Thereafter, ventricular burst pacing and interval pacing[3] were performed. In addition, we evaluated inducibility of ventricular arrhythmias

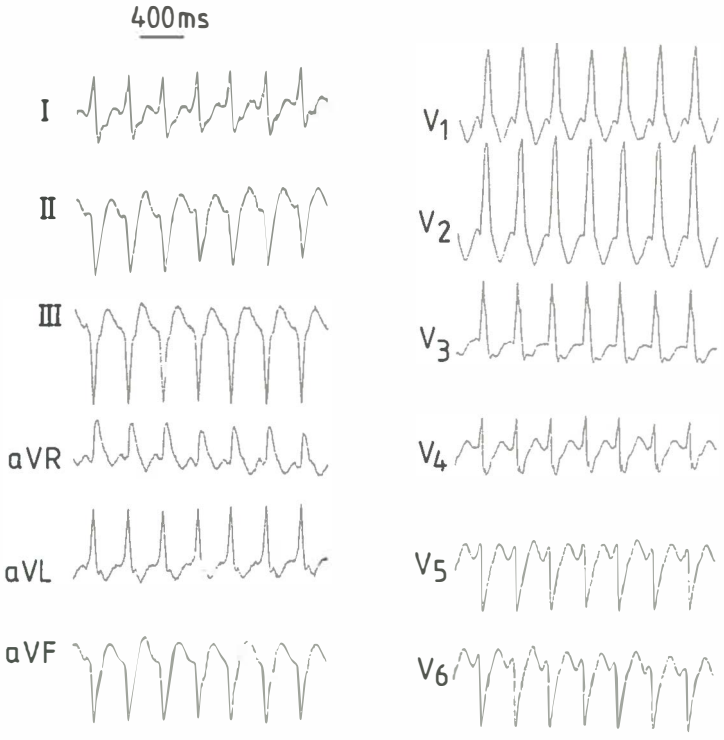

Figure 1. Electrocardiogram at admission. Ventricular tachycardia with right bundle branch block and left axis morphology. Calibration 1 cm = 1 mV.

from the right atrium with timed extrastimuli and atrial burst pacing. Finally, an infusion of isoprenaline was given. Programmed stimulation did not induce sustained ventricular arrhythmias. All induced ventricular premature beats and nonsustained ventricular tachycardias exclusively had a right bundle branch block, left axis morphology and were preceded by a short-long-short RR sequence. The duration of ventricular tachycardias did not increase with more agressive burst pacing or interval pacing. Also during isoprenaline ventricular tachycardias were observed without giving extrastimuli and only after a sufficiently long pause. These tachycardias became incessant due to post-tachycardia pauses (Figure 3).

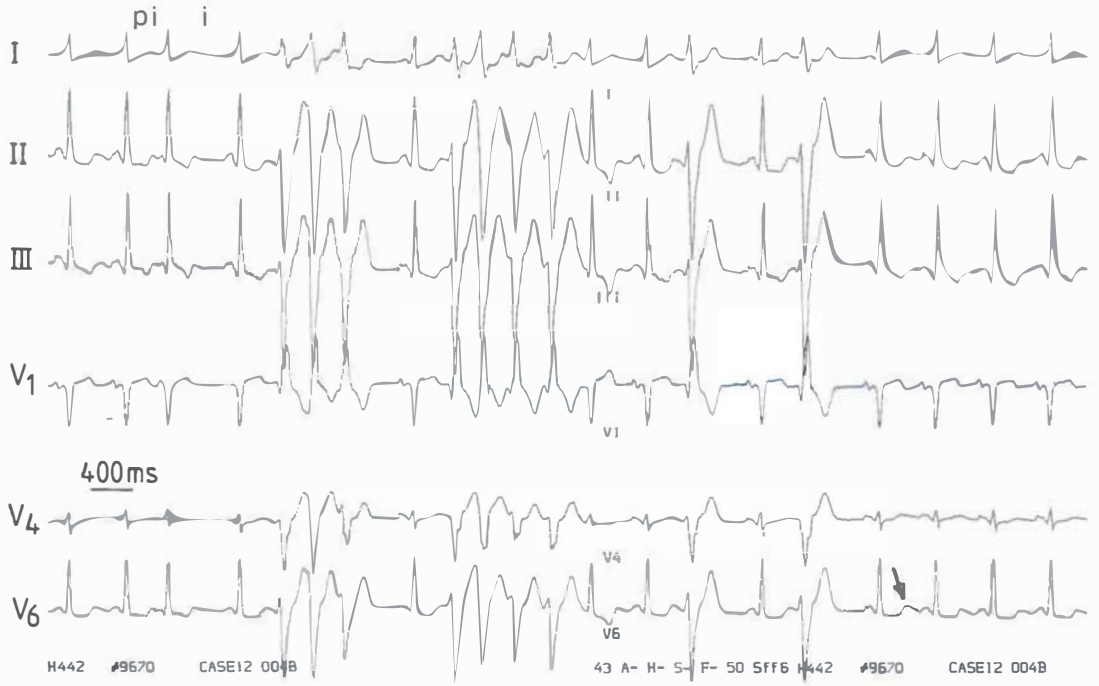

Figure 2. Nonsustained ventricular tachycardias during exercise testing. pi = pre-initiating cycle (short cycle), i = initiating cycle (long cycle). Note atrial premature beats setting the stage for short-long-short RR sequences accompanied by changes of the TU complex (arrow). Calibration 1 cm = 1 mV.

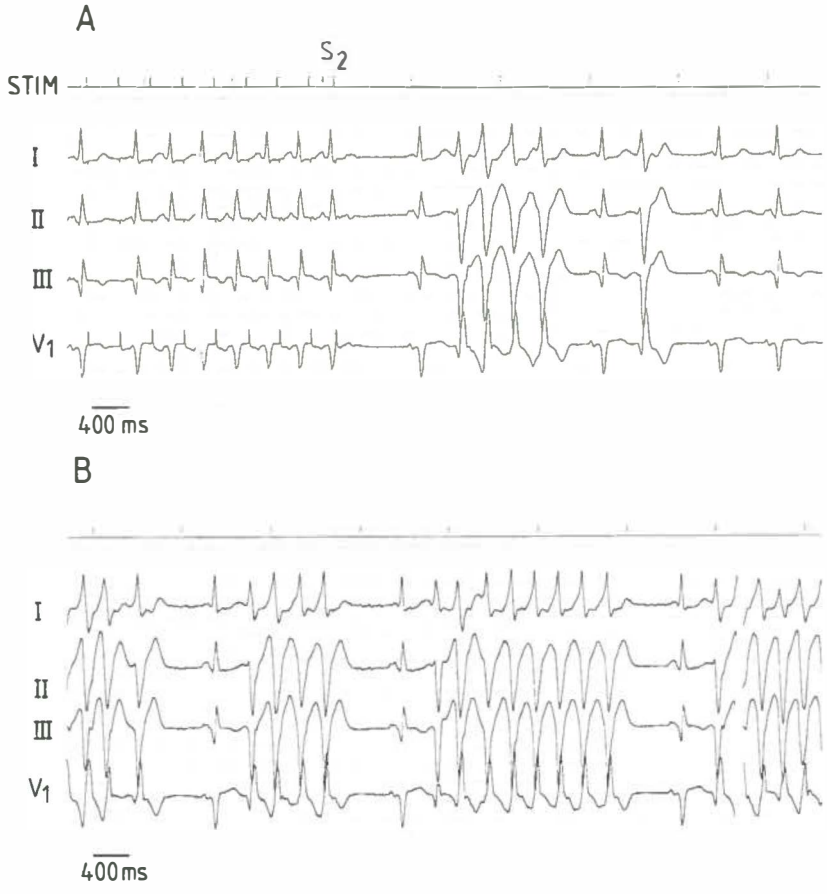

Figure 3. Ventricular arrhythmias during programmed stimulation.

A. Atrial pacing sequence followed by one atrial extrastimulus (S2), setting the stage for a short-long-short RR sequence followed by four ventricular premature beats.
B. After isoprenaline incessant nonsustained ventricular tachycardias initiated by short-long-short RR sequences.

Table I. Number of premature ventricular beats in relation to pre-initiating and initiating cycle length.

	number of PVB	number of S-L-S	PI	I	PI/I
A. No PVB					
PES:					
before isoprenaline	0	47	409±35	818±63	0.50±0.04
after isoprenaline	-	-	-	-	-
Exercise testing	-	-	-	-	-
B. 1 - 6 PVB					
PES:					
before isoprenaline	2	110	344±65*	792±130	0.45±0.11*
after isoprenaline	3	63	315±59	684±159	0.48±0.12
Exercise testing	3	12	373±38	697±94	0.55±0.10
C. 6 or more PVB					
PES:					
before isoprenaline	7(6-11)	3	320±35	580±173	0.57±0.09
after isoprenaline	8(6-17)	30	314±51	762±110#	0.42±0.08#
Exercise testing	6 and 17	2	320	590±99	0.55±0.09

I: initiating cycle length (ms, mean ± standard deviation); PES: programmed electrical stimulation; PI: pre-initiating cycle length (ms, mean ± SD); PI/I: the ratio of pre-initiating and initiating cycle length (mean ± standard deviation); PVB: premature ventricular beats, median (range); S-L-S: short-long-short RR sequences. * $p < 0.05$ compared to no PVB, # $p < 0.05$ compared to 1 to 6 PVB (Student's unpaired t-test).

Before isoprenaline, the shorter the pre-initiating cycle, the longer the ensuing tachycardia, although differences were not in all instances statistically significant (Table I). In addition, the initiating cycle preceding nonsustained ventricular tachycardias also tended to be shorter. After isoprenaline both pre-initiating and initiating cycles shortened significantly (from 363 ± 65 to 315 ± 56 ms and from 795 ± 119 to 709 ± 149 ms respectively, $p < 0.05$, Student's unpaired *t*-test). However, it appeared that after isoprenaline nonsustained ventricular tachycardias occurred only after long initiating cycles.

The patient was treated effectively with a beta blocker.

Discussion

In the present patient ventricular tachycardia developed only during atrial and ventricular stimulation if a sufficiently long pause followed a relatively short RR interval. This resembles the short-long-short RR sequences, which may precede the onset of torsades de pointes in the acquired long QT syndrome. In those patients, post-pause TU wave alterations, allegedly representing a cycle length dependent induction of early afterdepolarizations[4], can be seen. The occurrence of these phenomena in our patient led us to believe that triggered activity was the primary underlying mechanism. Also the hypokalemia found during the sustained ventricular tachycardia at admission may presume triggered activity.

The response to sympathetic stimulation does not argue against triggered activity due to early afterdepolarizations[5]. Although overdrive suppresses early afterpotentials, it may well be that adrenergic stimulation in the setting of an intercurrent pause, increases their amplitude[6]. In the present patient phenomena compatible with the above mentioned were found. In the absence of ventricular pauses there were no spontaneous tachycardias, also not after isoprenaline. Moreover, the arrhythmogenic mechanism was enhanced in the presence of increased adrenergic tone: tachycardias were longer and faster (cycle length decreased from 285 ± 9 ms to 267 ± 23 ms) after isoprenaline.

Other phenomena suggesting triggered activity, such as a positive relation between coupling interval of the paced beats and the RR interval of the ensuing tachycardia, were not found in our patient[1].

Induction of ventricular tachycardia by atrial burst pacing or premature stimuli does not necessarily indicate triggered activity. An alternative explanation, for the initiation of ventricular tachycardia in our patient, can be found in post-pause increase in dispersion of ventricular refractoriness[3]. This may become pronounced when diseased borders normal tissue or with increased plasmalevels of catecholamines. Regional differences in action potential duration may cause reentry due to focal reexcitation without a preceding triggering beat[7].

Another possible mechanism relates to differences in refractory periods between Purkinje cells and ventricular myocardium, which may predispose to bundle branch reentry[3]. Although we did not note the development of right bundle branch block or fascicular block during tachycardia induction, this mechanism cannot be excluded completely.

Finally, spontaneous arrhythmias in the setting of sympathetic stimulation and hypokalemia may be caused by abnormal automaticity. However, to our knowledge a cycle length dependent initiation has not been described previously, and therefore this mechanism probably did not play a role in our patient.

Drawing a parallel with the present case, atrial fibrillation with its intrinsic short-long-short RR sequences might also pose a patient to the threat of developing ventricular tachycardias especially during treatment with class 1A drugs. However, for the development of torsades de pointes atrial fibrillation appeared not to be a prerequisite. Roden et al.[8] noted torsades de pointes in patients with atrial fibrillation only after conversion to sinus rhythm. This may be explained by assuming that after restoration of sinus rhythm most patients still may have frequent atrial premature beats setting the stage for short-long-short RR sequences.

Our report stresses the potential advantages of using interval pacing in patients with clinically significant arrhythmias in whom during the standard stimulation protocol[2] ventricular tachycardia cannot be induced. Studies in patients with acquired forms of the long QT syndrome also have drawn attention to the interval dependency of associated tachycardias. More appropriate stimulation protocols incorporating short-long-short RR sequences may enhance induction of ventricular tachycardia and enable evaluation of therapeutic interventions in these patients.

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Appendix 7

Rate-dependent effects of the class III antiarrhythmic drug almokalant on refractoriness in the pig

Ans C.P. Wiesfeld, Cees D.J. De Langen, Harry J.G.M. Crijns, Klaas J. Bel, Hans L. Hillege, Harry Wesseling, Kong I. Lie

Abstract

The electrophysiologic effects of intravenously administered almokalant, a new class III antiarrhythmic drug, in 7 healthy pigs after low and high dose were investigated. Low dose almokalant included bolus infusion of 0.05 μmol/kg/min for 5 minutes followed by a continuous infusion of 0.0025 μmol/kg/min for 40 minutes. Thereafter, a high dose of 0.2 μmol/kg/min for 5 minutes and 0.01 μmol/kg/min for 40 minutes was given.

PR, QRS, AH and HV intervals did not change during almokalant. The rate corrected QT time increased dose-dependently from 474±17 to 551±17 ms at high dose ($p<0.05$). Atrial refractory periods (AERP) prolonged dose-dependently at pacing cycle length 500 ms from 178±15 at baseline to 227±27 and 253±23 ms during low and high dose almokalant, respectively. For pacing cycle lengths 400 and 300 ms these values were 180±11, 207±25, 259±34 ms and 157±12, 193±21, 234±28 ms, respectively.

At pacing cycle length of 500 ms mean ventricular effective refractory period (VERP) was 270±25 ms versus 306±24 and 337±17 during low and high dose, respectively. A similar pattern of VERP changes during both low and high dose infusion was seen at the shorter pacing cycle lengths, with an increase from 240±23 to 274±22 and 279±24 ms during cycle length 400 ms, and from 210±17 to 235±19 and 234±21 ms during cycle length 300 ms. The ratio of the ventricular effective refractory period and ventricular monophasic action potential duration did not change significantly. The Wenckebach cycle length increased with 36±36 ms and 83±37 ms at low and high dose almokalant, respectively. The percentual increase of AERP at pacing cycle length 500, 400 and 300 ms during high dose almokalant was 42, 44 and 49%, respectively. These figures were for VERP 25, 16 and 11%, respectively.

In conclusion, prolongation of refractoriness by almokalant was more pronounced at the atrial than the ventricular level. Prolongation of refractoriness was maintained at short pacing cycle lengths especially in the atrium, indicating absence of reverse-use dependence of almokalant in the porcine heart. The marked atrial effects, paralled by atrioventricular conduction slowing, and the absence of reverse use-dependence all add to the feasibility of almokalant in particular in the treatment of supraventricular tachyarrhythmias.

Introduction

Prolongation of refractoriness by selective potassium channel blockers may be more pronounced at longer cycle lengths. This reverse use-dependency may reduce their effectiveness during existing tachycardias. At long RR intervals this characteristic

may render them proarrhythmic by the induction of pause-dependent early afterdepolarizations giving rise to triggered activity[1,2]. Obviously, reverse use-dependence may limit the clinical applicability of these newer class III agents.

Almokalant ((4-[3-[ethyl[3-(propylsulfinyl)propyl]amino]-2-hydroxy-propoxy]-benzonitrile), H 234/09, Astra-Hässle, Sweden) is a new class III antiarrhythmic drug, which preferentially blocks the delayed rectifier potassium current[3]. Electrophysiologic studies in dogs and guinea pigs showed that almokalant prolongs the monophasic action potential duration and refractoriness of the atrium and ventricle without affecting conduction velocity. In postinfarction patients receiving almokalant intravenously a marked prolongation of the QT interval and suppression of spontaneous ventricular arrhythmias were observed[4]. Up till now use-dependence of almokalant has not been studied. The present study examines the electrophysiologic effects of intravenous almokalant in pigs with emphasis on the rate dependency of the drug's action on refractoriness.

Methods

In seven Yorkshire swine (weight 28±2 kg, mean±SD), pretreated with 120 mg azaperone intramuscularly (Stresnil^R, Janssen Pharmaceutica Beerse, Belgium), anaesthesia was induced by the intramuscular injection of ketamine 10 mg/kg and diazepam 2 mg/kg. Subsequently, a cuffed endotracheal tube was introduced for ventilation with a O_2/NO_2 mixture. Anaesthesia was done with the inhalation anaesthetic isoflurane (Forene^R, Abbott, U.S.A.) in a concentration of 0.5-1 % (closed loop system). Ventilation parameters were adjusted to keep arterial pCO_2 concentrations between 4.5 and 6.5 kPa and pO_2 concentrations between 16 and 20 kPa. Blood gas values were measured with a blood gas analysis system (type ABL 330, Radiometer, Copenhagen, Denmark). The levels of CO_2 in the expiratory air were monitored by capnography (Dräger Capnolog/Optocap system, Dräger Werke, Lübeck Germany). On-line inhalation gas monitoring was performed with an Ohmeda analyzer, type 5330 (Louisville, USA). Body temperature was kept between 36-38°C with a thermal mattress. Arterial blood pressure was monitored via a catheter in a femoral artery, which was also used for blood sampling to determine the plasma concentrations of almokalant. Subsequently, positioning of the catheters was done. After venasection, a 6 F USCI quadripolar catheter was introduced via the right femoral vein and positioned in the high right atrium. A 6 F quadripolar catheter was wedged under fluoroscopic control at the noncoronary cusp of the aortic valve through a carotid artery to record the His bundle electrogram. In addition, a combination pacing and monophasic action potential recording electrode (Monophasic Action Potential/Pacing Combination Catheter, Franz^R, EP Technologies Inc., U.S.A.) was introduced via the right jugular vein and positioned

at the right ventricular apex. Electrocardiographic lead II, atrial and His bundle electrograms, monophasic action potential as well as the arterial blood pressure were monitored on a polygraph system (Nihon-Kohden, Tokyo, Japan) and selected parts were recorded on an ink-jet Siemens Mingograf recorder at a paper speed of 100 mm/s. The amplifier filter cutoff settings for the intracardiac signals from the atrium and from the His bundle region were 50 and 1000 Hz. The monophasic action potential signal was not filtered.

Programmed electrical stimulation. Programmed electrical stimulation was done before antiarrhythmic drug infusion (baseline) and after low (starting at t=15 minutes) and high dose almokalant (starting at t=60 minutes) (Figure 1). Stimulation was performed with a Nihon-Kohden cardiac stimulator (model SEC 3102, Tokyo, Japan) delivering rectangular pulses of 2 ms duration at twice diastolic threshold. Atrial and ventricular diastolic current thresholds were determined before baseline stimulation and repeated before stimulation at low and high dose almokalant. Atrial and atrioventricular nodal refractoriness were determined at drive cycle lengths 500, 400 and 300 ms and a single extrastimulus (S_2) after eight atrial paced beats (S_1). S_2 was initially placed late in diastole and diastole was scanned in 10 ms decrements until refractoriness was reached. Ventricular refractoriness (VERP) was determined in the right ventricular apex with drive cycle lengths of 500, 400 and 300 ms (S_1) and a single extrastimulus (S_2).

Ventricular monophasic action potential duration at the 90% repolarization level (APD90) was measured at the eighth beat of each drive cycle and the VERP/APD90 ratio was calculated.

To attempt the induction of early afterdepolarizations and torsades de pointes, we induced cycle length alterations[5,6]. First, single cycle length perturbations were evaluated. Atrium and ventricle were paced simultaneously at a rate slightly above the sinus cycle length for eight beats followed by S_2 (ERP S_2 + 10ms) and S_3 at ERP S_3 + 10 ms. The S_2S_3 interval was prolonged with 10 ms until the first spontaneous sinus beat occurred. If no early afterdepolarizations or ventricular arrhythmias were induced this procedure was repeated with S_2S_3 as long as possible and S_3S_4 beginning at 400 ms and decreasing with 10 ms.

Dosing and blood sampling. After the assessment of the baseline parameters almokalant was given as a 5 minute intravenous bolus infusion of 0.05 μmol/kg/min into the abdominal caval vein, followed by a continuous infusion at a rate of 0.0025 μmol/kg/min for 40 minutes. Thereafter, the high dose level was started as a 5 minute intravenous bolus infusion of 0.2 μmol/kg/min followed by a continuous infusion at a rate of 0.01 μmol/kg/min for 40 minutes. This dosing regimen aimed at attaining a pseudo-steady state in the plasma concentration. To construct the concentration time curves blood sampling was done before almokalant infusion (t=0) and at 15, 30, 45, 60, 75 and 90 minutes after the start of the infusion (Figure 1). Blood samples were analyzed at Astra Hässle Laboratories (Mölndal, Sweden) using

reversed phase liquid chromatography.

Electrocardiographic and signal-averaged electrocardiographic parameters. The sinus cycle length, AH, HV and PR interval, QRS and QT duration were measured before almokalant infusion (t=0), at 30 and 75 minutes after the start of almokalant infusion (Figure 1), representing a pseudo steady state in the plasma concentration at low and high dose, respectively. In order to evaluate drug effects on intraventricular conduction and the high frequency QRS amplitude, signal-averaged electrocardiography was performed at the same time points. One hundred beats were averaged, vector summed and filtered at 50 Hz with a bidirectional digital filter[7]. The evaluated parameters were[7-9]: the root-mean-square voltage of the averaged QRS complex (Vtot, in μV), the root-mean-square voltage in the last 20 ms of the QRS complex (V20, in μV) and the duration of the activity in the terminal portion of the QRS complex below 30 μV (D30 in ms), the vector of the QRS complex, duration of the QT interval and the rate corrected QT interval derived from the unfiltered vector value. The QT interval was corrected for differences in heart rate with Bazett's formula[10].

Statistical analyses. Data are presented as mean $\pm$ the standard deviation. Student's *t* test was used for normally distributed data. P values <0.05 were considered to indicate statistical significance. All the statistical calculations were conducted with standardized biomedical algorithms (SPSS/PC+ and SPSSWIN, SPSS, Inc., Chicago, IL, USA).

Results

Almokalant plasma concentration. Pseudo-steady state plasma concentrations of almokalant were reached with both infusion schemes. The mean steady state plasma concentration at low dose and at high dose almokalant was 167 ± 44 nmol/L (t=30 minutes) and 1129 ± 217 nmol/L (t=75 minutes), respectively (Figure 1).

Electrophysiologic results. Almokalant did not alter sinus cycle length, the PR interval or the QRS duration on the surface electrocardiogram at either plasma level. During almokalant infusion the AH and HV interval remained unchanged. The signal-averaged QRS duration, Vtot, V20 and D30 did not change. However, the corrected QT interval derived from the vector summed X, Y and Z lead prolonged significantly at both steady state levels comparable to the corrected QT interval from the 12-lead surface electrocardiogram (Table I). The percentual prolongation of the corrected QT interval correlated with the almokalant plasma concentration both at the low (Figure 2A, $p<0.05$) and at the higher level (Figure 2B, $p<0.05$). The anterograde Wenckebach cycle length increased with 36 ± 36 ms and 83 ± 37 ms at low and high dose almokalant, respectively (p=ns). In addition, anterograde

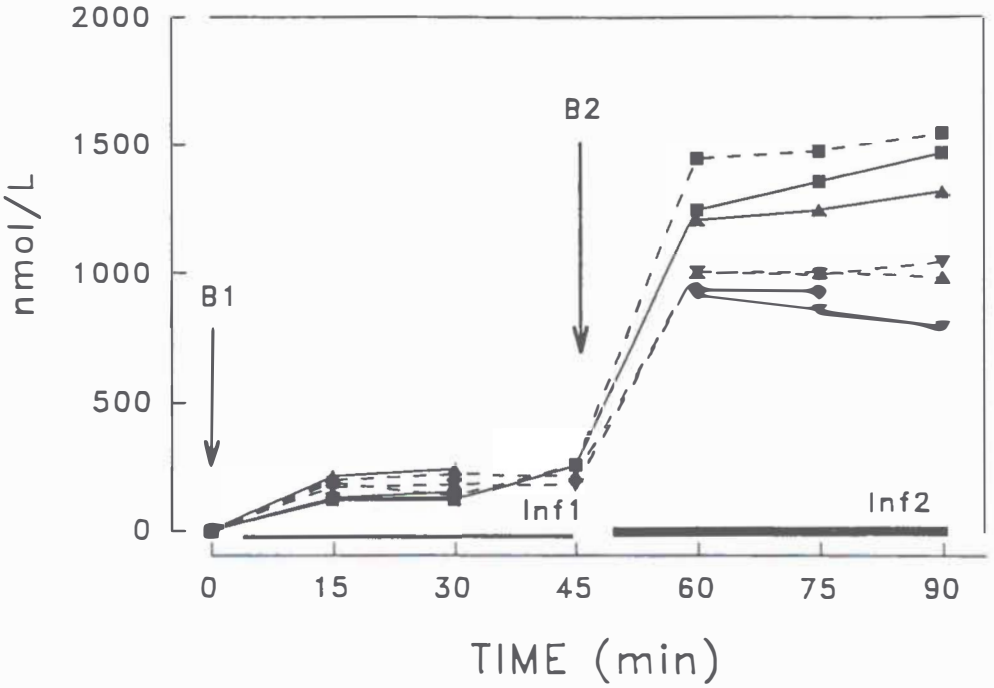

Figure 1. Almokalant plasma levels at baseline and at low and high dose almokalant. This figure shows that at t= 15 minutes, at which programmed stimulation started during low dose almokalant and at t=60 minutes, at which programmed stimulation started during high dose almokalant, stable almokalant plasma concentrations were obtained. X-axis time schedule protocol. Y-axis almokalant plasma level. B1 = 5 minute intravenous bolus infusion of 0.05 μmol/kg/min, followed by Inf 1, a continuous infusion at a rate of 0.0025 μmol/kg/min for 40 minutes. Thereafter, the high dose level was started as a 5 minute intravenous bolus infusion of 0.2 μmol/kg/min (B2) followed by Inf 2, a continuous infusion at a rate of 0.01 μmol/kg/min for 40 minutes.

Table I. Electrocardiographic, electrophysiologic and signal-averaged electrocardiographic data before and after infusion of low and high dose almokalant. For the time schedule see Figure 1.

Time	baseline	30'	75'
SCL (ms)	556±72	530±64	561±26
PR (ms)	102±17	100±15	103±17
QRS (ms)	56±16	60±17	59±19
QTc (ms)	474±17	509±28*	551±17*,@
AH (ms)	87±17	78±12	84±13
HV (ms)	24±4	23±4	26±9
SA-QRS (ms)	56±7	54±5	53±6
Vtot (μV)	241±94	222±97	210±86
V20 (μV)	13±7	13±6	16±4
D30 (ms)	24±6	21±8	21±3
SA-QT (ms)	338±13	364±23*	409±10*,@
SA-QTc (ms)	456±21	501±24*	546±7*,@

All data mean±SD. *SA-QRS*: computerized measurement of the QRS duration on the signal-averaged electrocardiogram; *SA-QT*: QT time measured at the signal-averaged, vector summed electrocardiogram; *SA-QTc*: rate corrected QT time measured at the signal-averaged, vector summed electrocardiogram; *SCL*: sinus cycle length. * $p < 0.05$ compared to baseline, @ $p < 0.05$ compared to 30'.

refractory period of the atrioventricular conduction system was reached at longer cycle lengths. Anterograde refractoriness of the atrioventricular conduction system at 500 ms and one extrastimulus increased from 266±29 ms, 310±70 ms to 334±61 ms at baseline, low and high dose almokalant, respectively ($p < 0.05$). At a pacing cycle of 400 ms these values were 267±18 ms and 257±44 ms at baseline and low dose almokalant, respectively. At the high dose the anterograde refractoriness of the atrioventricular conduction system could not be assessed, because the atrial refractory periods were longer.

Atrial refractory periods (AERP) prolonged dose-dependently at pacing cycle length 500 ms from 178±15 at baseline to 227±27 and 253±23 ms during low and high dose almokalant, respectively (Figure 3). For pacing cycle lengths 400 and 300 ms these values were 180±11, 207±25, 259±34 ms and 157±12, 193±21, 234±28 ms, respectively. The percentual increase of AERP at high dose compared

to baseline was 42, 44 and 49% for the pacing cycle lengths 500, 400 and 300 ms, respectively ($p < 0.01$ compared to values before drug in all cases).

At pacing cycle length of 500 ms mean ventricular effective refractory period (VERP) was 270±25 ms versus 306±24 and 337±17 during low and high dose, respectively (Figure 4A). A similar pattern of VERP changes during both low and high dose infusion was seen at the shorter pacing cycle lengths, with an increase from 240±23 to 274±22 and 279±24 ms during cycle length 400 ms, and from 210±17 to 235±19 and 234±21 ms during cycle length 300 ms. However, as can be seen from these results, at the short paced cycle lengths of 400 and 300 ms the effects of high dose were not significantly different from low dose effects. Concomitantly with the changes of ventricular refractoriness, statistically significant prolongation of the ventricular monophasic action potential duration at the 90% repolarization level was observed (Figure 4B). At pacing cycle length of 500 ms mean ventricular monophasic action potential duration (VAPD) was 282±29 ms versus 301±15 and 322±22 during low and high dose, respectively. VAPD increased from 247±18 to 273±17 and 279±15 ms during cycle length 400 ms, and from 211±14 to 233±13 and 233±18 ms during cycle length 300 ms. The percentual increase of VAPD at high dose compared to baseline was 14, 12 and 10% for the pacing cycle lengths 500, 400 and 300 ms, respectively. The ratio of the ventricular effective refractory period and ventricular monophasic action potential duration did not change (data not shown).

Observations during cycle length alterations. Before and during almokalant administration short-long-short RR sequences induced neither arrhythmias nor changes in the monophasic action potential morphology, which might have suggested early afterdepolarizations. Before almokalant the intervals S_1S_1, S_1S_2, S_2S_3 and S_3S_4 were 530±87, 310±34, 714±94 and 300±32 ms, respectively. During low dose almokalant these intervals were 520±51, 342±22, 686±92 and 360±19 ms. During high dose almokalant these intervals were 517±37, 347±33, 765±129 and 365±33 ms, respectively.

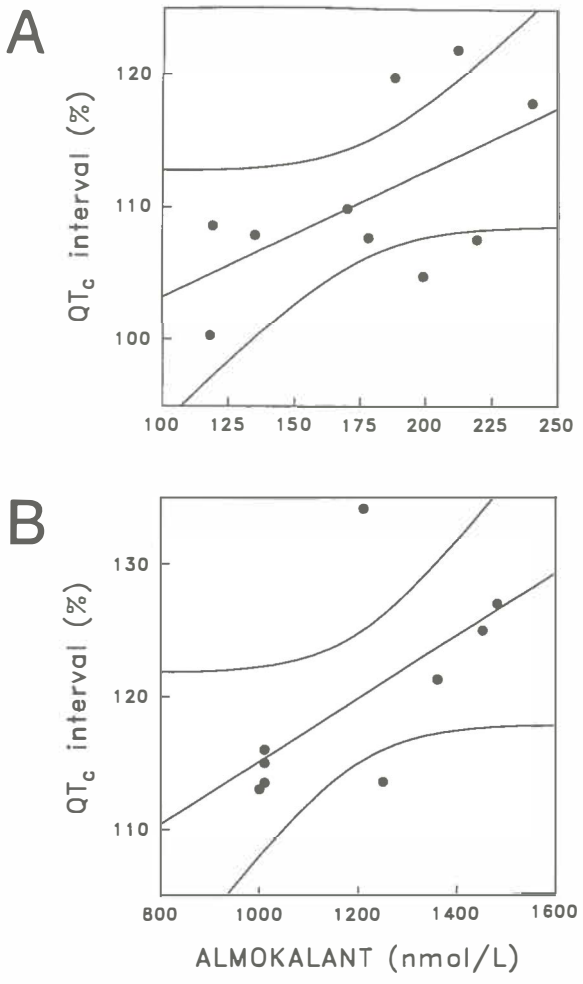

Figure 2. A. Relationship between corrected QT interval (in percentage increase) and almokalant plasma concentration 15 and 45 minutes after the start of almokalant infusion. Data represent 5 independent experiments (correlation coefficient r=0.58). 95% confidence interval is given. **B.** Relationship between corrected QT interval (in percentage increase) and almokalant plasma concentration 60 and 75 minutes after the start of almokalant infusion (t=60'). Data represent 5 independent experiments (correlation coefficient r=0.63). 95% confidence interval is given.

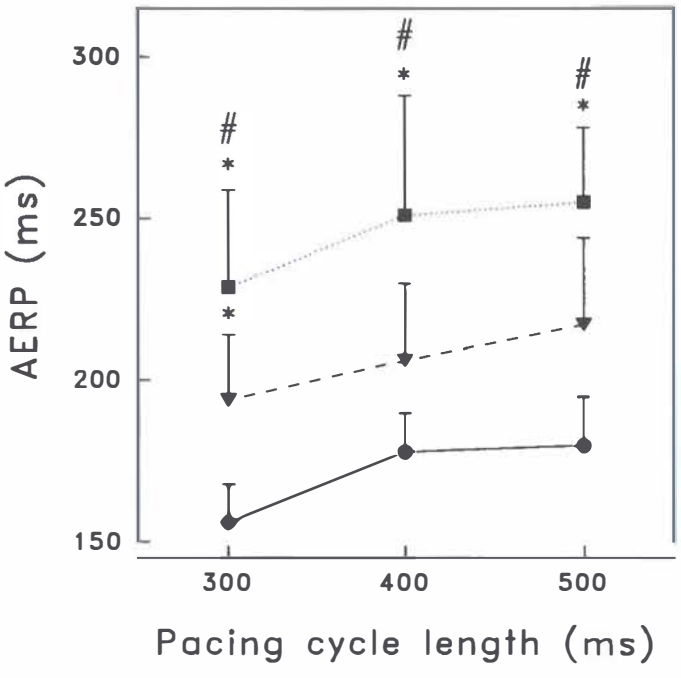

Figure 3. Atrial refractoriness at baseline and at low and high dose almokalant determined with one extrastimulus at drive cycle length 500, 400 and 300 ms. Atrial refractoriness remained prolonged at the shorter drive cycle lengths. • =at baseline; ▼=low dose almokalant ;■=high dose almokalant. * $p<0.05$ compared to baseline, # $p<0.05$ compared to low dose.

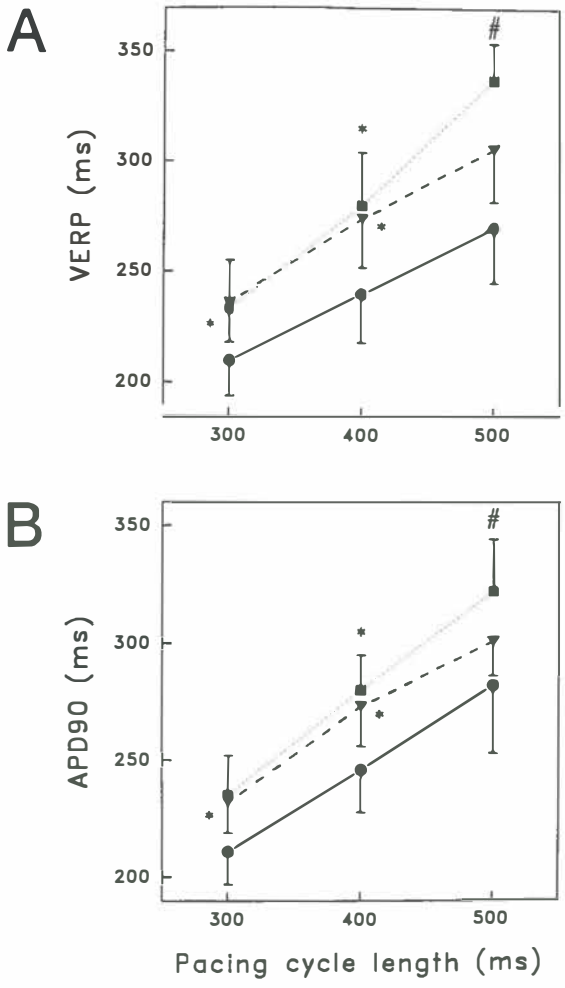

Figure 4. A. Ventricular refractoriness at baseline, at low and high dose almokalant determined with one extrastimulus at drive cycle length 500, 400 and 300 ms.
B. Ventricular monophasic action potential duration at the 90% repolarization level at baseline and at low and high dose almokalant at drive cycle length 500, 400 and 300 ms. • =at baseline; ▼=low dose almokalant; ■=high dose almokalant.
* $p < 0.05$ compared to baseline, # $p < 0.05$ compared to low dose.

Discussion

This study shows that almokalant prolongs atrial and ventricular refractoriness without affecting normal automaticity or conduction. Almokalant's effect on refractoriness was maintained at short cycle lengths, suggesting that this agent lacks significant reversed use-dependence. There was a clear differential effect on atrial versus ventricular refractoriness. First, the relative increase after both low and high dosage was larger at the atrial than at the ventricular level. Secondly, the relative increase of refractoriness at the shorter paced cycle lengths of 400 and 300 ms was more marked in the atrium compared to the ventricle. The latter indicates that especially the atrium lacks reverse use-dependence. These results suggest that almokalant might be particularly useful in atrial rather than ventricular arrhythmias. Feasibility in supraventricular arrhythmias is further enhanced by the fact that this agent also prolongs refractoriness of the atrioventricular conduction system.

Use-dependent prolongation of the refractory period is a desirable property of an antiarrhythmic agent, since it enhances chemical termination of a tachycardia immediately after its very onset[11]. The ideal antiarrhythmic should also exert use-dependent suppression of excitability in the vulnerable period. In fact the latter feature represents postrepolarization refractoriness. The only available drug combining these effects is amiodarone[11]. The present study suggests that almokalant maintains its action potential prolonging effect during rapid rates similar to amiodarone[12]. However, since the ratio of ERP/APD90 did not change, it does not produce significant postrepolarization refractoriness.

Proarrhythmia due to class III agents supposedly is due to bradycardia- or pause-dependent triggered activity[5,6]. The typical electrocardiographic pattern initiating torsades de pointes is a short-to-long sequence of RR intervals. Therefore we used abrupt changes of pacing cycle length to mimick short-long RR sequences, thereby enhancing pause-dependent afterdepolarizations. However, in the present study, we were unable to provoke early afterdepolarizations or torsades de pointes. Obviously, there were no electrolyte abnormalities which might have enhanced the induction of torsades. It may also relate to the fact that it was impossible to induce sufficiently long pauses due to a too high adrenergic drive during the experiments. It must be noted that apart from cycle lengths considerations, high catecholamine levels may by themselves prevent class III related afterdepolarizations. Another explanation for absence of inducible torsades de pointes relates to the recent finding that almokalant induces torsades especially if a too rapid infusion rate is used, both in the experimental and the clinical situation[2,13]. Such rapid infusions were not used in the present study.

Clinical implications. In postinfarct patients with symptomatic ventricular arrhythmias, almokalant effectively suppressed premature beats and nonsustained ventricular tachycardias[4]. Up till now it is not clear whether class III drugs are also

effective in the prevention of sudden death or sustained ventricular tachyarrhythmias. However, the present animal experiments showed that the effects of almokalant were more pronounced in the atrium. In this setting persistent prolongation of refractoriness at short cycle lengths, occurring especially in the atrium, is favorable. In addition, the effects on the atrioventricular conduction system suggest efficacy in several types of regular supraventricular tachycardias. Clinically, almokalant may therefore prove particularly effective in the treatment of patients with supraventricular arrhythmias.

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Appendix 8

Electropharmacologic effects and pharmacokinetics of almokalant, a new class III antiarrhythmic, in patients with healed or healing myocardial infarcts and complex ventricular arrhythmias

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Am J Cardiol 1992;70:990-996

Abstract

The electropharmacologic effects and pharmacokinetics of almokalant, a new class III antiarrhythmic, were investigated in a randomized, placebo-controlled, double-blind study, and efficacy was evaluated. Ten postinfarct patients with complex ventricular arrhythmias were included and received, in randomized order on consecutive days, 4.5 mg (12.8 μmol) of almokalant or placebo intravenously over 10 minutes. One patient received infusion at a higher rate and developed self-terminating torsades de pointes. In the remaining 9 patients the corrected QT interval increased significantly: at the end of placebo infusion the corrected QT was 445±18 ms and after almokalant 548±53 ms ($p=0.0015$). The signal-averaged electrocardiographic parameters did not change. The number of ventricular premature complexes decreased significantly during the first 15 minutes after almokalant infusion ($p=0.04$). No additional proarrhythmic or other significant adverse events were noted. The almokalant plasma concentration showed a biphasic decrease with an elimination half-life of 2.4±0.1 hours. Almokalant was rapidly cleared from the body with a clearance of 11±1 ml/min/kg. When given with certain precautions almokalant appears safe and well tolerated and may be antiarrhythmic by prolonging refractoriness.

Introduction

In animal experiments, the new class III antiarrhythmic almokalant ((4-[3-[ethyl[3-(propylsulfinyl)propyl]amino]-2-hydroxy-propoxy]-benzonitrile), H 234/09, Hässle, Sweden) prolongs the monophasic action potential and refractoriness of the atrium as well as the ventricle without affecting conduction velocity. In addition, it has positive inotropic effects, selectivity between cardiac and central nervous system effects, and is devoid of beta blocking properties. In studies on isolated human papillary muscle, almokalant has also had a selective action on cardiac repolarization and positive inotropic effects[1]. In this study the electropharmacologic effects and pharmacokinetics of a single infusion of almokalant were studied in postinfarct patients with complex ventricular arrhythmias. In addition, the efficacy in the suppression of ventricular arrhythmias was evaluated.

Methods

Patients. Patients with a myocardial infarct older than one month, and having ≥720 ventricular premature complexes or ≥10 episodes of symptomatic nonsustained ventricular tachycardia on 24-hour Holter monitor were included in the study.

Electrocardiographic exclusion criteria were sinus bradycardia (< 50 beats/min) and second- or third-degree atrioventricular block. Patients with bundle branch block or symptomatic sinus node dysfunction were also excluded. Patients with a QT interval > 520 ms and known proarrhythmic response with class Ia or III antiarrhythmic drugs were not allowed to participate. In addition, patients with angina pectoris, congestive heart failure class III and IV according to the criteria of the New York Heart Association, or other significant medical or mental conditions that would interfere with conduct or evaluation of the study were excluded. Before infusions, electrolyte disturbances, especially hypokalemia and hypomagnesemia, were ruled out. Therapy with beta blockade and nifedipine was allowed; however, digitalis and other antiarrhythmic drugs had to be withdrawn for at least 5 half-lives. This study was approved by the Institutional Review Board. The pharmacokinetic and biostatistical analyses were performed at Astra-Hässle Cardiovascular Research Laboratories.

Study design. The study was designed as a randomized, cross-over, double-blind, placebo-controlled trial. After written informed consent, the patients were admitted to the coronary care unit and received 4.5 mg (12.8 μmol) of almokalant or placebo intravenously over 10 minutes in randomized order on consecutive days. The patients were in an overnight fasting condition and stayed in bed before and until 3 hours after each infusion. The effects were evaluated by 12-lead electrocardiograms, signal-averaged electrocardiography[2,3], continuous Holter monitoring, and blood sampling for plasma concentration determination of the drug. During each infusion, the 12-lead electrocardiogram was continuously monitored. In addition, electrocardiography, signal-averaged electrocardiography and blood sampling were performed before, at the end (t=0) and 5, 15, 30, 60, 90, 120 and 180 minutes after the end of infusion. Normal values for signal-averaged electrocardiography were: QRS < 114 ms, D40 < 38 ms and V40 > 20 μV[4]. If one or more of these variables were abnormal, the signal-averaged electrocardiogram was considered abnormal.

Holter monitoring. Holter monitoring was performed with the Marquette Laser System (Marquette Electronics, Milwaukee, Wisconsin) using modified leads V1, V5 and aVF. To evaluate the antiarrhythmic efficacy of almokalant, the number of ventricular premature complexes was determined for each 5-minute interval during 30 minutes before and 30 minutes after each infusion. The incidence of couplets and nonsustained ventricular tachycardia was too low during this period to be analyzed.

Evaluation of antiarrhythmic mechanism. To evaluate the effect of action potential prolongation on spontaneous ventricular arrhythmias, the coupling interval of ventricular premature complexes with identical morphology was measured before and at the end of each infusion. During each time period, ≥3 coupling intervals were measured and averaged. Patients with complete suppression of ventricular

arrhythmias, or in whom the morphology changed, were excluded from this analysis.

Pharmacokinetic analysis. The plasma samples were analyzed for almokalant by a reversed phase liquid chromatography. Maximal plasma concentration (C_{max}) was taken as the observed plasma concentration at the end of drug infusion. The equation of a two compartment model was fitted to the individual plasma concentrations by least-squares nonlinear regression[5]. The area under the plasma concentration versus time curve (AUC) was calculated by integration of the computer derived equation:

$$AUC = \frac{C_1}{\tau_1} + \frac{C_2}{\tau_2}$$

where the C_n and the τ_n are the intercepts and rate constants of the equation fitted to the plasma data. Total plasma clearance (CL) was calculated as: CL = dose/AUC. The volume of distribution at steady state (V_{ss}), and the volume at distribution equilibrium (V_z) were determined by the following equations, where AUMC is the area under the first moment versus time curve:

$$V_{ss} = \frac{AUMC - Dose}{[AUC]^2} \quad \text{and} \quad V_z = \frac{Dose}{AUC \cdot \tau_2}$$

The half-lives of the different phases of the plasma concentration versus time curve ($t_{½}$), were calculated from: $t_{½} = 0.693/\tau_n$, where τ_n is the rate constant of the separate phases determined by log-linear regression of the declining plasma levels.

Statistical analysis. Effect was defined as the absolute measurement at the end of almokalant and placebo infusion of the electrocardiographic and signal-averaged electrocardiographic parameters. The number of ventricular premature complexes was analyzed before and after the end of each infusion. Carryover effects were studied by Student's unpaired *t* test. Period effects and direct-treatment effects were analyzed with use of Student's *t* test expressed as 95% confidence intervals. For asymmetric-distributed data, we used the Wilcoxon's rank sum test. A p value <0.05 was defined as significant. All data are expressed as mean $\pm$ 1 SD. The maximal corrected QT[6] prolongation was calculated with the Lineweaver-Burk equation. To analyze the concentration-effect relation, we used the percentage of the maximal effect as the dependent variable and the logarithm of the plasma concentration as the independent variable in a linear regression model.

Table I. Baseline characteristics.

Pt/Age(yrs) Sex	LVEF (%)	Echocardiogram LVESD/ LVEDD (mm)	LA (mm)	24-hour Holter VPB	Runs	Frequency fastest run (bpm)	Signal-averaged ECG LP	D40 (ms)	V40 (μV)	QRS (ms)
1. 54 M	61	45/60	54	37595	2	129	yes	43	17	105
2. 49 M	45	37/59	43	6213	7	106	yes	37	17	115
3. 66 F	35	46/63	40	28168	136	134	yes	29	17	143
4. 62 M	42	49/65	39	833	1	101	yes	38	18	108
5. 38 M	27	46/63	46	6103	35	140	no	28	32	103
6. 57 M	57	35/54	34	17788	20	125	yes	36	17	103
7. 65 M	47	-/-	-	4870	16	112	n.e.	-	-	-
8. 65 M	32	-/55	37	40157	537	128	n.e	-	-	-
9. 62 M	22	57/74	50	27138	367	199	yes	46	17	113
10. 52 M	28	51/66	36	8425	58	158	no	20	71	95

Bpm: beats per minute; *ECG:* electrocardiogram; *F:* female; *LA:* left atrial dimension long axis; *LP:* late potential; *LVEDD:* left ventricular end-diastolic dimension; *LVEF:* left ventricular ejection fraction; *LVESD:* left ventricular end-systolic dimension; *M:* male; *n.e.:* not evaluable; *Runs:* nonsustained ventricular tachycardias during 24-hour Holter; *VPB:* ventricular premature beats during 24-hour Holter.

Results

Baseline characteristics. Table I lists the baseline characteristics of the 10 patients. Six patients had a healed inferior myocardial infarct, 1 patient inferoanterior, 1 patient inferoposterior and 2 patients an anterior infarct. No patient had symptoms or signs of heart failure. Only 2 patients received concomitant beta blockade and 2 an angiotensin converting enzyme inhibitor. The first patient was excluded from the analysis because of a proarrhythmic response after an infusion at too high a rate.

Electrocardiographic results. During and after infusion of almokalant no significant changes in heart rate, PR interval and QRS duration were noted compared with placebo (Table II). However, the QT interval was significantly prolonged (Figure 1). At the end of the placebo infusion the corrected QT was 445 ± 18 ms versus 548 ± 53 ms at the end of almokalant infusion (confidence interval 1.15-1.40; $p=0.0015$). The maximal observed effect occurred at the end of the almokalant infusion and the interval was significantly prolonged until 120 minutes after the end of infusion. No changes in the signal-averaged electrocardiographic parameters occurred (Table II).

The effect on the coupling interval between sinus beat and ventricular premature complex was evaluable in 6 patients. It remained unchanged after placebo infusion (605 ± 78 ms before and 607 ± 70 ms at the end of infusion). In contrast, almokalant prolonged the coupling interval significantly from 592 ± 66 ms before infusion to 719 ± 74 ms at the end of infusion (confidence interval 44-180; $p=0.008$) (Figure 2).

Antiarrhythmic efficacy. Antiarrhythmic evaluation of almokalant with respect to suppression of ventricular premature complexes was possible within the limited period of 30 minutes because the number of ventricular premature complexes was high and constant in almost all patients. Compared with placebo, almokalant significantly suppressed isolated ventricular premature complexes until 15 minutes after the end of infusion ($p=0.04$) (Figure 3). None of the 9 evaluated patients had a proarrhythmic response[7,8].

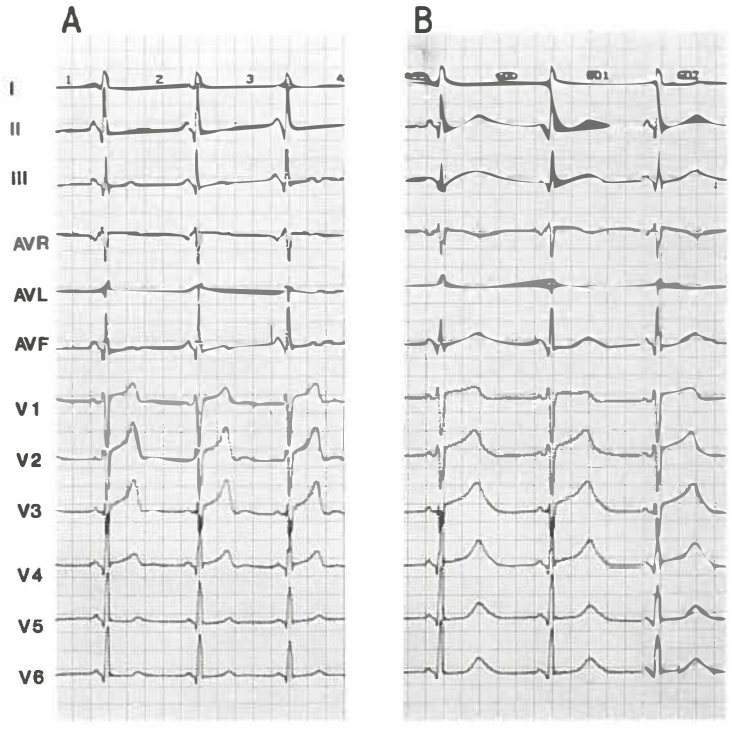

Figure 1. Observed changes of the QT interval and the morphology of the ST-U segment after almokalant infusion in patient 10. Similar changes were seen in all other patients. Note the prolongation of the QT interval accompanied by flattening of the T wave. In addition, the U wave became more pronounced or incorporated in the TU complex. (1 cm = 1 mV, paperspeed 1 cm = 400 ms).

A. Electrocardiogram before almokalant infusion.

B. Electrocardiogram at the end of almokalant infusion.

Table II. Data of the electrocardiogram and the signal-averaged electrocardiogram

	Before	0	5	15
Data of the electrocardiogram before and after placebo or almokalant				
Placebo (10)				
HR (bpm)	62±6	62±7	64±7	64±9
PR (ms)	161±24	157±26	153±25	156±25
QRS (ms)	106±8	108±8	105±12	104±8
QT (ms)	441±25	439±15	432±19	436±32
QTc (ms)	447±21	445±18	446±21	448±32
Almokalant (10)				
HR (bpm)	63±5	59±9	58±6	58±6
PR (ms)	155±26	159±27	158±25	159±30
QRS (ms)	105±9	107±8	108±11	108±9
QT (ms)	440±34	560±75*	530±67*	500±46*
QTc (ms)	450±31	548±53*	517±55*	489±48*
Data of the signal-averaged electrocardiogram before and after placebo or almokalant				
Placebo				
QRS (ms)	113±15(6)	111±17(6)	112±15(7)	109±14(7)
D40 (ms)	32±11(6)	31±11(6)	37±13(7)	32±13(7)
V40 (μV)	31±25(6)	31±27(6)	28±25(7)	28±23(7)
Almokalant				
QRS (ms)	112±15(7)	117±19(6)	113±17(6)	111±16(7)
D40 (ms)	33±8(7)	36±12(6)	31±11(6)	31±11(7)
V40 (μV)	29±19(7)	29±19(6)	30±22(6)	29±21(7)

* $p<0.05$. All data mean ± 1 SD. Numbers between parentheses are the numbers of available patients. Before = before infusion; 0= end infusion (thereafter 5, 15, 30, 60, 90, 120, and 180 minutes after the end of infusion); HR= heart rate.

Table II. (continued)

	30	60	90	120	180
Data of the electrocardiogram before and after placebo or almokalant					
Placebo (10)					
HR (bpm)	62±6	61±6	61±8	63±9	60±4
PR (ms)	158±30	157±30	153±30	152±27	150±23
QRS (ms)	106±6	105±8	105±10	106±9	108±9
QT (ms)	444±30	442±32	442±39	438±18	444±26
QTc (ms)	449±34	443±33	446±34	446±32	443±32
Almokalant (10)					
HR (bpm)	58±7	56±4	57±7	59±5	63±6
PR (ms)	156±26	156±25	153±26	152±28	153±25
QRS (ms)	107±7	108±10	107±9	106±10	106±10
QT (ms)	499±59*	477±42*	472±41*	466±29*	451±31
QTc (ms)	490±63*	462±38*	457±34*	462±30*	460±30
Data of the signal-averaged electrocardiogram before and after placebo or almokalant					
Placebo					
QRS (ms)	112±15(7)	111±14(7)	115±14(6)	113±15(6)	111±13(7)
D40 (ms)	33±15(7)	33±12(7)	36±7(6)	32±5(6)	31±11(7)
V40 (μV)	29±23(7)	28±25(7)	20±7(6)	20±6(6)	29±27(7)
Almokalant					
QRS (ms)	111±18(6)	113±19(7)	106±9(6)	113±15(6)	112±16(7)
D40 (ms)	30±10(7)	30±8(7)	32±14(5)	30±12(6)	32±8(7)
V40 (μV)	29±20(6)	28±18(7)	29±21(6)	29±25(6)	27±18(7)

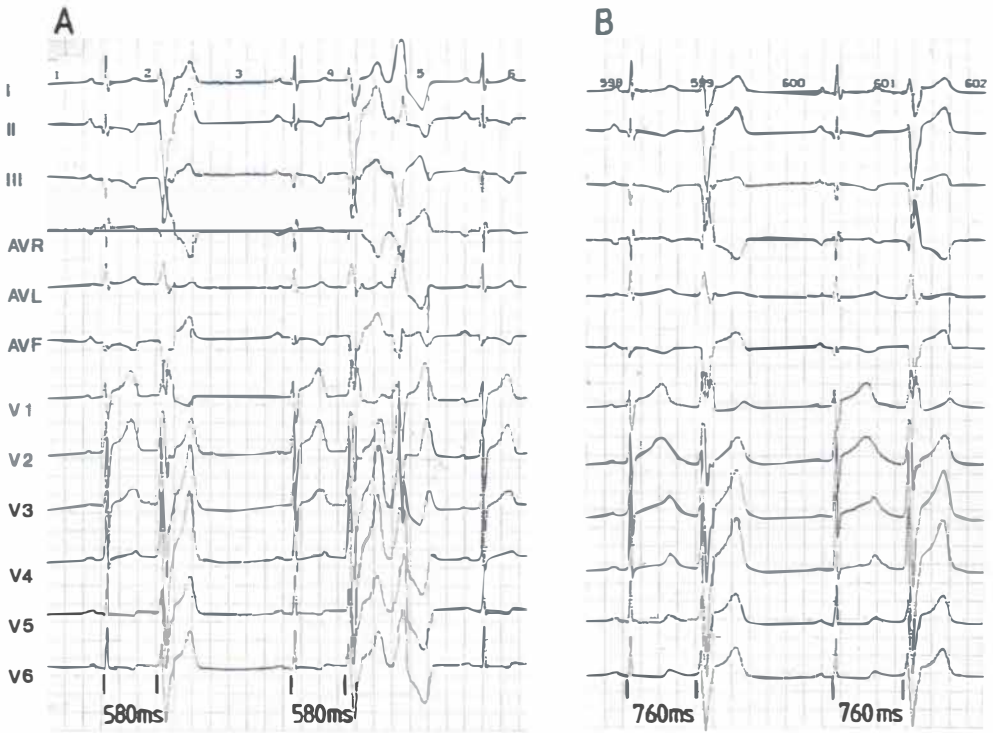

Figure 2. The coupling interval of a premature ventricular complex in a patient before (A) and at the end (B) of almokalant infusion (1 cm = 1 mV, paperspeed 1 cm = 400 ms).

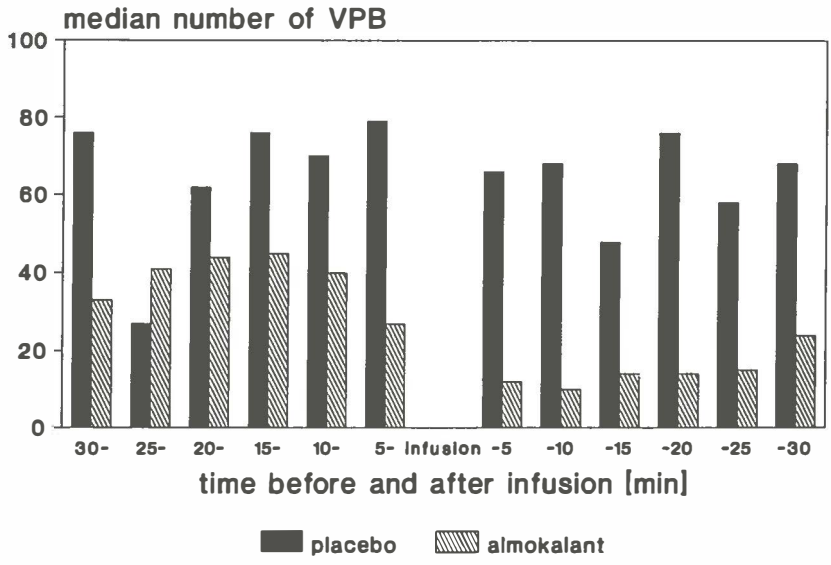

Figure 3. Antiarrhythmic effects of almokalant in all patients.
Median number of ventricular premature beats with 5-minute intervals during 30 minutes before and after placebo and almokalant infusion.

Pharmacokinetic results. The almokalant plasma concentrations at the end of infusion showed a wide range, from 216 to 690 nmol/L with a mean C_{max} of 390±157 nmol/L (Table III, Figure 4). The pharmacokinetics were best described by the equation of a 2-compartment model. There was a very rapid distribution to extravascular tissues, which accounted for the large interindividual differences in the C_{max} and in the central volumes of distribution. However, the difference between individual plasma levels during the elimination phase was small and a half-life of 2.4±0.1 hours was observed. The volume of distribution at steady state and at equilibrium were similar. The total plasma clearance of 11±1 ml/min/kg indicates that almokalant was rapidly cleared from the body. The 5 patients with ejection fractions ≤35% had a maximal plasma concentration of 457±160 nmol/L, whereas this value in the 4 patients with ejection fractions >35% was 258±54 nmol/L. However, no statistically significant relation between these parameters was found.

Table III. Pharmacokinetic data of almokalant.

Maximum plasma concentration	390±157 nmol/L
Distribution half-life	1.9±0.2 min
Elimination half-life	2.4±0.1 h
Area under the plasma concentration versus time curve	244±30 nmol/L.h
Central volume of distribution	0.16±0.07 L/kg
Volume at distribution equilibrium	2.3±0.3 L/kg
Volume of distribution at steady state	1.8±0.4 L/kg
Total plasma clearance	11.3±1.4 ml/min/kg

Corrected QT interval and almokalant plasma concentration were both maximum at the end of infusion and decreased thereafter without any sign of a hysteresis effect. The relation between these parameters could be best described by: percentage maximal prolongation of corrected QT interval = - 139 + (105 * log plasma concentration). Interpolating the regression line showed a value of log (A50) = 1.8, so that A50 = 63.1 nmol/L. A50 represents the plasma concentration at 50 % of the maximum prolongation of the corrected QT interval (Figure 5).

Adverse events. The first patient had to be withdrawn because the rate of the almokalant infusion was too high. This patient experienced self-terminating episodes of torsades de pointes, from which he recovered uneventfully. In stead of 4.5 mg almokalant in 10 minutes, 3 mg in 3 minutes were given. Also, hypomagnesemia was inadvertently present. No patient developed signs of left ventricular dysfunction or a decrease of blood pressure. One patient reported a transient metallic taste during almokalant infusion.

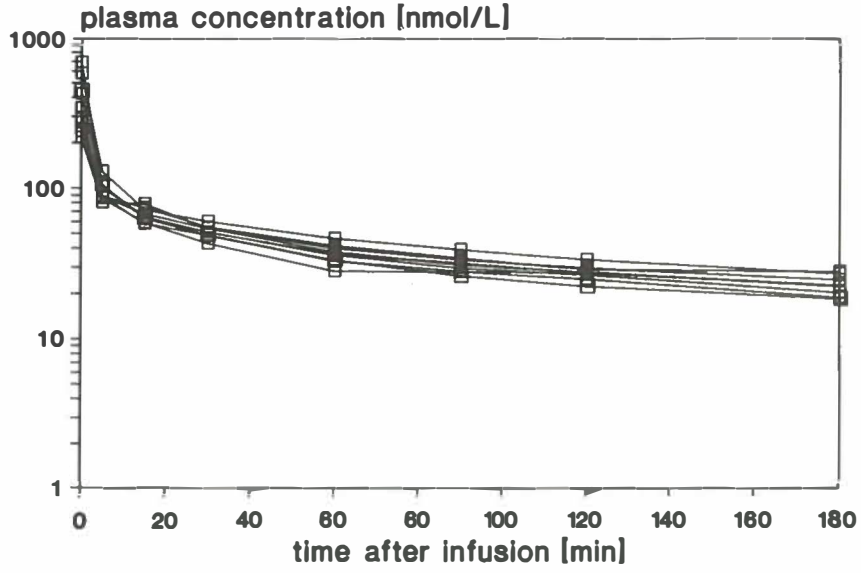

Figure 4. Plasma concentration of almokalant versus time after the infusion of all patients (Y-axis is log scale).

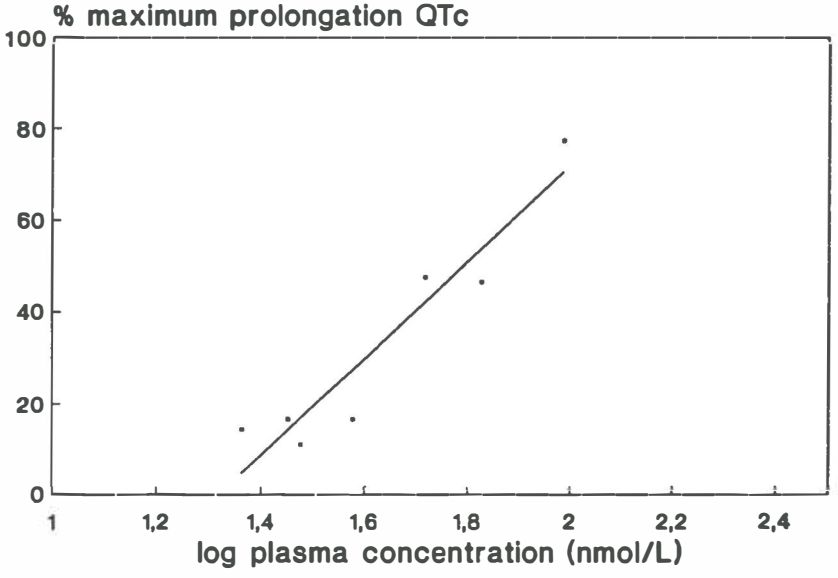

Figure 5. Relation between prolongation of the corrected QT interval and almokalant plasma concentration. Mean values at each time interval were used.

Discussion

The main electrocardiographic effect of almokalant was a significant QT prolongation persisting at least 120 minutes after a single 10-minute infusion. The relatively low sinus rate[9] (preexisting and throughout the study) and the high plasma concentrations[10] may have contributed to the pronounced QT prolongation. Almokalant infusion was accompanied by evident changes of the morphology of the ST-U segment: a flattening of the T wave with increasing U wave. The absence of heart rate changes confirms animal data showing absence of beta blocking effects. In addition, the unchanged PR duration in this study suggests lack of effects on intraatrial or atrioventricular conduction. Finally, almokalant does not influence intraventricular conduction because QRS prolongation was not observed.

Previous studies have shown changes in the signal-averaged electrocardiogram during treatment with antiarrhythmic drugs, which depress conduction velocity[11,12]. To date the disappearance of a late potential has only been observed after antiarrhythmic surgery[13-15]. In animal experiments and in the present study, almokalant had no effects on conduction velocity and therefore no changes in the parameters of the signal-averaged electrocardiogram were found.

The prolongation of refractoriness after almokalant was accompanied by clear antiarrhythmic effects. It reduced the number of ventricular premature complexes for a short time, but this was clinically and statistically significant. In general, the class III effect of an antiarrhythmic drug is not associated with suppression of premature complexes, but with prevention or termination of reentrant phenomena. One may speculate that if prolongation of refractoriness could influence the arrhythmia substrate, the result might be (a) a sudden disappearance of ventricular premature complexes, or (b) an increase in the coupling interval of the premature complex with or without eventual suppression of the arrhythmia. The sudden suppression of ventricular premature complexes during almokalant in 2 patients may be compatible with arrhythmia due to reflection, reentry or abnormal automaticity. Theoretically, these arrhythmia mechanisms are not influenced by potassium channel blockade and their temporal coupling to the normal sinus beat would remain unchanged. As a consequence, extension of the refractory period in the normal myocardium precludes expression of these arrhythmia mechanisms because of exit block. In contrast, the other patients with incomplete suppression of ventricular arrhythmias had a significant increase of the coupling interval. This suggests an arrhythmia mechanism linked to the end of the action potential, resulting in longer coupling intervals of premature complex when the action potential is prolonged by almokalant. It is tempting to hypothesize triggered activity as arrhythmogenic mechanisms.

After infusion, almokalant was rapidly distributed and thereafter rapidly cleared from the body. The pharmacokinetic constants obtained in our patients were comparable to those observed in young healthy male subjects[10]. However, the plasma

level at the end of infusion was higher and the elimination half-life was shorter in our study group. This was mainly due to the smaller volume of distribution, which may have resulted from depressed left ventricular function. However, the difference may also be due to the fact that the pharmacokinetic constants in the healthy subjects are derived from plasma concentrations up to 24 hours after drug administration.

Looking at the changes in the corrected QT intervals after the almokalant infusion, there was an evident concentration-effect relationship. This suggests that the action potential-prolonging effects may be predictable in individual patients, thereby enhancing the clinical applicability of almokalant. Applicability would also include a predictable relation between QT prolongation and antiarrhythmic efficacy. However, a relation between degree of QT prolongation and antiarrhythmic efficacy has so far not been observed[16-18].

With use of the normal infusion rate, no clinically significant side effects or proarrhythmic events occurred. Therefore, almokalant appears safe at the dose tested. In this respect one should note that in the present study, peak plasma concentrations were much higher than in healthy male subjects[10]. Such high concentrations may not be necessary to reach antiarrhythmic efficacy in clinical practice. Only the first patient, receiving infusion at too high a rate, had a proarrhythmic response. Recently, the hypothetical relation between almokalant infusion rate and induction of torsades de pointes was confirmed in animal studies (Carlsson et al., unpublished observations).

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Appendix 9

Torsades de pointes with almokalant, a new class III antiarrhythmic drug

Ans C.P. Wiesfeld, Harry J.G.M. Crijns, Robert H. Bergstrand,

Olle Almgren, Hans L. Hillege, Kong I. Lie

Am Heart J 1993;126:1008-1011

Introduction

Almokalant ((4-[3-[ethyl[3-(propylsulfinyl)propyl]amino]-2-hydroxy-propoxy]-benzonitrile), H 234/09, Astra-Hässle, Sweden) is a new class III antiarrhythmic drug that preferentially blocks the delayed rectifier potassium current[1,2]. It prolongs the monophasic action potential and refractoriness of the atrium and the ventricle without affecting conduction velocity. In addition, it shows positive inotropic effects[1], selectivity between cardiac and central nervous system effects, and is devoid of beta blocking properties.

One of the main issues in the development of new antiarrhythmic drugs is their potential to produce proarrhythmia. Recognition of factors predisposing to class III-related torsades de pointes is mandatory to improve the safety of these agents. We present the first case of torsades de pointes in a patient given almokalant and describe the factors predisposing this patient to this arrhythmia.

Case report

A 54-year-old man with a 13-year-old inferior infarct had palpitations. Physical examination revealed no abnormalities. Hypertension was treated with enalapril. The electrocardiogram showed sinus bradycardia, normal corrected QT interval, and ventricular premature beats. The postextrasystolic pauses ended with a sinus beat accompanied by a change of the TU complex (Figure 1). During exercise testing there were no signs of ischemia, and the incidence of ventricular premature beats remained unchanged. The corrected QT interval increased from 367 to 444 ms at peak exercise. The 48-hour Holter recording showed 1375 ventricular premature beats/hr (median). The echocardiogram was normal, with a left ventricular ejection fraction of 61%. Coronary angiography revealed a 100% occlusion of the right coronary artery. After giving written informed consent, the patient participated in a double-blind, placebo-controlled study on the effects of almokalant[3]. The study was approved by the Institutional Review Board. During infusion of almokalant the TU complex showed extreme changes: marked widening and flattening of the T wave, which separated clearly from a giant U wave, followed by a ventricular tachycardia (Figure 2). The infusion was stopped prematurely after 3 minutes (total dose 3 mg). Frequent self-terminating episodes of torsades de pointes and tachycardias occurred during the next 6 minutes (Figure 3). All tachycardias were preceded by a short-long-short RR sequence. All long intervals ended with a normally conducted sinus beat. This beat showed a significant malformation of the TU complex and was followed by ventricular tachycardia (Figure 2).

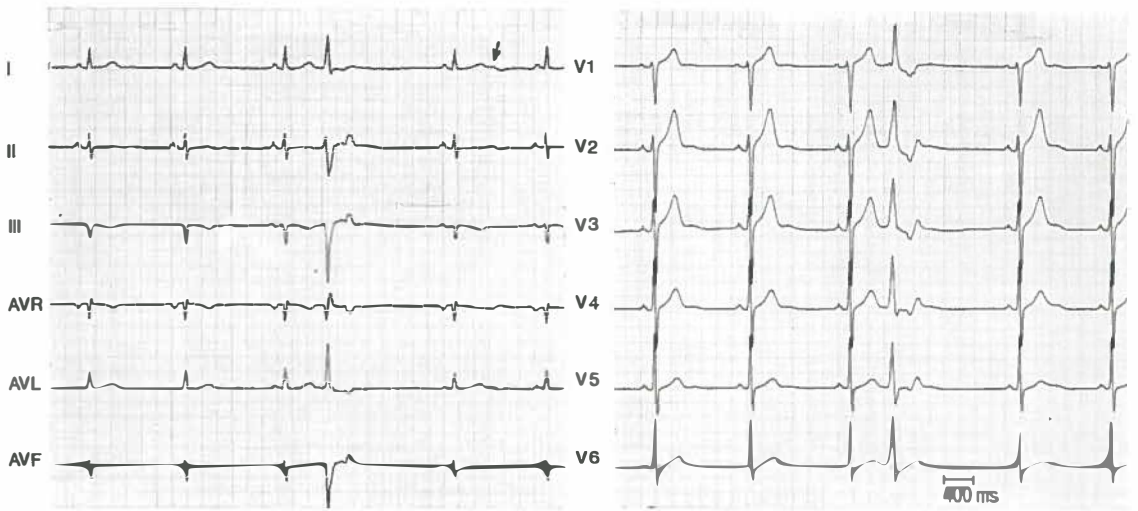
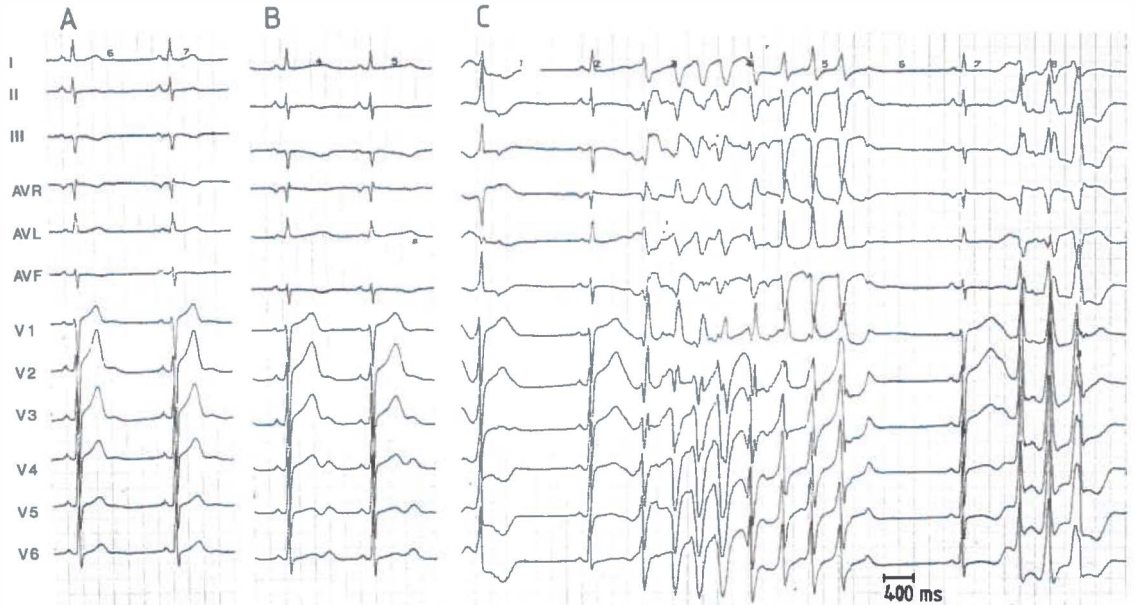


Figure 1. Electrocardiogram before almokalant infusion. Corrected QT interval 398 ms. Note the TU complex change after the long pause (arrow).


A
B
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I
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AVR
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400 ms

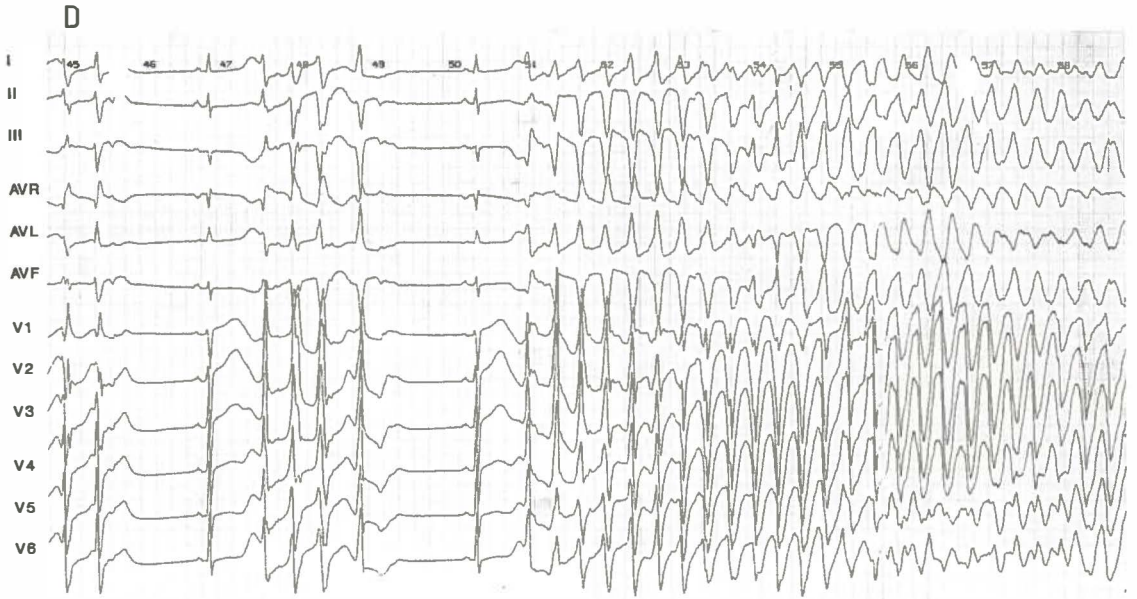

Figure 2. Electrocardiogram during infusion of almokalant. At A infusion starts. During infusion (B) there is a progressive change in the TU complex with marked widening and flattening of the T wave, which seperated clearly from a giant U wave, followed by nonsustained polymorphic ventricular tachycardia (C). Note RR short-long-short sequences at initiation of the tachycardia. Occurrence of ventricular tachycardias did not depend on duration of first short cycle (the pre-initiating cycle)[4] or following long cycle (the initiating cycle)[4] (regression analysis, $p>0.05$). However, number of tachycardia beats increased at shorter pre-initiating cycle lengths (Spearman rank correlation $r=-0.32$, $p=0.03$). At C the infusion was stopped, but a few moments later the patient had torsades de pointes (D).

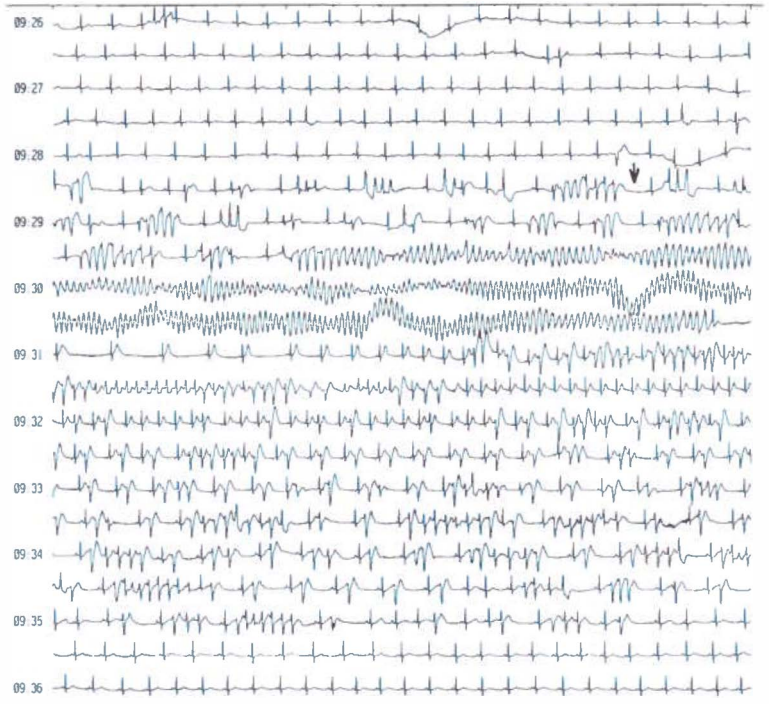

Figure 3. Holter recording during infusion of almokalant.
At 9.26 hours the infusion started. Arrow: infusion stopped prematurely.

The ratio of the U and T wave amplitude increased from 0.2 to 1.4. After clinical stabilization, blood samples were taken. Magnesium concentration was 0.69 mmol/L (normal >0.74). Although delay of sampling and the short half-life of almokalant must betaken into account, the plasma concentration was low: 76 nmol/L. Almokalant given as 4.5 mg over 10 minutes in nine other patients showed an increase of the corrected QT interval from 445±18 to 548±53 ms (mean±SD) at a plasma concentration of 390±157 nmol/L. In these patients no proarrhythmic events were observed[3]. When the pharmacokinetic parameters from this group were used to calculate the supposed maximum plasma concentration in our patient, it could have been 400 nmol/L. When the calculation was based on the highest range of concentrations, the peak level might have been as high as 900 nmol/L. However, the terminal half-life of almokalant in the present patient was 2.2 hours, which is close to the mean value of the total group (2.4±0.1 hours).

After informed consent was obtained, the antiarrhythmic efficacy of 1 mg/kg sotalol in 10 minutes was evaluated. Sotalol suppressed spontaneous ventricular bigeminy and trigeminy (plasma concentration 7.5 mg/L). This procedure was uneventful.

Discussion

The present patient exhibited a proarrhythmic response to an investigational class III drug. Several previously described predisposing factors were identified[4-6]. An important feature in this case was the observation that occurrence of the torsades de pointes could be related to infusion rate. Studies in a rabbit model of proarrhythmia[7] indicated that increased dispersion of refractoriness was present when the arrhythmia appeared at infusion of almokalant or other developmental class III agents. More importantly, the dispersion and the arrhythmia incidence was significantly greater at rapid than at slow infusion rates (unpublished observations).

The present proarrhythmic event may be related to the infusion rate, which was suggested by the almost immediate restoration of sinus rhythm after termination of the infusion. An arrhythmia resulting from an idiosyncratic response would, in all probability, have been of longer duration. It may be conjectured that an excessive catecholamine level induced by tachycardia related hypotension prevented an ongoing idiosyncratic reaction through overdrive. However, overdrive from a sinus mechanism was not seen in the immediate period after the torsades de pointes (Figure 3).

In retrospect, this patient may have been prone to drug-related torsades de pointes. This is suggested by preexisting electrocardiographic characteristics also found in the acquired long-QT syndrome: pause-dependent TU complex changes[5] and an abnormal response of the QT interval during exercise[6]. These features point

at a forme fruste of the long QT syndrome with associated susceptibility for the development of triggered activity in the presence of appropriate triggers. Also, comparable to torsades de pointes during quinidine treatment, the proarrhythmia occurred soon after the first almokalant administration, maybe even before therapeutic or toxic plasma concentrations were reached. Further, it must be noted that the preexisting sinus bradycardia may have facilitated an adverse response by exposing reversed use-dependent effects. Finally, the absence of torsades de pointes during standard intravenous (i.e. at a normal infusion rate) and oral sotalol testing does not exclude an idiosyncratic response, because torsades de pointes during one antiarrhythmic drug does not imply the same reaction during another class Ia or III drug.

In view of the above mentioned, torsades de pointes with almokalant may be primarily infusion-rate related, yet only occurring in the setting of predisposing factors. Although the predictive value of predrug electrocardiographic abnormalities remains to be established, the present report supports the view that torsades de pointes on drugs may be predicted by closely examining the baseline electrocardiogram for characteristics suggesting a forme fruste of the long-QT syndrome[4-6]. Meanwhile, it seems advisable to use almokalant only at a slow infusion rate, especially in presumed susceptible patients, and to be alert on TU complex changes at the initial stages of the infusion.

Preliminary in vitro animal experiments with almokalant suggested differential effects on Purkinje fibers and ventricular muscle cells, inducing prolongation of the action potential duration and early afterdepolarizations in Purkinje fibers, but not in ventricular muscle cells. In addition, in vivo animal experiments suggested that the induction of dispersion of refractoriness, as reflected by the difference between the shortest and the longest QT interval on the 12-lead electrocardiogram, was related to the rate of almokalant infusion (unpublished observations). This suggests the presence of both early afterdepolarizations and dispersion of refractoriness, as mechanisms for proarrhythmia during almokalant administration in the present patient.

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Appendix 10

Retrospective case-control study

on drug-induced long QT-related arrhythmias

Description of the protocol and

preliminary report of the patients with torsades de pointes

Introduction

Torsades de pointes is the Achilles' heel of class Ia and 3 antiarrhythmic drug treatment. It appears that selective delayed rectifier blockers may also produce this complication[1]. Further development of these new drugs is however highly desirable since they may be more effective and could be an alternative for other ineffective or arrhythmogenic drugs. Recognition of the factors predisposing to antiarrhythmic drug related torsades de pointes is mandatory to improve the safety of these agents. Moreover, these drugs cannot be used for patients with non-life-threatening arrhythmias if the patient at risk cannot be definitely identified. Previous studies described predisposing factors for the development of a proarrhythmic response during quinidine treatment[2-7]. More recently, attention has been focused on the predictive value of predrug electrocardiographic abnormalities suggesting a forme fruste of the long QT syndrome[1,7-9]. These abnormalities can also be found in the acquired long QT syndrome: pause-dependent TU complex changes, an abnormal response of the QT interval during exercise[10] and QT dispersion on the 12-lead electrocardiogram[11,12]. To diagnose the patient susceptible to the development of a proarrhythmic event, it is essential to document extensively all cases of torsades de pointes occurring during treatment with antiarrhythmic drugs prolonging the cardiac action potential.

To identify patient and electrocardiographic characteristics relevant to the development of torsades de pointes during treatment with antiarrhythmic drugs delaying repolarization, we performed a retrospective case-control study. Data of proarrhythmia patients were compared with those of matched-control patients to identify characteristics possibly predisposing to torsades de pointes. In the present preliminary report the methods of the study will be described. Subsequently, preliminary data on the 40 torsades de pointes cases included in this study will be given.

Methods

Study design. This is an exploratory retrospective, case-control study. Patients who had experienced torsades de pointes either nonsustained or sustained with deterioration in ventricular fibrillation during either oral or intravenous treatment with an antiarrhythmic drug delaying repolarization, were studied and compared with matched-control patients.

Recruitment of the patients with proarrhythmia. Identification of patients was carried out by contacting hospitals with a department of cardiology and coronary care facilities. The hospitals enrolled were from countries in Europe and in the United States. A clinician was identified as co-investigator in each hospital. This

clinician was requested to inform the field-investigator concerning possible patients. It was arbitrarily decided to include a total number of 40 patients with proarrhythmia. Recruitment of these patients started in July 1994 and was completed in November 1994. Included were patients who had experienced torsades de pointes during oral or intravenous treatment with a class Ia or 3 antiarrhythmic drug. This included the following drugs: d,l-sotalol, quinidine, procainamide, disopyramide, amiodarone and investigational class 3 agents. Excluded were poorly documented patients. The final decision whether a patient qualified as a case with proarrhythmia was made by the principal investigators.

Recruitment of the matched-control patients. The matched-control patients were recruited from 2 centers: Groningen University Hospital, The Netherlands and Sahlgrenska Hospital Göteborg, Sweden. In these hospitals the departments of cardiology have a computerized registry of patients with arrhythmias and their antiarrhythmic drug treatment. Two matched-control patients had to be identified for each patient with proarrhythmia. The matching criteria were: (a) age (within the range of $\pm$ 5 years), (b) sex, (c) the arrhythmia treated, (d) antiarrhythmic drug, (e) phase of treatment (loading or maintenance), (f) comparable ejection fraction, and (g) if applicable, conversion to sinus rhythm. Excluded as matched-control patients were those with a history of proarrhythmia during antiarrhythmic drugs delaying repolarization. Patients were also excluded in case of poor electrocardiographic documentation before initiation or during antiarrhythmic drug treatment. The final decision whether a patient qualified as a matched-control patient was made by the principal investigators.

Description of the patients with proarrhythmia. The following patient characteristics were collected: demographic data, cardiovascular and noncardiovascular history, arrhythmia and family history, smoking or alcohol abuse, concomitant medication and preceding changes of all medications including the antiarrhythmic drug. The New York Heart Association classification for exercise tolerance at the proarrhythmic event was noted. The results of physical examination before and at the proarrhythmic event were evaluated with special attention for signs of heart failure. Laboratory data were noted at the same points in time, including electrolyte disturbances (sodium, potassium, calcium, magnesium) and representatives of renal, hepatic, and thyroid function. In case of missing data at the proarrhythmic event the data were taken from either before or after the event within 24 hours.

A routine 12-lead electrocardiogram before and during antiarrhythmic drug treatment was analyzed. In the case patients the last electrocardiogram before the proarrhythmic event was taken as electrocardiogram during antiarrhythmic treatment. If this was not available, the first after the proarrhythmic event was taken. Evaluation included heart rate and rhythm, PR, QRS and QT intervals, pathological Q waves, ST-segment abnormalities, QT dispersion, and TU wave morphology. TU-

morphology was classified according to Figure 1. This classification was modified after Moss and Robinson[13].

If available, results of exercise tolerance tests and 24-hour Holter monitoring with or without antiarrhythmic drug were included in the analysis. Attention focused on rate-dependent changes of the QT interval and TU wave morphology.

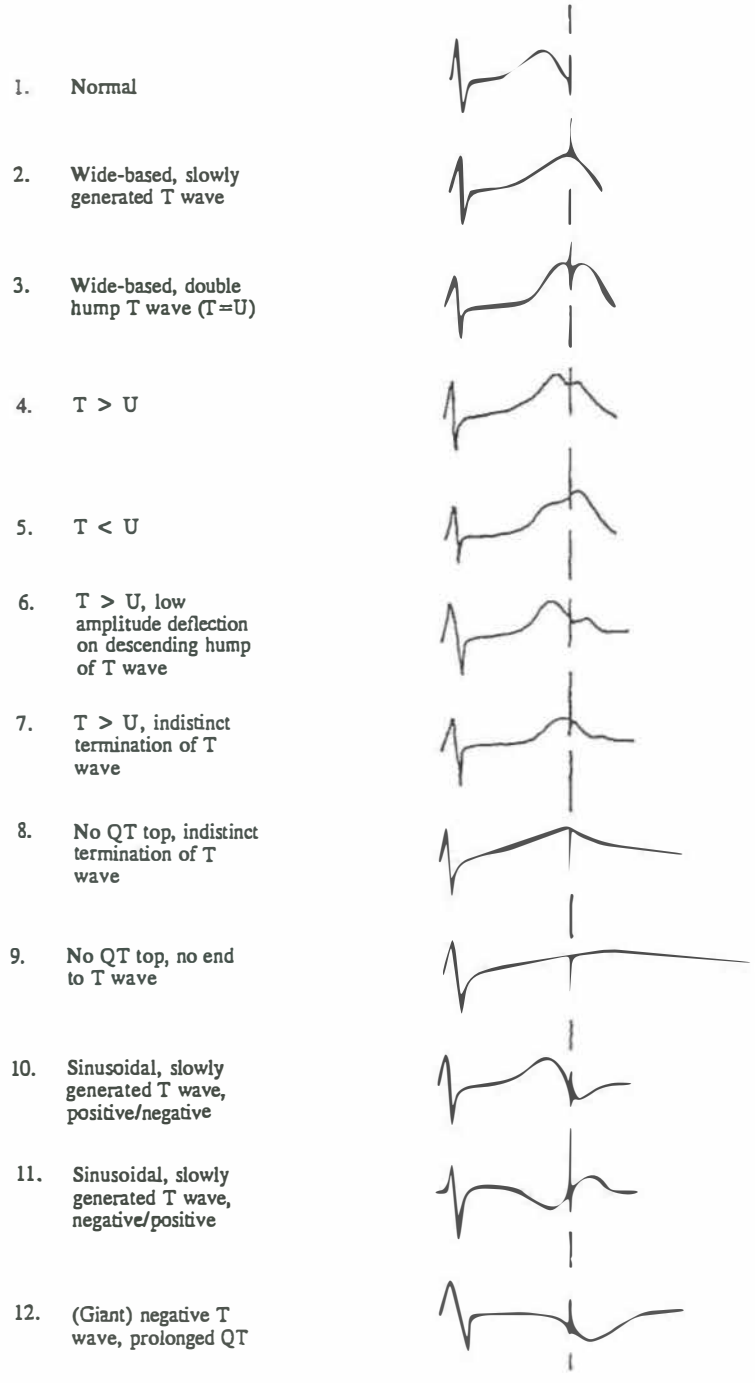
Description of the proarrhythmic event. The electrocardiographic initiation of the proarrhythmic event was analyzed carefully. This included: the preceding heart rate and rhythm, QT interval, preceding RR sequences. In addition, actions taken to terminate the proarrhythmia and outcome were noted.

Description of the characteristics of the matched-control patients. The same data as noted above in the case patients were collected in the controls. For comparison with data at the proarrhythmic events in the cases, data obtained in control patients were taken either during the loading or maintenance phase.

Definitions. Torsades de pointes was defined as a ventricular tachyarrhythmia with undulating peaks of sequential QRS complexes and T waves, occurring in the setting of QT interval prolongation and abnormal TU wave[7,14]. Nonsustained ventricular tachycardia was defined as a tachycardia of at least 6 ventricular beats with a rate above 100 per minute and lasting for less than 30 seconds, without hemodynamic collapse. A sustained ventricular tachycardia was defined as lasting for more than 30 seconds or requiring an intervention within 30 seconds because of hemodynamic collapse. Sudden cardiac death was defined as natural death due to a cardiac cause, heralded by an abrupt loss of consciousness within 1 hour after onset of symptoms or during sleep, in the absence of increasing angina or overt heart failure[15].

Measurement of QT interval. For comparing QT intervals the same lead (as a rule lead V2 or V3) was chosen before and during antiarrhythmic drug treatment. In each lead 3 QT intervals were measured and averaged. The QT was measured from the beginning of the QRS to the end of the U wave. Correction of the QT interval (QTc) was done with Bazett's correction formula, i.e. $QTc = QT(ms)/\sqrt{RR(s)}$, and the QT linear corrected according to Sagie and colleagues, i.e. $QT_{LC} = QT + 0.154*(1 - RR)$ [16,17]. In case of atrial fibrillation the following formulas were used[18]: modified $QTc = QT \times \sqrt{RR\text{-modified}}$, where $RR\text{-modified} = (5(RR1) + 2(RR2) + RR3 + RR4 + RR5) / 10$. In the latter formulas the minimum required RR intervals was 3. QT dispersion was expressed as the difference between the shortest and the longest QT duration. QT normalization for QT dispersion is obtained by dividing the QT dispersion by the square root of the number of available leads[19]. QT dispersion < 50 ms was considered normal[20-22].

Figure 1. TU wave classification.



Statistical considerations. Statistical analysis was performed by the Trial Coordination Center (University Hospital Groningen, The Netherlands). The design of this study was an exploratory case-control study. No pretest hypothesis concerning exposure rates of presumed risk factors were made and no sample sizes have been calculated. In the first analysis phase the case and control subjects were compared for statistical equality on a variety of clinical features including those used as matching variables. In the second phase the odds ratios (OR) were calculated for the association between antiarrhythmic drugs delaying repolarization, patient specific parameters and the risk of subsequent proarrhythmia. Since both cases and controls were assembled using matching techniques, all the ORs were calculated whenever possible using procedures for matched data. Stochastic significance of the OR were estimated using 95% confidence intervals. After estimating the univariate OR, additional logistic multivariate analysis based on matched data were performed to refine the relationship further and to assess the presence of possible biases.

In the present preliminary report of the proarrhythmia patients descriptive statistics were used. Normally distributed data are given as mean $\pm$ 1 standard deviation. All the statistical calculations were conducted with standardized biomedical algorithms (SPSS/PC+, SPSS, Inc., Chicago, IL, USA).

Preliminary results of the patients with proarrhythmia.

Baseline characteristics of the proarrhythmia patients. The baseline characteristics of the 40 patients with proarrhythmia are summarized in Table 1 and described in Table 2. There was a female predominance. A relatively high number of patients were in New York Heart Association class $\geq$III for exercise tolerance. Digoxin and diuretics were used simultaneously in 16 patients. One patient used amitriptyline.

Noncardiovascular diseases were noninsulin-dependent diabetes mellitus in 5 patients, chronic obstructive pulmonary disease in 3 patients, corrected thyroid dysfunction in 3 patients, treated cancer in 6 patients, and cerebrovascular accidents in 3 patients. One patient had Morbus Steinert and was treated with an investigational class 3 antiarrhythmic drug intravenously because of atrial fibrillation. This patient had neither electrocardiographic conduction disturbances nor signs of a sick sinus syndrome, and left ventricular function was normal.

Seven patients had their proarrhythmic event during intravenous infusion, in all 7 cases a class 3 drug: 1 patient during d,l-sotalol and 6 patients during an investigational class 3 drugs. Two of these 7 patients received a therapeutic dose, 3 patients received a high therapeutic dose and 2 patients received a too high intravenous dose.

Table 1. Characteristics of the proarrhythmia patients

Number of patients (female %)	40	(68%)
Age (years)	65±10	
History of smoking	17	(43%)
History of alcohol abuse	4	(10%)
Underlying heart disease *		
Old myocardial infarct	7	(18%)
Cardiomyopathy	11	(28%)
Valve disease	8	(20%)
Hypertension	13	(33%)
No evident structural heart disease	8	(20%)
Arrhythmia treated		
Atrial fibrillation ± atrial flutter	34	(87.5%)
Atrioventricular nodal tachycardia	1	(2.5%)
Premature ventricular beats ± nonsustained VT	2	(5%)
Sustained VT/VF	2	(5%)
History of treated arrhythmia, median (range)	2 years (1 day-16 years)	
NYHA for exercise tolerance ≥III at event	11	(28%)
LVEF >40% (n)	27	(68%)
≤40% (n)	10	(25%)
Echocardiographic data (n=36)		
LVEDD (mm)	54±7	
LVESD (mm)	38±9	
LA (mm)	44±6	
Septal thickness (mm)	11±2	
Posterior wall thickness (mm)	10±1	
Antiarrhythmic drug: oral / intravenously	33/7	(82/18%)
Quinidine	7	(18%)
Disopyramide	1	(2.5%)
d,l-Sotalol	23	(57.5%)
Investigational class 3 drugs	9	(23%)
Daily dose: low-therapeutic dose	25	(62.5%)
high therapeutic dose	12	(30%)
too high dose	3	(7.5%)
Concomitant medication (n) *		
digoxin	22	
diuretics	25	
ACE inhibitors	9	
beta blocker	3	
calcium antagonists	14	
nitrates	4	
coumarines	25	

All data mean ± SD. Abbreviations see Table 2. *ACE:* angiotensin converting enzyme; *LVEF:* left ventricular ejection fraction; *n:* number of patients. * more than one entity possible per patient.

Table 2. Baseline characteristics of all patients with proarrhythmia in the order they were reported to the field-investigator

Pn/Sex/ Age(yrs)/ Arrhythmia	Underlying HD	AAD/iv	Duration of R_x (days)	NYHA	EF (%)	Echocardiographic data LVEDD /LVESD (mm)	LA (mm)	Septum/ Posterior wall (mm)	QTc/ QTcAAD (ms)
1. M54 nsVT, VPC	OMI,HYT	3,iv	*	I	61	60/45	-	11/9	401/661
2. F59 AVNT	none	s	1	I	>40	-	39	-	493/960
3. F58 AF	none	3,iv	*	I	65	41/29	32	10/9	467/552
4. F74 AF	none	s	18	II	>40	61/53	-	-	-
5. M51 AF	DCM	3,iv	*	II	17	70/60	49	-	385/473
6. M61 AF	OMI	3,iv	*	I	46	51/39	50	16/11	464/641
7. F75 AF/AFL	HYT	3	1	I	>40	40/-	44	-	408/667
8. M68 AF	OMI	3,iv	*	I	36	41/29	46	10/10	-
9. F72 AF/AFL	MS,MR,AoS,AoR	q	4974	I	81	47/27	52	15/12	411/697
10. F70 AF	none	3	3	II	>40	59/39	43	10/9	378/555
11. M67 AF	MR	q	*	I	26	58/50	48	8/7	506/631
12. M63 AF	none	q	6	I	>40	48/30	-	-	471/688
13. F62 AF	HYT, LVH	s	>30	I	64	45/32	43	11/10	490/596
14. F64 AF	MVR	s	5	III	35	56/43	65	11/11	410/538
15. F70 AF	HYT	s	53	I	≤40	60/50	50	-	513/566
16. F54 AF	MS, HYT,(Tubbs)	d	4	I	?	54/34	50	10/9	437/729
17. M65 AF	CM	q	*	IV	≤40	65/50	45	-	404/701
18. F74 AF	none	s	5	I	>40	50/40	36	7/7	-
19. F80 AF	CM	s	7	IV	≤40	60/48	37	11/10	445/598
20. M52 sVT,VF	OMI (CABG)	s	1	III	11	-	-	-	474/644

21. F74	AF	OMI, HYT	s	628	II	>40	54/32	46	16/10	646/743
22. F81	AF	none	s	62	I	>40	49/32	40	11/9	—/619
23. F67	AF	HYT	s	2	II	>40	55/45	48	11/8	390/567
24. M75	AF	CM	s	45	III	?	63/45	43	11/9	437/486
25. F64	AF/AFL	HYT, ASD	3,iv	*	I	>40	46/27	44	10/-	462/772
26. M57	AF	CM	s	33	III	41	50/39	48	10/11	-
27. M61	AF	CM	s	1	III	?	65/-	-	-	492/645
28. F67	AF	none	s	595	I	65	50/27	-	11/9	435/635
29. F54	AF	MS, MVR	q	10	II	74	53/34	55	9/9	-
30. M52	AF	CM	3	*	I	47	57/46	-	12/10	295/636
31. F72	AF,VPC	HYT, MI	q	1	I	>40	-	38	-	477/600
32. F25	sVT,VPC	cong HD, VT surgery	s	557	I	68	48/33	31	10/-	-
33. F70	AF/AFL	HYT, MVP, MR	q	1	III	>40	55/31	42	10/-	-
34. F73	nsVT,VPC	CM, HYT	s	5	II	40	58/38	-	-	407/655
35. F59	AF,APC	HYT	s	1088	II	>40	51/39	43	8/11	434/717
36. F80	AF	OMI	s	249	IV	45	-	-	-	458/602
37. F73	AF/AFL	HYT	s	22	II	78	50/27	51	14/12	467/791
38. M56	AF	CM	s,iv	*	III	53	62/-	45	-	-
39. F79	AF/AFL	OMI	s	95	IV	>40	49/26	44	-	405/642
40. F80	AF	CM, AoS	s	1390	I	30	56/-	-	-	-

AAD: antiarrhythmic drug (d=disopyramide, q=quinidine, s=d,l-sotalol, 3=investigational class 3 drug); *AF/AFL:* atrial fibrillation/atrial flutter; *AoR:* aortic valve regurgitation; *APC:* atrial premature contraction; *ASD:* atrial septal defect; *AoS:* aortic valve stenosis; *AVNT:* atrioventricular nodal tachycardia; *CABG:* coronary artery bypass grafting; *CM:* cardiomyopathy; *cong HD:* congenital heart disease; *EF:* ejection fraction; *i.v.:* intravenously; *LA:* left atrium; *LVEDD:* left ventricular end-diastolic diameter; *LVESD:* left ventricular end-systolic diameter; *LVH:* left ventricular hypertrophy; *MR:* mitral valve regurgitation; *MS:* mitral valve stenosis; *MVP:* mitral valve prolaps; *MVR:* mitral valve replacement; *nsVT:* nonsustained ventricular tachycardia; *NYHA:* New York Heart Association classification for exercise tolerance; *OMI:* old myocardial infarct; *pn:* patient number; *QTc:* QT interval corrected for heart rate; *HYT:* hypertension; *Rx:* duration of treatment in days; *sVT,VF:* sustained VT, ventricular fibrillation; *VPC:* ventricular premature contractions. * proarrhythmia within 24 hours after the first prescription of the antiarrhythmic drug.

The other 33 patients had their proarrhythmic event during oral treatment. Three patients received a therapeutic oral dose of an investigational class 3 drug. A daily dose of quinidine below 1200 mg was considered low therapeutic (4 patients) and 1200 to 1500 mg daily was considered therapeutic (3 patients). None of the patients received a daily dose above 1500 mg. A daily dose of 80-120 mg d,l-sotalol was considered as low therapeutic dose (3 patients), 160 mg and 240 mg daily were considered therapeutic (9 patients), while 320 mg and 480 mg were considered high therapeutic (9 patients). One patient performed attempted suicide with 1600 mg of d,l-sotalol (nr. 32). The patient with the proarrhythmia during disopyramide received 600 mg daily which was considered therapeutic.

The potassium plasma level was below the lower limit at the proarrhythmic event in 9 out of 38 patients (24%), the magnesium plasma level in 2 out of 19 patients (11%) and the calcium level in 2 out of 23 patients (9%). The number of patients with significantly abnormal laboratory values of renal and hepatic function at the time of the proarrhythmic event, was high. Creatinine was above the upper limit of normal in 3% and 8% of the patients, at the start of the antiarrhythmic drug and at the proarrhythmic event, respectively. These values were for aspartate aminotransferase 9% and 36%, and for alanine aminotransferase 8% and 40%.

Sixteen patients had their proarrhythmic event $\leq$24 hours after the start of the antiarrhythmic drug (including the 7 patients treated intravenously), 8 patients within 1 week, 4 patients within 1 month and 12 patients after more than 1 month treatment with the antiarrhythmic drug. In Table 3 the patients having their proarrhythmic event early ($\leq$ 24 hours) and late (>24 hours) after the start of the antiarrhythmic drug are compared. The early patients seem to have more frequently an old infarct and less frequently no underlying heart disease. In addition, these patients had a higher heart rate preceding the event and a lower left ventricular ejection fraction. However, New York Heart Association for exercise tolerance is comparable in both groups. Although QTc without antiarrhythmic drug was shorter in the patients with early proarrhythmia, the QTc during antiarrhythmic drug treatment was longer than in the patients with late proarrhythmia. The incidence of electrolyte disturbances at the proarrhythmic event was comparable in both groups. Patients with late proarrhythmia used more frequently digoxin and diuretics. In a rather high percentage of the patients with late proarrhythmia the antiarrhythmic drug dose was increased recently.

Table 3. Early versus late proarrhythmia

	Early ≤ 24 hours	Late >24 hours
n	16	24
Underlying heart disease		
Old myocardial infarct	4 (25%)	3 (13%)
Cardiomyopathy	5 (31%)	6 (25%)
Valve disease	3 (19%)	5 (21%)
Hypertension	5 (31%)	8 (33%)
No evident structural heart disease	2 (13%)	6 (25%)
Arrhythmia treated		
Atrial fibrillation ± atrial flutter	13	22
Atrioventricular nodal tachycardia	1	-
Premature ventricular beats ± nonsustained VT	1	1
Sustained VT/VF	1	1
NYHA ≥ III	5 (31%)	6 (25%)
LVEF >40 (n)	10 (63%)	17 (71%)
≤40 (n)	5 (31%)	5 (21%)
Daily dose		
low-therapeutic dose	10 (63%)	15 (63%)
high therapeutic dose	4 (25%)	8 (33%)
too high dose	2 (12%)	1 (4%)
Heart rate at event (bpm)	61±19	53±12
QTc without AAD (ms)	441±57	459±72
QTc with AAD (ms)	660±110	635±78
Digoxin and diuretics	5 (31%)	11 (46%)
Electrolytes below normal value at proarrhythmic event	31%	29%
potassium (n)	3	6
magnesium (n)	1	1
calcium (n)	1	-
Increase of AAD dose (n)	1*	8 (33%)@

For explanation of the abbreviations see Table 1 and 2. * This patient received several antiarrhythmic drugs within 24 hours. @ All patients used d,l-sotalol.

Analysis of the 12-lead electrocardiograms. The results of the 12-lead electrocardiogram with and without antiarrhythmic drug are summarized in Table 4. Heart rate was lower during antiarrhythmic drug treatment. On the 12-lead electrocardiogram the incidence of premature (supra)ventricular beats was very low. PR interval and QRS duration were unaffected by the antiarrhythmic drug. In 15 patients the QTc interval was above 440 ms without antiarrhythmic drug treatment. This high number of patients with a prolonged QT interval may be due to the fact that we measured the QT interval until the end of the U wave.

Table 4. Data of the 12-lead electrocardiogram

	Without AAD	With AAD
Available number of ECGs	38	37
Heart rate (bpm)	80±31	61±17
Rhythm		
Sinus rhythm	21	31
Sinus bradycardia	8 (38%)	19 (61%)
Atrial fib/flutter	17	4
AV nodal escape rhythm	-	1
Junctional tachycardia	-	1
PR interval (ms)	168±32	176±34
QRS duration (ms)	97±24	97±27
QT interval (ms)	413±79	652±110
QTc interval (ms)	451±67	645±94

Data are given as mean ± SD. *AAD:* antiarrhythmic drug delaying repolarization; *Atrial fib:* atrial fibrillation; *AV:* atrioventricular; *bpm:* beats per minute; *ECG:* electrocardiogram.

TU wave morphology was considered abnormal in one of the leads of the 12-lead electrocardiogram in 6 patients (16%) in the absence of antiarrhythmic drug treatment. By contrast, during antiarrhythmic drug treatment the incidence was 89%. Without antiarrhythmic drug treatment 46% of the total number of classified leads were considered abnormal versus 96% during antiarrhythmic treatment (Table 5). On treatment the classifications 2, 9 and 12 were scored most frequently. Classes 9 and 12 seemed to emerge only after initiation of treatment.

Table 5. Classification of TU wave morphology. Percentages are given of the incidence of a TU class on the total number of leads scored.

		Without AAD	With AAD
Number of ECGs		38	37
Number of ECGs with abnormal TU wave		6 (16%)	33 (89%)
TU wave morphology class	1	45%	4%
	2	17%	25%
	3	8%	1%
	4	4%	3%
	5	6%	6%
	6	-	4%
	7	-	0.5%
	8	-	1%
	9	6%	19%
	10	2%	0.7%
	11	8%	9%
	12	4%	25%

AAD: antiarrhythmic drug delaying repolarization; *ECG:* 12-lead electrocardiogram.

Table 6. Observations during proarrhythmic event

Registration of torsades de pointes	36
Number of available ECG leads	
1-lead rhythm strip	21
2-leads	8
3-leads	1
6-leads ECG	1
12-leads ECG	5
Heart rate before arrhythmia (bpm)	57±16
Preceding short-long-short RR sequences (n)	
yes	33
no	1
unknown*	6
Initiation of short-long-short RR sequences by	
premature supraventricular beats	1
premature ventricular beats	26
both	6
Preinitiating cycle length (ms)	502±141
Initiating cycle length (ms)	1337±353
Coupling interval of arrhythmia (ms)	598±113
Actions taken to terminate the arrhythmia:	
Spontaneous recovered	
without any interventions	7
Cardioversion	17
Potassium intravenously	6
Magnesium intravenously	8
Isoprenaline intravenously	8
Pacing	10

All data mean±SD. *bpm:* beats per minute; *n:* number of patients. * In 4 patients the recording of the proarrhythmic event was not available and in 2 patients the initiation of the proarrhythmic event was not recorded.

Observations regarding the proarrhythmic event. Observations during the proarrhythmic event are summarized in Table 6. Torsades de pointes was recorded mostly on a one lead rhythm strip. Of the total group 24 patients were in sinus rhythm with premature beats and 8 patients in atrial fibrillation. Other rhythms observed at the event were atrial tachycardia with short-long-short RR sequences (1

patient), atrioventricular nodal rhythms (3 patients) and sinus rhythm with 2:1 atrioventricular block (1 patient). In 3 patients the rhythm could not be determined. Of note, 20 of the 35 patients (57%) with atrial fibrillation or flutter as treated arrhythmia were in sinus rhythm with supraventricular and/or ventricular premature beats immediately before the proarrhythmic event.

In all patients, except one, torsades de pointes was preceded by a short-long-short RR sequence. In 6 patients these sequences were initiated by supraventricular or ventricular premature beats. In 1 patient only supraventricular premature beats were seen.

None of the patients died because of the proarrhythmia. However, 17 patients underwent cardioversion because of the tachyarrhythmia. Baseline New York Heart Association classification for exercise tolerance and left ventricular function were not diiferent between those who were cardioverted and those who were not (Table 7).

Interestingly, in one patient with atrial fibrillation (nr. 11) torsades de pointes on quinidine was reproduced by disopyramide. On both accasions bradycardia was present, first due to high levels of digoxin, significantly reducing the ventricular rate during atrial fibrillation and on the second occasion due to beta blockade with atenolol, depressing the spontaneous sinus rate.

One patient's history (nr. 12) revealed atrial fibrillation with collapse and commotio cerebri. After electrical cardioversion the electrocardiogram showed first degree atrioventricular block and right bundle branch block with left posterior hemiblock. During subsequent treatment with quinidine this patient developed torsades de pointes (ECG data not available). In retrospect this patient had already severe atrioventricular conduction disturbances and presumably quinidine caused bradycardia through advanced atrioventricular block, thereby setting the stage for reversed use-dependent torsades de pointes.

Table 7. Left ventricular function in the case patients who underwent cardioversion versus those who did not (3 missing values).

		No cardioversion	Cardioversion
n		23	17
NYHA ≥ III		30%	24%
LVEF	>40%	17	10
	≤40%	6	4

Abbreviations see Table 1 and 2.

Discussion

The last decade the prescription of antiarrhythmic drugs changed tremendously. Due to the results of the Cardiac Arrhythmia Suppression Trial[23] and meta-analyses[24-28] clinicians prescribe more often class 3 drugs. Unfortunately, like class 1a antiarrhythmic drugs, class 3 drugs also may show the typical proarrhythmia torsades de pointes. In the present study 80% of the proarrhythmic events were during treatment with a class 3 drug, either d,l-sotalol (58%) or an investigational class 3 drug (22%). The risk of torsades de pointes with the newer class 3 drugs may be higher than with d,l-sotalol or amiodarone. The proarrhythmia risk probably is: new class 3 antiarrhythmic drugs > d,l-sotalol > amiodarone[29-31]. This brings into question if selective potassium channel blockade is desirable. In the present study the high incidence of proarrhythmia with class 3 drugs probably reflects the higher prescription rates of these agents rather than a higher incidence of proarrhythmia with these drugs compared to class 1a drugs.

Identification and definition of torsades de pointes. In a rather high number of patients torsades de pointes was diagnosed from a one lead rhythm strip. The definite identification of proarrhythmia from a one lead rhythm strip is however difficult, especially in patients with underlying ventricular tachyarrhythmias. In these patients, an arrhythmia recurrence during antiarrhythmic drug treatment may represent either inefficacy or proarrhythmia. In addition, polymorphic ventricular tachycardia often resembles torsades de pointes on a one lead rhythm strip. In this setting the initiation and the morphology of the arrhythmia has to be taken into account and compared with baseline in that patient. In the present study this problem was not frequently encountered since only few patients had a ventricular tachycardia as underlying arrhythmia.

Previous reports stressed that drug-induced torsades de pointes are typically associated with a prolonged QT interval and preceded by a short-long-short RR sequence[4,5,7,32]. All presented patients, except one, showed these characteristics. Only in a very few instances, torsades de pointes will start without cycle length changes. For example, Bauman et al.[4] described this in 1 out of 10 patients and Kay et al.[32] in 3 out of 44 episodes. Roden et al.[5] noted in all patients short-long-short sequences preceding the proarrhythmic event. Therefore, to prevent overestimation of proarrhythmia (e.g. by the exclusive use of one lead rhythm strips) the definition of torsades de pointes should include: an arrhythmia preceded by short-long-short RR sequences in the setting of a prolonged QT interval.

During the search for control patients it was noticed that short-lasting and asymptomatic episodes of torsades de pointes may pass unrecognized. Reviewing the 12-lead electrocardiograms recorded continuously during the infusion of an investigational class 3 drug for conversion of atrial fibrillation, we discovered 1 patient showing a typical nonsustained torsades de pointes. Obviously, this episode

was associated with a long QT interval and a short-long-short sequence. Another patient had an unrecognized torsades de pointes of 6 beats during d,l-sotalol treatment and normal potassium plasma level on 24-hour Holter (these patients were not included in the present report). In the latter patient d,l-sotalol treatment was continued uneventfully. No collapse had occurred previously or during follow-up. These observations suggest that the incidence of torsades de pointes is underestimated. Whether these short-lasting asymptomatic torsades de pointes are a separate entity and never become symptomatic or may become sustained and symptomatic in the setting of triggering factors (for example hypopotassemia, hypomagnesemia, or congestive heart failure) is unknown. It is however, beyond debate that such a finding should prompt immediate cessation of therapy.

Torsades de pointes may present as hemodynamically stable or unstable. One would expect that the patients with a more depressed left ventricular function have unstable episodes. Alternatively, longer lasting and more frequent ('incessant') episodes may enhance instability. Obviously, deterioration into ventricular fibrillation also leads to hemodynamic collapse. In addition, the cycle length of the arrhythmia may determine instability. Torsades de pointes due to antiarrhythmic drugs may have relatively long cycle lengths. Unfortunately, we were unable to record the latter 3 torsades de pointes characteristics.

Female predominance. The high incidence of women (68%) with proarrhythmia was in agreement with the recent findings of Makkar et al.[33]. They performed a meta-analysis of 93 articles incorporating a total number of 332 patients with torsades de pointes during antiarrhythmic drug treatment. They found a female predominance irrespective of other possible predisposing factors like hypopotassemia, hypomagnesemia, digoxin treatment, hypertension, bradycardia, left ventricular dysfunction, coronary artery disease or rheumatic heart disease or treated arrhythmia. The pathophysiological background is as yet unknown.

Cardiovascular and noncardiovascular history. Structural heart disease is a known risk factor for the development of torsades de pointes[7]. In 4 previous studies the underlying heart disease could be identified in a total of 114 patients: 31% coronary artery disease, 11% cardiomyopathy, 18% valve disease, 25% hypertension and 2% no evident heart disease[4,5,8,32]. By contrast, in the present study there was a low incidence of coronary artery disease. On the other hand, a remarkably high incidence of hypertension was found. Hypertension increases left ventricular wall tension, leading to structural, biochemical, and physiological changes in the myocardium. It may be hypothesized that hypertrophy of the myocardium may lead to increased dispersion of refractoriness or triggered activity[34,35]. If a localized disproportionate increase of M cells plays a role remains to be resolved[36].

One of the patients had myotonic dystrophy, i.e. Morbus Steinert. It is known that myotonic dystrophy can be accompanied by cardiac conduction

disturbances[37]. Also in other diseases that influence contractile function in heart and skeletal muscle, the cardiac conduction system frequently is affected. Recently, Bies and colleagues[38] suggested that dystrophin may be an important molecule for membrane function in the Purkinje conduction system of the heart. Their findings support the hypothesis that defective dystrophin expression contributes to the cardiac conduction disturbances seen in Duchenne and Beckers muscular dystrophy. This may suggest that these patients with muscle diseases may be prone to the development of proarrhythmia. The first predisposing arrhythmogenic factor may be the conduction disturbances accompanied by bradycardia, in this way exaggerating reverse use-dependent effects. A second factor may be the presence of increased dispersion of refractoriness between the Purkinje system and ventricular muscle.

Three patients had cerebrovascular accidents in their history. Recently, in a review Davis et al.[39] stressed the importance of electrocardiographic abnormalities in patients with cerebrovascular attacks. These central nervous system lesions may be accompanied by a prolonged QT interval. It remains a matter of discussion if these centrally mediated forms of QT prolongation predispose to the development of torsades de pointes on drugs. To illustrate the complexity of this discussion we can give the following example. In 1 of the patients with a cerebrovascular accident increase of d,l-sotalol dosage led to conversion of atrial fibrillation to sinus rhythm, which unfortunately was associated with acute cerebral embolism. However, only 24 hours later, she developed torsades de pointes. Obviously, it is difficult to conclude in this case whether QT prolongation was purely due to sotalol and reverse use-dependent effects or that the 'central' QT prolongation was crucial for the development of torsades de pointes.

Underlying treated arrhythmia. The underlying arrhythmia was atrial fibrillation or flutter in most patients. Combining 3 previous studies (total number of 84 patients), the treated arrhythmia was atrial fibrillation or flutter in 51% of the patients, ventricular premature beats in 30%, nonsustained ventricular tachycardia in 11%, sustained ventricular tachycardia in 2%, and more than 1 arrhythmia in 6% [4,5,32]. In the meta-analysis of Makkar and colleagues[33] of 332 patients with drug-induced torsades de pointes, atrial arrhythmias were present in 92 patients (28%) and ventricular arrhythmias in 111 patients (33%). In the remaining 129 patients the underlying arrhythmia diagnosis was not given. In sight of these studies, 85% of the patients with atrial fibrillation/flutter as underlying arrhythmia in the present study was high. However, from all the available data one cannot conclude whether the type of arrhythmia predisposes to torsades de pointes since the total number of patients treated for one specific arrhythmia was not known. Therefore, unlike class 1c drugs, which produce proarhythmia more often in ventricular tachycardia patients, class 1a or 3 do not seem to be more arrhythmogenic in that setting.

Electrocardiographic observations. Enhanced QT dispersion predisposes for torsades de pointes. The group of Campbell found a decreased dispersion of the QT

interval in postinfarct patients treated with d,l-sotalol[40]. Hii and colleagues[11] treated patients with torsades de pointes during quinidine subsequently with amiodarone. During amiodarone treatment less QT dispersion was measured on the 12-lead electrocardiogram suggesting a more homogeneous prolongation of repolarization, which may explain the low arrhythmogenic potential of amiodarone. The importance of QT dispersion was underscored by the findings of Hohnloser et al.[12]. QT dispersion decreased in 19 VT/VF patients responding to d,l-sotalol treatment and remained unchanged in 20 nonresponders. By contrast, QT dispersion increased in 11 patients with torsades de pointes. In the present preliminary report data of QT dispersion are not presented, because the blinded data were not yet available.

The value of TU wave changes in predicting future drug-induced torsades de pointes is still unknown. TU wave classification was performed before and during antiarrhythmic treatment. In all case patients the electrocardiogram during treatment was within 24-hours of the proarrhythmic event. On drug therapy, the TU classes 9 and 12 emerged most frequently. The blinded comparison with the control patients may further substantiate these preliminary observations and whether these TU classes are predictive.

The present data confirm previous observations that torsades de pointes is associated with bradycardia, whether or not in association with conversion of 'rapid' atrial fibrillation to 'slow' sinus rhythm. During bradycardia the repolarization delaying effects of class 1a and 3 antiarrhythmic drugs are more pronounced, i.e. reverse use-dependency. Hence, bradycardia may be an important predisposing factor. Bradycardia was present in the majority of the presented patients. It is tempting to assume that digoxin might be associated with proarrhythmia because of its atrioventricular conduction delaying effect which might be important in atrial fibrillation patients. If beta blocker treatment or calcium antagonists like verapamil predispose a patient to proarrhythmia in that setting has never been described.

Early versus late proarrhythmia. In the present study 7 patients had their proarrhythmic event during the first intravenous administration of an antiarrhythmic drug. It has been suggested that induction of dispersion of refractoriness depends on the rate of infusion of an antiarrhythmic drug[41]. This brings into question whether these patients would have had their proarrhythmic event if they had received the antiarrhythmic drug at a slower infusion rate or were treated orally.

It is supposed that in the patients with their proarrhythmic event during chronic treatment, an intercurrent provoking factor may be present like electrolyte disturbances, ischemia, progressive congestive heart failure, drug interactions, progressive renal or hepatic failure[7]. Also in the present study electrolyte disturbances were present in a high number of patients. A potassium plasma level below normal was found in 9 patients. Moreover, renal and hepatic dysfunction, not present at baseline, was found in some cases. Decreased renal function was found to be related to torsades de pointes during d,l-sotalol (Investigators' Meeting Bristol-

Myers Squibb, Amsterdam 1993). However, in the present study it cannot be excluded that renal or hepatic dysfunction was the result of hemodynamic deterioration during the event.

During quinidine treatment change of the antiarrhythmic drug dose (or compound) has been associated with proarrhythmia. In the present group d,l-sotalol dose was increased recently in 8 patients. This suggests that also a change in dose of class 3 drugs may be associated with proarrhythmia.

Implications of this preliminary report. Considering the preliminary character of this report, the implications are given with restrictions. Nevertheless, the following recommendations can be put forward. In case of intravenous administration of antiarrhythmic drugs delaying repolarization it seems appropriate to infuse the agent slowly and to use a stepped dosing-approach. Infusion of antiarrhythmic drugs should be performed under close observation of the 12-lead electrocardiogram looking for changes of the TU wave and rapid increase of the QT interval. Measurement of QT dispersion may appear useful in risk assessment. Also one might consider hospital admission if the dose of class 3 drugs is increased.

Limitations of this preliminary report. In the present preliminary report, all electrocardiographic evaluations were performed by one clinician, who was unblinded for the concomitant medication and history of the patient. The principal investigators decided to repeat these measurements by independent clinicians unaware of the underlying disease or medication of the patients. In case of disconcordance between the observers definite decisions will be made by one of the principal investigators.

A retrospective study is hampered by less optimal documentation of arrhythmic events. However, considering registration of torsades de pointes this will remain the case in prospective studies. Nevertheless, retrospective studies may give directions for future investigations.

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Samenvatting

Kamertachycardieën en kamerfibrilleren (VT/VF) zijn levensbedreigende hartritmestoornissen. Deze ritmestoornissen kunnen zowel farmacologisch als niet-farmacologisch behandeld worden. De plaats van de farmacologische behandeling veranderde het laatste decennium enorm. Bovendien worden niet-farmacologische methodieken klinisch toepasbaar. Heroriëntatie in de evaluatie en behandeling van VT/VF patiënten was noodzakelijk. Dientengevolge startte in januari 1989 in het Academisch Ziekenhuis te Groningen een gestandaardiseerde benadering van VT/VF patiënten 'Het VT/VF protocol'. Deze benadering heeft tot doel het nader evalueren van de rol van het onderliggend hartlijden, de risico stratificatie van VT/VF patiënten en het analyseren van uitlokkende aritmogene factoren. Anti-aritmische therapie werd alleen voorgeschreven bij afwezigheid van een corrigeerbare aritmogene factor. In het algemeen waren anti-aritmica de behandeling van eerste keuze.

De rol van een onderliggend hartlijden bij VT/VF patiënten werd onderzocht. De meest frequente onderliggende oorzaak van VT/VF is een oud infarct. Het klinisch belang van de coronair anatomie bij VT/VF patiënten met een oud infarct werd geëvalueerd (**appendix 1**). Tweeëntachtig VT/VF patiënten met een oud infarct ondergingen coronair angiografie waarbij 3 groepen konden worden geïdentificeerd betreffende de aritmogene rol van ischemie. Ischemie werd beschouwd als enige oorzaak (Groep A, 17%) of als een coexistente factor van de aritmie (Groep B, 16%). In groep C (67%) speelde ischemie geen significante rol. De prognose van groep A was uitstekend betreffende het optreden van een recidief. Groep B en C hadden een ongunstige prognose. Na 2 jaar was 100%, 56%, 52% van de patiënten in groepen A, B en C vrij van ritmestoornissen gebleven. Bij de groepen B en C was de prognose gerelateerd aan de linker kamer ejectie fractie en de tijdsduur tussen de aritmie en het laatste infarct. Met deze benadering kunnen post-infarct VT/VF patiënten geïdentificeerd worden die het beste behandeld kunnen worden met anti-ischemische therapie. Het belang van een verminderde linker kamer functie werd bevestigd in een studie die linker kamer functie parameters evalueerde (**appendix 2**). Negenenzestig VT/VF patiënten werden prospectief gevolgd om de predictieve waarde van functionele capaciteit (NYHA classificatie en maximale zuurstof consumptie) en linker kamer functie in rust (linker kamer ejectie fractie bepaald met behulp van isotopen, angiografische linker kamer wandbewegingsscore en echocardiografische dimensies) te bepalen met betrekking tot het optreden van een recidief aritmie. Gedurende een follow-up van 19 maanden hadden 18 patiënten (26%) een recidief. Parameters voor functionele capaciteit en echocardiografische dimensies toonden geen relatie met het optreden van een recidief. Linker kamer ejectie fractie en wandbewegingsscore waren slechter bij patiënten met een recidief. Multivariant analyse identificeerde de linker kamer wandbewegingsscore als de

belangrijkste prognostische parameter.

Een kleine groep patiënten had kamerfibrilleren zonder onderliggend cardiaal lijden, zogenaamd idiopathisch kamerfibrilleren (**appendix 3**). Endocardiale biopsieën van de rechter kamer toonden echter microscopische afwijkingen passende bij rechter kamerdysplasie bij 6 van de 9 patiënten. Het belang van een meer accurate definitie van deze patiënten met idiopathisch kamerfibrilleren wordt benadrukt. Identificatie van een specifieke oorzaak kan gevolgen hebben voor de diagnose en prognose van deze patiënten.

Alvorens anti-aritmische therapie bij de VT/VF patiënten in te stellen werden uitlokkende factoren uitgesloten. Identificatie van uitlokkende factoren en behandeling of modificatie kan anti-aritmische behandeling voorkomen. Dit werd bevestigd door de bevinding dat anti-ischemische therapie in een subgroep van post-infarct patiënten gepaard ging met een uitstekende prognose (appendix 1). Bovendien konden patiënten met idiopathisch VF voorafgegaan door een hoge sympathicotonus effectief behandeld worden met een beta blokker (**appendix 4**).

Appendix 5 vat de effecten van beta blokkade bij patiënten met VT/VF samen en onderstreept de ondergewaardeerde rol die deze anti-aritmica spelen bij de behandeling. Beta blokkade is de therapie van eerste keuze bij patiënten met VT/VF voorafgegaan door een hoge sympathicotonus. Maar ook bij patiënten zonder duidelijk verhoogde sympathicotonus kan beta blokkade effectief zijn, zeker in de aanwezigheid van hartfalen (hetgeen gepaard gaat met een verhoogde neurohumorale activatie). Beta blokkers kunnen ook gebruikt worden om de effectiviteit van klasse 1 of 3 anti-aritmica te verhogen of als adjuvante therapie bij de implanteerbare 'cardioverter-defibrillator' om frequente ontladingen te voorkomen. Beta blokkers zijn een belangrijk alternatief ten opzichte van conventionele anti-aritmica bij de behandeling van VT/VF patiënten, indien zij hemodynamisch goed worden verdragen.

Bij afwezigheid van uitlokkende factoren werd anti-aritmische therapie overwogen. Bij VT/VF patiënten vormen anti-aritmica de hoeksteen van de behandeling. De reproduceerbaar induceerbare VT/VF patiënten ondergingen seriële evaluatie van anti-aritmica met behulp van de geprogrammeerde electrische stimulatie techniek (appendix 1,2,4). In incidentele gevallen werd gepoogd het aritmogene electrofysiologische mechanisme te identificeren met behulp van (niet)invasieve methodieken om zodoende geïndividualiseerde anti-aritmische therapie voor te schrijven. In de post-infarct patiënt van **appendix 6** waren de tachycardieën alleen induceerbaar na kort-lang RR intervallen. Na isoprenaline traden de tachycardieën onophoudelijk op, allen voorafgegaan door kort-lang RR intervallen. Dit suggereert dat vroege nadepolarisatie, bevorderd door een verhoogde sympathicotonus, als aritmogeen electrofysiologisch mechanisme optrad. Beta blokkade was succesvol.

De eigenschappen van almokalant, een nieuw klasse 3 anti-aritmicum, werden

geëvalueerd in een dierexperiment (**appendix 7**) met nadruk op de veranderingen in de frequentie afhankelijkheid van de refractaire perioden tijdens toediening van almokalant. Verlenging van de refractaire periode door almokalant was meer uitgesproken op boezem dan op kamer niveau. Verlenging van de refractaire periode persisteerde bij korte stimuleringsintervallen, vooral op atriaal niveau, wijzende op afwezigheid van 'reverse use-dependence' van almokalant in het varkenshart. In **appendix 8** werden de electrofarmacologische effecten en de farmacokinetiek van almokalant onderzocht in een gerandomiseerde, placebo-gecontroleerde, dubbelblinde studie van 10 post-infarct patiënten met complexe kamerritmestoornissen. Dit bood ons de mogelijkheid om anti-aritmische effecten op kamerritmestoornissen van een nieuw zogenaamd puur klasse 3 anti-aritmicum te bestuderen. De electrocardiografische veranderingen gedurende toediening van almokalant worden beschreven.

Het grote nadeel van anti-aritmica is het altijd aanwezige risico van pro-aritmie. Een van de patiënten beschreven in appendix 8 kreeg almokalant toegediend met een hogere infusie snelheid en ontwikkelde zelf-terminerende torsades de pointes (**appendix 9**). Het is mogelijk dat pro-aritmie tijdens de nieuwere klasse 3 anti-aritmica dosisafhankelijk is. Bovendien lijkt de incidentie van pro-aritmie tijdens de nieuwe klasse 3 anti-aritmica hoger te zijn dan met sotalol of amiodarone. Het is daarom van het grootste belang om de patiënten met een verhoogd risico te identificeren. De electrocardiografische veranderingen voorafgaand aan torsades de pointes in de gepresenteerde casus zijn illustratief (appendix 9). Retrospectief gezien is het mogelijk dat de gepresenteerde patiënt een hoger risico had op het ontwikkelen van torsades de pointes. Dit wordt gesuggereerd door pre-existente electrocardiografische karakteristieken zoals die ook gevonden worden bij het verworven lange QT syndroom: pauze-afhankelijke TU complex veranderingen en een abnormale respons van het QT interval bij inspanning. Tevens trad de pro-aritmie snel op na de eerste almokalant toediening, hetgeen vergelijkbaar is met torsades de pointes tijdens quinidine behandeling. Ofschoon de predictieve waarde van electrocardiografische bevindingen in de afwezigheid van anti-aritmische behandeling bevestigd dient te worden, is het belangrijk aandacht te schenken aan electrocardiografische karakteristieken die geassocieerd kunnen worden met pro-aritmie. Bovendien, kan het waardevol zijn om hierop te letten tijdens chronische behandeling. De 'Retrospective case-control multicenter study on drug-induced long QT-related arrhythmias' werd uitgevoerd om het klinische profiel vast te stellen van de patiënt met een verhoogd risico op het ontwikkelen van pro-aritmie tijdens anti-aritmica die de repolarisatie vertragen. Er wordt speciale aandacht geschonken aan electrocardiografische karakteristieken die geassocieerd kunnen worden met het optreden van pro-aritmie. In **appendix 10** worden de 40 patiënten met torsades de pointes, die werden ingesloten in de retrospectieve studie, beschreven.

Er is zeer veel in beweging in 'Ritmeland' betreffende de identificatie van patiënten met een verhoogd risico op het optreden van plotse hartdood, en wat betreft farmacologische en niet-farmacologische behandeling. Dit proefschrift benadrukt dat VT/VF patiënten accuraat gedefiniëerd dienen te worden alvorens aan hen anti-aritmische therapie voor te schrijven. De prognostische verschillen tussen patiënten met verschillend onderliggend cardiaal lijden benadrukken het belang van prospectieve studies in homogene populaties. Tevens dient de discussie gericht te worden op het eindpunt van de studies. Mortaliteit schijnt van groter belang te zijn dan het optreden van een recidief aritmie, met name bij de studies die implanteerbare 'cardioverter-defibrillators' toepassen. Bovendien kan adequate behandeling van uitlokkende factoren anti-aritmische behandeling overbodig maken en zo de altijd aanwezige kans op pro-aritmie voorkomen. Tenslotte, indien mogelijk dient de anti-aritmische behandeling gericht te zijn op het onderliggende aritmogene electrofysiologische mechanisme.

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