Predicting the effect of D,L-sotalol on ventricular tachycardia inducibility from the RR variability response

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Abstract

Aim—To find a rapid way of identifying non-responders to D,L-sotalol in patients with ventricular tachycardia.

Methods—Programmed ventricular stimulation and RR variability were studied in the control state and 10 days after treatment with 160 to 320 mg of D,L-sotalol in 36 consecutive patients with ventricular tachycardia.

Results—In 14 patients (group I) D,L-sotalol suppressed ventricular tachycardia inducibility. In 22 patients (group II) sustained ventricular tachycardia remained inducible during D,L-sotalol treatment. The ventricular tachycardia rate was slowed in eight patients and unchanged or accelerated in 14. At baseline, heart rate variability was similar in both groups. During treatment with D,L-sotalol, variables reflecting parasympathetic activity (pNN50, rMSSD, and high frequency amplitude (HF)) increased in both groups: HF increased from (mean (SD)) 75 (68) to 146 (134) in group I ($p < 0.05$) and from 60 (49) to 125 (79) in group II ($p < 0.05$). Other variables were unchanged in group I. In group II, the variables associated with sympathetic activity (coefficient of variance (CV), ratio of low frequency amplitude (LF) to HF) decreased significantly: CV decreased from 13 (4) to 9 (2) ($p < 0.001$) and LF/HF from 4.74 (3.02) to 3.00 (2.02) ($p < 0.05$).

Conclusions—The β blocking effect of D,L-sotalol produced a significant improvement over control values in indices of parasympathetic tone in all treated patients. However, the heart rate variability indices related to sympathetic activity were decreased only in non-responders. This effect of D,L-sotalol on heart rate variability could help detect non-responders to the drug and avoid an electrophysiological study.

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Heart rate variability represents one of the most promising markers of autonomic activity and has been the subject of several studies in recent years.¹ These studies confirmed its role as a strong and independent predictor of mortality following acute myocardial infarction.²⁻⁵ Changes in autonomic activity expressed as

sympathetic activation and vagal withdrawal facilitate the development of ventricular tachyarrhythmias, in particular when combined with myocardial infarction.⁶ Ventricular tachycardia also constitutes an independent risk factor for sudden cardiac death.⁷ Therefore antiarrhythmic drugs are often used in these patients. Some of these drugs may increase mortality, as shown by the cardiac arrhythmia suppression trial.⁸ Only amiodarone,⁹ dofetilide,¹⁰ and D,L-sotalol¹¹ have been found not to be associated with increased mortality when used after myocardial infarction. The antiarrhythmic action of D,L-sotalol is potent,¹² though more recent studies have not reported a reduction in mortality in patients with malignant arrhythmias or in comparison with the use of defibrillators.^{13 14} The positive and negative effects of D,L-sotalol may be related to changes in sympathovagal interaction; however, D,L-sotalol is also a β blocker and β blockers have been shown to reduce sudden death after recent myocardial infarction.¹⁵

Our aims in this study were thus to evaluate the actions of D,L-sotalol on heart rate variability in patients with spontaneous ventricular arrhythmias, and to correlate these effects with those on the induction of ventricular tachycardia.

Methods

STUDY GROUP

We studied a group of 42 consecutive patients, 35 men and seven women, aged 29 to 75 years (mean (SD) 58 (14)), admitted for documented ventricular tachycardia or fibrillation ($n = 35$) or for syncope subsequently found to be caused by ventricular tachycardia ($n = 7$). Sustained ventricular tachycardia could be induced in all patients, though they were in sinus rhythm under normal conditions.

The underlying heart disease was coronary artery disease. Twenty three patients also had sequelae of myocardial infarction (occurring more than six months earlier). Left ventricular ejection fraction was measured by radionuclide studies.

Patients were excluded from the study for the following reasons: acute myocardial infarction within the preceding six months, unstable angina pectoris, systolic blood pressure < 90 mm Hg, uncompensated congestive heart failure, sick sinus syndrome, second or third degree atrioventricular block, frequent salvos of atrial or ventricular premature beats, previous pacemaker implantation, QT interval > 450 ms before the administration of sotalol,

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significant hepatic or renal dysfunction and other contraindications for β receptor blockade, and left ventricular ejection fraction < 0.30 .

STUDY PROTOCOL

Informed consent was obtained from all patients. Programmed ventricular stimulation and 24 hour Holter monitoring were performed in the basal state and repeated after 10 days of D,L-sotalol treatment.

Programmed ventricular stimulation

Programmed ventricular stimulation was performed after all antiarrhythmic drugs and digitalis were discontinued for at least five half lives.

Stimulation was performed with a programmable stimulator (Explorer 2000, Ela Medical, Ela France, Le plessis-Robinson, France). A constant current source delivered rectangular impulses, 1.8 ms in duration, at twice diastolic threshold. Our stimulation protocol has been reported previously.¹⁶ After atrial pacing and programmed atrial stimulation, ventricular pacing was performed at rate increments up to 200 beats/min. Programmed ventricular stimulation was as follows: a single premature ventricular extrastimulus (S2) was introduced in late diastole during sinus rhythm and paced cycle lengths (600 to 400 ms) and the interval was shortened until the ventricles became refractory; double ventricular extrastimuli (S2 and S3) were introduced during sinus rhythm and during paced cycle lengths starting with an S1-S2 interval that was 10 ms longer than the ventricular refractory period; the S2-S3 interval was shortened in 10 ms decrements until S3 did not depolarise the ventricles. This protocol was performed at the apex and was repeated at the right ventricular outflow tract. A third extrastimulus (S4) was introduced following the same protocol if no sustained ventricular tachycardia was induced by two extrastimuli.

Holter monitoring

Holter monitoring was done for 24 hours before programmed ventricular stimulation was performed. Patients in whom < 18 hours of monitoring were achieved and those in whom $< 60\%$ was analysable were excluded. No patients were receiving drugs known to affect heart rate variability, such as β blockers, digoxin, calcium antagonists, angiotensin converting enzyme inhibitors, or any antiarrhythmic drug including amiodarone.

The 24 hour recordings were digitised on an Ela (Anatec) Holter system and submitted to the standard Ela algorithms for QRS labelling and editing. Ambulatory ECG recordings of bipolar leads CM1 and CM5 were scanned with total visual verification and correction of beat morphology and timing by BB-P.

The heart rate variability module (Elatec) for the Ela Holter system was used. For time domain analysis, heart rate variability required an accurate selection of the normal RR intervals. To achieve this, three interactive screens in the time domains allowed the user to easily check and adjust the non-normal RR fil-

tering. For frequency domain analysis, a power density spectrum was calculated with fast Fourier transformation in 256 second periods for 24 hours. Three graphs in the frequency domain displayed changes in sympathetic and vagal tone, reflecting circadian fluctuations as well as the occurrence of local events.

For the purpose of the present study, the following time domain indices of heart rate variability were determined:

Mean RR (ms): mean value of all normal RR intervals during 24 hours.

SDNN (ms): standard deviation of the mean RR intervals.

rMSSD (ms): root mean square of successive differences in RR intervals among consecutive normal beats.

pNN50 (%): per cent differences between normal RR intervals that are greater than 50 ms computed over the entire 24 hour recording.

CV (%): coefficient of variance calculated as SDNN/mean RR

In the frequency domain we determined:

Low frequency amplitude (LF) (ms^2): square root of the total power from 0.04 to 0.15 Hz.

High frequency amplitude (HF) (ms^2): square root of the total power from 0.15 to 0.40 Hz.

LF/HF ratio: ratio of low to high frequency power.

Drug testing

After programmed ventricular stimulation and 24 hour Holter monitoring were completed, each patient received 160 to 320 mg/day of D,L-sotalol; patients older than 70 years and those with a decreased left ventricular ejection fraction received an initial dose of 160 mg of D,L-sotalol after which the dose was increased as tolerated. The drug was continued at the same dose until the study was completed. Twenty six patients received 320 mg/day of sotalol and 10 patients received 160 mg/day. Other cardiac drugs were unchanged during this period.

Programmed ventricular stimulation using the protocol described above and 24 hour Holter monitoring were repeated 10 days after the initial study.

DEFINITIONS

Sustained ventricular tachycardia was defined as monomorphic ventricular tachycardia lasting more than 30 seconds or requiring termination because of haemodynamic heart failure. *Response to antiarrhythmic treatment* was considered as effective if the complete programmed ventricular stimulation during treatment did not induce sustained or non-sustained ventricular tachycardia. *Response to antiarrhythmic treatment* was considered ineffective if the sustained ventricular tachycardia remained inducible during treatment. The ventricular tachycardia was generally unchanged, but could sometimes be slowed (basal ventricular tachycardia cycle length $+20\%$) or accelerated (basal ventricular tachycardia cycle length -20%).

STATISTICAL ANALYSIS

Results are presented as mean (SD). Differences between treatment groups were analysed

Table 1 Features of the study population

	Group I	Group II	
Number	14	22	
Sex (male:female)	12:2	19:3	NS
Age (years)	58 (17)	59 (13)	NS
LVEF (%)	48 (11)	44 (10)	NS
VT rate (beats/min)	232 (52)	229 (37)	NS

Values are mean (SD) or n.

Group I, responders to D,L-sotalol (inducibility of ventricular tachycardia suppressed); group II, non-responders to D,L-sotalol; LVEF, left ventricular ejection fraction; VT rate, rate of the ventricular tachycardia induced in the basal state.

Table 2 Heart rate variability in the control state

	Group I	Group II	
SDNN (ms)	90 (25)	113.5 (37)	NS (p < 0.1)
pNN50 (%)	5 (4)	5 (5)	NS
NN (ms)	845 (134)	891 (117)	NS
CV (%)	11 (3)	13 (4)	NS (p < 0.2)
rMSSD (ms)	26 (15)	27 (12)	NS
LF (ms)	345 (395)	263 (225)	NS
HF (ms)	75 (68)	60 (49)	NS
LF/HF	3.94 (2.63)	4.7 (3.02)	NS

Values are mean (SD).

CV, coefficient of variance (SDNN/mean RR); group I, responders to D,L-sotalol (inducibility of ventricular tachycardia suppressed); group II, non-responders to D,L-sotalol; HF, high frequency amplitude; LF, low frequency amplitude; NN, mean RR interval; pNN50, per cent differences between normal RR intervals that are greater than 50 ms, computed over 24 hours; rMSSD, root mean square of successive differences in RR intervals among consecutive normal beats; SDNN, standard deviation of the mean RR intervals.

by comparing the change from the baseline with use of analysis of variance and the Student's *t* test or χ^2 analysis as appropriate. For all comparisons, a *p* value < 0.05 was required for rejection of the null hypothesis.

Results

Six patients were excluded from the study because their ECG recording were unsuitable or, in two cases, because of the need for pacemaker implantation during the protocol. The data on the remaining 36 patients were analysed.

PROGRAMMED VENTRICULAR STIMULATION AT BASELINE AND DURING D,L-SOTALOL TREATMENT
In the control state the entire population had an inducible sustained ventricular tachycardia. In those with documented sustained ventricular tachycardia, the morphology and rate of the

induced tachycardia were similar to the spontaneous arrhythmia. In those presenting only with syncope, the induced ventricular tachycardia reproduced the clinical symptoms preceding the syncope.

D,L-sotalol was effective in 14 patients (group I) and ineffective in the remaining 22 (group II). In group II the rate of inducible ventricular tachycardia was slowed in eight patients (from 260 (33) to 201 (13) beats/min) and unchanged or accelerated in the remaining 14 (from 215 (34) to 227 (29) beats/min).

Clinical data and laboratory findings for each group are summarised in table 1. There were no statistical differences between the groups. Left ventricular ejection fraction was relatively preserved in both groups.

BASELINE HEART RATE VARIABILITY

These results are shown in table 2. There were no statistically significant differences between the two groups with regard to time and frequency domain indices of heart rate variability. Paradoxically, the time domain indices tended to be lower in group I than in group II, but spectral analysis of heart rate variability did not confirm this tendency. Only one patient in group II had severe impairment of baseline heart rate variability (SDNN 53 ms).

EFFECTS OF D,L-SOTALOL TREATMENT ON HEART RATE VARIABILITY

These results are shown in table 3. As expected, the sinus cycle length was prolonged significantly with D,L-sotalol in both groups.

In group I, SDNN (the coefficient of variance and LF/HF ratio) did not differ significantly between the control state and the treatment period. All indices reflecting parasympathetic activity (pNN50, rMSSD, and the HF component) increased significantly. The LF component also tended to increase and thus the LF/HF ratio remained unchanged.

In group II, all indices reflecting parasympathetic activity (pNN50, rMSSD, and the HF component) increased significantly (*p* < 0.05), as in group I. However, in contrast to group I, the coefficient of variance and the LF/HF ratio decreased significantly between the control state and the treatment period.

ANALYSIS OF RESULTS IN GROUP II PATIENTS

In group II, basal heart rate variability was able to differentiate the patients in whom the induced ventricular tachycardia was slowed by sotalol from those in whom the tachycardia was unchanged or accelerated. In the latter group, the indices reflecting parasympathetic activity and in particular the HF component were lower than in the former group (*p* < 0.05) (table 4). Sotalol might also have a more depressant effect on heart rate variability in patients with unchanged or accelerated ventricular tachycardia than in those with slowed ventricular tachycardia. However, the differences were not significant.

Table 3 Evolution of heart variability in control state and during treatment with D,L-sotalol

	Group I		Group II	
	Control	Sotalol	Control	Sotalol
SDNN (ms)	90 (25)	116 (142)	113.5 (37)	96 (28)
pNN50 (%)	5 (4)	10 (10)*	5 (5)	9 (7)
NN (ms)	845 (134)	1007 (116)**	891 (117)	1067.5 (125)***
CV (%)	11 (3)	11.5 (4)	13 (4)	9 (2)***
rMSSD (ms)	25 (15)	39 (20)*	27 (12)	38 (14)*
LF (ms)	345 (395)	432 (466)	263 (225)	376 (288)
HF (ms)	75 (68)	146 (134)*	60 (49)	125 (79)*
LF/HF ratio	3.94 (2.63)	3.05 (1.24)	4.74 (3.02)	3.00 (2.02)*

Values are mean (SD).

Comparisons were made in each group between control values and values with sotalol: **p* < 0.05; ***p* < 0.01; ****p* < 0.001.

CV, coefficient of variance (SDNN/mean RR); group I, responders to D,L-sotalol (inducibility of ventricular tachycardia suppressed); group II, non-responders to D,L-sotalol; HF, high frequency amplitude; LF, low frequency amplitude; NN, mean RR interval; pNN50, per cent differences between normal RR intervals that are greater than 50 ms, computed over 24 hours; rMSSD, root mean square of successive differences in RR intervals among consecutive normal beats; SDNN, standard deviation of the mean RR intervals.

Table 4 Evaluation of ventricular tachycardia rate and heart rate variability in the control state and during treatment with sotalol in group II patients

	Sotalol positive (n = 8)		Sotalol negative (n = 14)	
	Control	Sotalol	Control	Sotalol
VT rate (beats/min)	260 (33)	201 (13)	215 (34)	227 (29)
SDNN (ms)	112 (30)	107 (29)	113 (39)	90 (27)
pNN 50 (%)	7 (4)	10.5 (5)	3.4 (5)	7.7 (6)
NN (ms)	911 (88)	1229 (96)***	879 (136)	1046 (133)***
CV (%)	12 (3)	9 (2)	13 (5)	9 (3)**
rMSSD (ms)	35 (11)	40 (11)	27 (22.5)	33 (14)
LF (ms)	388 (254)	476 (193)	189 (177)	310 (320)
HF (ms ²)	95 (54)	149 (52)	38 (32)*	97 (76)**
LH/HF ratio	4.02 (1.87)	2.52 (1.44)	4.87 (3.60)	3.12 (2.30)

Values are mean (SD).

Comparisons are made between control state and sotalol in each group: *p < 0.05; **p < 0.01; ***p < 0.001.

CV, coefficient of variance (SDNN/mean RR); HF, high frequency amplitude; LF, low frequency amplitude; NN, mean RR interval; pNN50, per cent differences between normal RR intervals that are greater than 50 ms, computed over 24 hours; rMSSD, root mean square of successive differences in RR intervals among consecutive normal beats; SDNN, standard deviation of the mean RR intervals; sotalol negative, unchanged or accelerated VT with sotalol; sotalol positive, slowed VT with sotalol; VT, ventricular tachycardia.

Discussion

In this study we report similar positive effects of D,L-sotalol on the heart rate variability indices associated with parasympathetic tone, irrespective of the effect of the drug on ventricular tachycardia inducibility. Furthermore, responders to D,L-sotalol could be differentiated from the non-responders by the absence of depressant effects of the drug on heart rate variability indices associated with sympathetic tone: these indices were decrease in non-responders.

The general effects of D,L-sotalol on the indices reflecting parasympathetic tone could be related to the β blocking effects of the drug. At a dose of 80 to 160 mg/day D,L-sotalol is only a β blocker drug. Some studies^{15 17 18} have previously shown that β blockers enhance vagal activity after myocardial infarction or in heart failure,^{15 19} but also decrease sympathetic activity.

D,L-sotalol at a dose of 320 mg is also a class III antiarrhythmic drug. Previous studies have reported the effects of antiarrhythmic drugs on heart rate variability. Flecainide,^{20 21} propafenone,²² quinidine,²³ and amiodarone^{20 24} have been reported to decrease heart rate variability. However, while flecainide, encainide, and moricizine decrease heart rate variability and low frequency amplitude, the drug induced decrease in heart rate variability did not predict death.^{20 21} The depressant effect of class Ic antiarrhythmic drugs on heart rate variability was found to be independent of the action of the drug on ventricular arrhythmias documented on 24 hour monitoring.²⁰

Hohnloser *et al* previously reported a significant improvement over control values in indices of parasympathetic tone in patients with ventricular arrhythmias treated with sotalol.²⁵ In their study, this improvement was not related to drug induced changes in the mean heart rate or the suppression of ventricular ectopic activity. Our findings were similar with respect to the indices of parasympathetic tone. However, the decrease in other indices of RR variability in non-responders in our study differs from Hohnloser's findings. This could be explained by discrepancies between the

results of Holter monitoring and those of the electrophysiological study previously reported for D,L-sotalol.¹²

The β blocking effect of D,L-sotalol on variables associated with parasympathetic activity may contribute to the overall efficacy of this agent in patients with ventricular arrhythmias.²⁶ In the present study, some patients also had a decrease in sympathetic activity. This effect is associated with a negative or adverse effect of the drug on the inducibility of ventricular tachycardia. The depressant effect of D,L-sotalol on some aspects of heart rate variability was particularly marked in patients with unchanged or more rapid ventricular tachycardia after treatment with the drug. Thus the finding of a negative effect of sotalol on heart rate variability could avert the need for repeat programmed ventricular stimulation with D,L-sotalol in these patients, especially in those who do not have spontaneous ventricular arrhythmias on 24 hour Holter monitoring. In those with spontaneous arrhythmias on their recording, the electrophysiological study versus electrocardiographic monitoring (ESVEM) trial¹² showed the value of repeated 24 hour Holter monitoring in predicting the effects of D,L-sotalol on ventricular arrhythmias.

LIMITATIONS

Our study is limited by the exclusion of patients with ventricular tachycardia and severely decreased left ventricular ejection fraction. These patients are not normally considered for antiarrhythmic treatment.¹⁴ A second limitation is that some of our patients received only 160 mg a day of sotalol and the drug has mainly β blocker effects at this dose; however, it was not possible to achieve a dose of 320 mg a day in these patients.

CONCLUSIONS

In all patients with ventricular tachycardia, D,L-sotalol increased the indices of heart rate variability associated with a parasympathetic effect. Only in non-responders to the drug did D,L-sotalol decrease the indices associated with a sympathetic effect. Thus heart rate variability could be used to detect the non-responders to D,L-sotalol, especially those patients who have unchanged or more rapid ventricular tachycardia with the treatment, who require the installation of a defibrillator.

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