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

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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.

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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.

References

Adhar GC, Larson LW, Ba
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Akthar M, Tchou PJ, Jazayer
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Allessie MA, Bonke FIM, Sch
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Almendral J, Ormaetxe J, De
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Anastasiou-Nana MI, Anderso
Occurrence of exercis
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Heart J 1987;113:107

Antman EM, Berlin JA. Dec
Circulation 1992;86;76

Antzelevitch C, Sicouri S. Clin
Role of M cells in the
Coll Cardiol 1994;23:2

Arsenian MA. Magnesium and

Avitall B, Khan M, Krum D,
Physics and engineer
1993;22:921-932.

Bayés de Luna A, Coumel
production of fatal a
1989;117:151-159.

Bazett HC. An analysis of the ti

Belhassen B, Shapira I, Kauli
supraventricular beats.

Belhassen B, Shapira I, Shos
fibrillation: inducibility
1987;4:809-816.

Belhassen B, Viskin S. Idiopath
1993;4:356-368.

Bigger JT Jr. Why patients
Circulation 1987;75(Sup

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arrhythmogenic right ve

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Cardiac positron emissio
on advanced cardiac ima
Heart Association. Circul

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