Effect of low dose sotalol on the signal averaged P wave in patients with paroxysmal atrial fibrillation

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Abstract

Objective—To investigate the effects of low dose sotalol on the signal averaged surface P wave in patients with paroxysmal atrial fibrillation.

Design—A longitudinal within patient crossover study.

Setting—Cardiac departments of a regional cardiothoracic centre and a district general hospital.

Patients—Sixteen patients with documented paroxysmal atrial fibrillation. The median (range) age of the patients was 65.5 (36–70) years; 11 were men.

Main outcome measures—Analysis of the signal averaged P wave recorded from patients not receiving antiarrhythmic medication and after 4–6 weeks' treatment with sotalol. P wave limits were defined automatically by a computer algorithm. Filtered P wave duration and energies contained in frequency bands from 20, 30, 40, 60, and 80 to 150 Hz of the P wave spectrum expressed as absolute values (P20, P30, etc) and as ratios of high to low frequency energy (PR20, PR30, etc) were measured.

Results—No difference in P wave duration was observed between the groups studied (mean (SEM) 149 (4) without medication and 152 (3) ms with sotalol). Significant decreases in high frequency P wave energy (for example P60: 4.3 (0.4) v 3.3 (0.3) $\mu\text{V}^2\cdot\text{s}$, $P = 0.003$) and energy ratio (PR60: 5.6 (0.5) v 4.7 (0.6), $P = 0.03$) were observed during sotalol treatment. These changes were independent of heart rate.

Conclusions—Treatment with low dose sotalol reduces high frequency P wave energy but does not change P wave duration. These results are consistent with the class III effect of the drug and suggest that signal averaging of the surface P wave may be a useful non-invasive measure of drug induced changes in atrial electrophysiology.

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Keywords: sotalol; paroxysmal atrial fibrillation; signal averaged P wave; antiarrhythmic treatment

Analysis of the signal averaged P wave in patients with paroxysmal atrial fibrillation has repeatedly shown a longer P wave duration in patients with the arrhythmia compared with that in controls.^{1–4} Within the frequency

domain a few studies have suggested that increased P wave energy is also present in patients with paroxysmal atrial fibrillation.^{4–6} The exact mechanism by which these changes in the surface P wave are generated is unresolved, but it is generally assumed that they are a consequence of the changes in intra-atrial conduction that have been detected at invasive electrophysiological study.^{7–9} We have recently observed that changes in the signal averaged P wave found in paroxysmal atrial fibrillation are not related to differences in left atrial size,¹⁰ and others have reported a relation between intra-atrial conduction times and signal averaged P wave duration.¹¹

The apparent ability of the signal averaged P wave to reflect differences in atrial electrophysiology associated with atrial arrhythmias suggests that the technique might also detect the effects of antiarrhythmic drug treatment on atrial electrophysiology. We tested this hypothesis by performing serial signal averaged P wave recordings in patients taking no antiarrhythmic medication and during treatment with low dose sotalol.

Patients and methods

STUDY DESIGN

Consecutive patients with paroxysmal atrial fibrillation documented by either 12 lead electrocardiography or ambulatory monitoring were recruited from outpatient attendances (20) or ward admissions (one). Patients with contraindications to β blockade (two), who were taking antiarrhythmic medication that could not be discontinued (one), or who were taking amiodarone (two) were excluded. The remaining 16 patients gave informed consent to the study which was approved by the local hospital ethical committees.

All patients had a signal averaged P wave recording either after discontinuation of all antiarrhythmic medication for at least five half lives, or before any specific treatment for paroxysmal atrial fibrillation had been started. Patients were commenced on sotalol 40 mg twice daily increasing after 1 week to 80 mg twice daily. If the 80 mg twice daily dosage caused adverse effects a dose of 40 mg twice daily was continued instead. After 4–6 weeks' treatment with sotalol all patients returned for a second signal averaged P wave recording under identical conditions and using the same signal averaging equipment and protocol as on the first occasion.

As the study design was sequential, with all patients studied initially while taking no

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antiarrhythmic treatment and subsequently during treatment with sotalol, we also performed paired signal averaged recordings under identical conditions, but without antiarrhythmic treatment at the time of either recording in a further eight individuals to exclude a time effect. These recordings were made between 4 and 16 weeks apart using the same signal averaging equipment as for the patients taking sotalol.

SIGNAL AVERAGED P WAVE RECORDINGS

Our signal averaging and P wave analysis methodology have been previously described.^{10,12} Participants were recorded supine and relaxed in a quiet room. A modified orthogonal lead system was used. Analogue signals were amplified between 4000 and 20 000 times and bandpass filtered between 1 and 300 Hz. A fourth trigger signal was derived from one of the orthogonal leads and used to align P waves during signal averaging. The latter signal was bandpass filtered with a low pass of 50 Hz and a variable high pass of between 0 and 20 Hz. Analogue data were then digitised at 1 kHz with 12 bit resolution.

Voltage threshold triggering using the R wave of the signal selected for the trigger channel was used to identify each electrocardiographic cycle. However, P waves were then aligned by template matching to an evenly spaced 15 point P wave derived template—that is, true P wave triggered averaging. An algorithm that automatically determined the most frequently occurring P wave morphology for each participant was used to select the averaging template. P waves with morphologies that failed to match this template accurately were rejected from the signal average.

Time domain analysis

Each orthogonal lead was high pass filtered at 40 Hz using a symmetrical, 30 term finite impulse response filter. The leads were then combined to produce a vector magnitude plot of the P wave according to the formula:

$$V = \sqrt{X^2 + Y^2 + Z^2}$$

P wave limits were set automatically by an algorithm that identified the P wave beginning as the point at which the vector magnitude rose to greater than three standard deviations above its baseline value and the P wave end point as the point at which the vector magni-

tude fell to within three standard deviations of the baseline value of the minimum PR segment magnitude. These limits were used to determine the P wave duration.

Frequency domain analysis

Baseline wander was removed from each lead by subtracting from each data point a ramp generated between the beginning and end of the P wave. The signal was then high pass filtered at 15 Hz. The P wave signal was placed at the beginning of an array that was zero filled to 1024 points. A double precision fast Fourier transform was performed on these data for each lead and the outputs were summed algebraically for each frequency band.

From the aforementioned analysis P wave energy was quantified by summing the energies contained in frequency bands extending from 20, 30, 40, 60, and 80 to 150 Hz. These were expressed as absolute values (P20, P30, P40, P60, and P80 respectively) and as energy ratios defined as:

$$PR(F) = 100 \frac{\sum_{f=F}^{150 \text{ Hz}} P}{\sum_{f=10}^{F \text{ Hz}} P}$$

where F was set to 20, 30, 40, 60, and 80 Hz (PR20, PR30, PR40, PR60, and PR80). For example, P30 was the total absolute energy contained in frequency bands from 30 Hz to 150 Hz and PR30 was the ratio of P30 to the total energy contained in frequency bands from 10 Hz to 30 Hz multiplied by 100.

STATISTICAL METHODS

Results are expressed as mean (SEM). Comparisons between paired data were performed by the Wilcoxon test for paired observations and correlations between heart rate and P wave variables were sought by Spearman's rank test. Minitab computer software was used.

Results

PAIRED RECORDINGS WITHOUT ANTIARRHYTHMIC TREATMENT

These recordings were performed in eight individuals with a median (range) age of 56 (39–66) years and comprising five men and three women. All except one with atrioventricular nodal re-entrant tachycardia had documented paroxysmal atrial fibrillation. Other cardiac conditions present were ischaemic heart disease (two), myocarditis (one), and hypertension (one). The cardiovascular system was thought to be normal in the remaining three participants. No time effect on any frequency domain variable was noted (table 1).

PATIENT DETAILS

Sixteen patients were recruited into the study. Their median (range) age was 65.5 (36–70) years; 11 were men. All patients underwent cross sectional and Doppler echocardiography, and assessment of thy-

Table 1 Repeated frequency domain analysis of signal averaged P waves recorded from eight individuals between 1 and 4 months apart*

	Mean 1 (SEM)	Mean 2 (SEM)	Mean difference
P20 ($\mu\text{V}^2\cdot\text{s}$)	57.6 (10.7)	56.0 (13.7)	1.6
P30 ($\mu\text{V}^2\cdot\text{s}$)	30.1 (4.4)	31.5 (4.9)	-1.4
P40 ($\mu\text{V}^2\cdot\text{s}$)	15.4 (3.0)	15.3 (2.9)	0.1
P60 ($\mu\text{V}^2\cdot\text{s}$)	4.9 (1.2)	4.9 (1.1)	0.005
P80 ($\mu\text{V}^2\cdot\text{s}$)	1.8 (0.3)	1.9 (0.4)	-0.13
PR20	248.7 (61.7)	190.2 (41.0)	58.5
PR30	59.5 (6.8)	62.1 (8.2)	-2.6
PR40	23.0 (3.4)	23.3 (3.5)	-0.31
PR60	6.02 (0.6)	6.0 (0.7)	0.007
PR80	2.3 (0.3)	2.3 (0.3)	-0.02

*See text for definition of terms. Values are not significant.

Table 2 Details of patients analysed to assess the effect of sotalol on the signal averaged P wave

	Age (years)	Sex	Cardiac disease	Dose (mg)
1	68	M	Idiopathic	80 twice daily
2	68	M	Hypertension, MR	40 twice daily
3	69	M	CAD	40 twice daily
4	51	M	Sinoatrial disease	40 twice daily
5	58	F	Idiopathic	80 twice daily
6	58	M	?Alcoholic	40 twice daily
7	64	F	Sinoatrial disease	40 twice daily
8	48	M	Idiopathic	40 twice daily
9	70	F	MR, bicuspid aortic valve, left ventricular hypertrophy	40 twice daily
10	67	M	CAD	80 three times a day
11	70	F	Hypertension, asymmetric septal hypertrophy	40 twice daily
12	69	M	Idiopathic	80 twice daily
13	46	M	Idiopathic	80 twice daily
14	54	M	Idiopathic	80 twice daily
15	36	F	Idiopathic	80 twice daily
16	70	M	Idiopathic	80 twice daily

CAD, coronary artery disease; MR, mitral regurgitation.

roid function. Cardiac pathology in nine patients comprised hypertension (two), mitral regurgitation (two), coronary artery disease (two), left ventricular hypertrophy (two, asymmetric in one), sinoatrial disease (two), bicuspid aortic valve (one), and probable alcoholic cardiomyopathy (one); some patients having more than one condition (table 2). In the remaining seven patients no specific cause could be identified. At the time of the second recording eight patients were taking sotalol 40 mg twice daily, six were taking 80 mg twice daily, and one required 80 mg three times a day to control his arrhythmia (table 1). Over the 4–6 week follow up period 12 patients reported a

Figure 1 Signal averaged P waves recorded from patient 1 while taking (A) no antiarrhythmic drugs and (B) during treatment with sotalol 80 mg twice daily. Signals have been high pass filtered at 40 Hz and are presented as a vector magnitude plot. The P wave during treatment with sotalol is similar in morphology to that without medication, but is reduced in amplitude. P wave duration in this patient is slightly longer with sotalol; this was not a consistent finding in the overall group.

Table 3 Analysis of the P wave in patients before and after treatment with low dose sotalol

	No drug	Sotalol	P value
Noise (μV)	0.18 (0.02)	0.24 (0.07)	NS
Heart rate (beats/min)	70 (4)	60 (4)	0.05
Duration (ms)	149 (4)	152 (3)	NS
P20 ($\mu V^2.s$)	57.3 (5.9)	57.0 (7.1)	NS
P30 ($\mu V^2.s$)	33.9 (3.0)	32.4 (4.2)	NS
P40 ($\mu V^2.s$)	17.5 (1.9)	13.8 (1.3)	0.02
P60 ($\mu V^2.s$)	4.3 (0.4)	3.3 (0.3)	0.003
P80 ($\mu V^2.s$)	1.9 (0.3)	1.4 (0.2)	0.03
PR20	207 (21)	246 (36)	NS
PR30	71.8 (6.5)	74.9 (13.4)	NS
PR40	27.6 (3.3)	24.9 (4.8)	NS
PR60	5.6 (0.5)	4.7 (0.6)	0.03
PR80	2.3 (0.3)	2.0 (0.3)	NS

See text for definition of terms. NS, not significant.

reduction in attack frequency, while the remaining four noticed no difference. No patient reported an increase in symptoms.

SIGNAL AVERAGED P WAVES

No differences were found in P wave duration or low frequency energy between P waves recorded while not receiving treatment and when taking low dose sotalol. In contrast, a significant decrease in high frequency energy was observed when patients were taking sotalol compared with control values (P40: 17.5 (1.9) *v* 13.8 (1.3) $\mu V^2.s$,

Figure 2 Changes in (A) P60 and (B) PR60 from P waves recorded from patients while not given antiarrhythmic medication and during treatment with sotalol. Lines represent individual pairs of results; bars are the 95% confidence limits of each mean.

$P = 0.02$; $P60$: $4.3 (0.4) v 3.3 (0.3) \mu V^2.s$, $P = 0.003$; $P80$: $1.9 (0.3) v 1.4 (0.2) \mu V^2.s$, $P = 0.03$). These reductions in absolute high frequency energy were reflected by a significant decrease in higher frequency energy ratio ($PR60$: $5.6 (0.5) v 4.7 (0.6)$, $P = 0.03$), (table 3, figs 1 and 2). Not surprisingly, heart rate was also significantly lower during treatment with sotalol than when not receiving medication ($70 (4) \text{ beats/min} v 60 (4) \text{ beats/min}$, $P = 0.05$), but within the two groups no correlation between change in high frequency energy and change in heart rate was found, for example change in $P60 v$ change in heart rate, $r = -0.02$).

Discussion

As far as we are aware this is the first study to examine the effects of antiarrhythmic drug treatment on the signal averaged P wave. We found that, while there were no measurable effects on P wave duration, significant decreases in high frequency energy compared with that of baseline values occurred when patients were taking low dose sotalol.

The mechanism by which sotalol produced a decrease in high frequency P wave energy is not clear. In vitro investigations have shown that it prolongs action potential duration without affecting conduction velocity in atrial and ventricular tissue.¹³ In humans similar class III activity has been reported in the atria,^{14,15} accessory pathways,^{16,17} and on normal and infarcted ventricle.^{18,19} The lack of effect of sotalol on P wave duration demonstrated in the study is consistent with a lack of effect on conduction velocity in the atrium. Low frequency energy (which remained unaffected) may also reflect conduction velocity, as found in ventricular tissue.^{20,21} The significant decreases in higher frequency energy suggest a reduction in fractionation of atrial activation. Increased action potential duration could reduce fractionation by either increasing entrance block to areas of slow conduction¹⁸ or reducing heterogeneity in repolarisation.

Our results are consistent with the effects of higher doses of sotalol on the signal averaged QRS complex.²² In a time domain analysis of ventricular late potentials in patients not given antiarrhythmic treatment and while receiving larger doses of sotalol than were used in our patients a decrease in filtered QRS duration was observed in patients in whom sotalol prevented inducible ventricular tachycardia at electrophysiological study, but QRS duration increased in those who remained inducible. If the QRS complex was divided into an initial portion, representing normal ventricular activation, and a fractionated, high frequency (late potential) terminal portion, all of the changes in QRS complex duration were due to lengthening or shortening of the high frequency terminal part of the QRS. Thus, efficacy of sotalol in the ventricle was predicted by reduction in high frequency fractionated activity on the surface electrocardiogram. Similar fractionation during right atrial activation may occur in patients with paroxysmal atrial fibrilla-

tion within the P wave rather than at its end. Our findings suggest that sotalol reduces this high frequency activity in the atria as well as in the ventricles.

The dose of sotalol used in this study was low (80–240 mg daily). The electrophysiological effects of sotalol in humans have been observed during either intravenous administration of 1–3 mg/kg of the drug or oral dosing with 160 mg or more daily. Kunze *et al* reported prolongation of the refractory period of accessory pathways in patients with Wolff-Parkinson-White syndrome at oral doses of sotalol ranging from 160 to 320 mg per day¹⁷ and lengthening of atrial action potential has been found after a single intravenous dose of 1 mg/kg—that is about 70 mg.¹⁵ Some authors have suggested that sotalol at low doses acts predominantly as a β blocker,²³ but more sophisticated analysis of ventricular repolarisation during exercise has not confirmed these findings.¹⁹ Nevertheless, it is possible that the effects on the signal averaged P wave that we have observed might not be related to the class III effect of the drug, but to its β blocking action, although the lack of any correlation between heart rate reduction and decrease in high frequency energy would not support this. Further study of patients taking serial drugs, including sotalol, “pure” β blockers, and possibly class I agents is required to investigate more fully the relation between the effects of different classes of antiarrhythmic drugs and changes in the surface P wave.

Limitations of this study include its sequential design and unblinded analysis of the P wave. However, the results of repeated signal averaged P wave recordings in a small group of individuals presented in this paper do not show any trend towards a decrease in energy over time. Blinded assessment of the P wave end points is unlikely to have altered the results, as with our system these are defined entirely automatically.

Analysis of serial signal averaged P wave recordings is likely to be a useful technique for studying the effects of antiarrhythmic drugs on atrial electrophysiology. Further investigation of changes in the signal averaged P wave after treatment with other antiarrhythmic agents, the effects of which on the atria are known, may allow more detailed correlation between the characteristics of the surface P wave and changes in underlying atrial electrophysiology. Future potential applications for this technique include the non-invasive assessment of the electrophysiological properties of drugs under development and prediction of efficacy for antiarrhythmic treatment in patients with atrial arrhythmia.

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- Engel TR, Vallone N, Windle J. Signal-averaged electrocardiograms in patients with atrial fibrillation or flutter. *Am Heart J* 1988;115:592–7.
- Kawano S, Hiraoka M, Sawanobori T. Electrocardiographic features of P waves from patients with transient atrial fibrillation. *Jp Heart J* 1988;29:57–67.

- 3 Opolski G, Stanislawska J, Slomka K, Kraska T. Value of the atrial signal-averaged electrocardiogram in identifying patients with paroxysmal atrial fibrillation. *Int J Cardiol* 1991;30:315-9.
- 4 Stafford PJ, Turner I, Vincent R. Quantitative analysis of signal averaged P waves in idiopathic paroxysmal atrial fibrillation. *Am J Cardiol* 1991;68:751-5.
- 5 Baciarello G, Bella R, Di Maio F, Sgrigna V, Villani M, Villatico Campbell S, et al. Analysis of high resolution atrial activation: report on 403 cases. *Am Heart J* 1987;113:307-15.
- 6 Yamada T, Fukunami M, Ohmori M, Kumagai K, Sakai A, Kondoh N, et al. Characteristics of frequency content of atrial signal-averaged electrocardiograms during sinus rhythm in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1992;19:559-63.
- 7 Leier CV, Meacham JA, Schaal SF. Prolonged atrial conduction. A major predisposing factor for the development of atrial flutter. *Circulation* 1978;57:213-6.
- 8 Buxton AE, Waxman HL, Marchlinski FE, Josephson ME. Atrial conduction: effects of extrastimuli with and without atrial dysrhythmias. *Am J Cardiol* 1984;54:755-61.
- 9 Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanchez MA, Tamargo L. Electrophysiologic studies in atrial fibrillation. Slow conduction of premature impulses: a possible manifestation of background for reentry. *Am J Cardiol* 1983;61:122-30.
- 10 Stafford PJ, Robinson D, Vincent R. Optimal analysis of the signal averaged P wave in patients with paroxysmal atrial fibrillation. *Br Heart J* 1995;74:413-8.
- 11 Pellerin D, Attuel P, Davy JM, Slama M, Motte G. Evaluation of signal averaged P-wave in patients with and without history of atrial arrhythmias. Comparison with ECG and electro-physiological study [abstract]. *Eur Heart J* 1991;12(suppl):278.
- 12 Stafford PJ, Denbigh P, Vincent R. Frequency analysis of the P wave: comparative techniques. *PACE* 1995;18:261-70.
- 13 Strauss HC, Bigger JT, Hoffman BF. Electrophysiological and beta-receptor blocking effects of MJ 1999 on dog and rabbit cardiac tissue. *Circ Res* 1970;26:661-77.
- 14 Echt DS, Berte LE, Clusin WT, Samuelsson RG, Harrison DC, Mason JW. Prolongation of the human monophasic action potential by sotalol. *Am J Cardiol* 1982;50:1082-6.
- 15 Hayward RP, Taggart P. Effect of sotalol on human action potential duration and refractoriness: cycle length dependency of class III activity. *Cardiovascular Res* 1986;20:100-7.
- 16 Bennett DH. Acute prolongation of myocardial refractoriness by sotalol. *Br Heart J* 1982;47:521-6.
- 17 Kunze KP, Schluter M, Kuck KH. Sotalol in patients with Wolff-Parkinson-White syndrome. *Circulation* 1987;75:1050-7.
- 18 Cobbe SM, Hoffman E, Ritzenhoff A, Brachmann J, Kubler W, Senges J. Action of sotalol on potential reentrant pathways and ventricular tachyarrhythmias in conscious dogs in the late postmyocardial infarction phase. *Circulation* 1983;68:865-71.
- 19 Funck-Brentano C, Kibleur Y, Coz FL, Poirier JM, Mallet A, Jaillon P. Rate dependence of sotalol-induced prolongation of ventricular repolarisation. *Circulation* 1991;83:536-45.
- 20 Piccolo E, Raviele A, Delise P, Dainese F, Pascotto P, Totaro G, et al. The role of left ventricular conduction in the electrogenesis of left ventricular hypertrophy. *Circulation* 1979;59:1044-55.
- 21 David D, Naito M, Michelson E, Watanabe Y, Chen C, Morganroth J, et al. Intramyocardial conduction: a major determinant of R wave amplitude during acute myocardial ischaemia. *Circulation* 1982;65:161-7.
- 22 Freedman RA, Karagounis LA, Steinberg JS. Effects of sotalol on the signal-averaged electrocardiogram in patients with sustained ventricular tachycardia: relation to suppression of inducibility and changes in tachycardia cycle length. *J Am Coll Cardiol* 1992;20:1213-9.
- 23 Wang T, Bergstrand RH, Thompson KA, Siddoway LA, Duff HJ, Woolsey RL, et al. Concentration-dependent pharmacologic properties of sotalol. *Am J Cardiol* 1986;57:1160-5.