**Electrophysiology**

# Effect of Metoprolol and *d,l*-Sotalol on Microvolt-Level T-Wave Alternans

## Results of a Prospective, Double-Blind, Randomized Study

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| **OBJECTIVES** | The study evaluated the effects of metoprolol, a pure beta-blocker, and *d,l*-sotalol, a beta-blocker with additional class III antiarrhythmic effects, on microvolt-level T-wave alternans (TWA). |
| **BACKGROUND** | Assessment of TWA is increasingly used for purposes of risk stratification in patients prone to sudden death. There are only sparse data regarding the effects of beta-blockers and antiarrhythmic drugs on TWA. |
| **METHODS** | Patients with a history of documented or suspected malignant ventricular tachyarrhythmias were eligible. All patients underwent invasive electrophysiologic (EP) testing including programmed ventricular stimulation and determination of TWA at increasing heart rates using atrial pacing. Reproducibility of TWA at two consecutive drug-free baseline measurements was tested in a random patient subset. Following baseline measurements, all patients were randomized either to double-blind intravenous infusion of sotalol (1.0 mg/kg) or metoprolol (0.1 mg/kg). Results of TWA assessment at baseline and after drug exposure were compared. |
| **RESULTS** | Fifty-four consecutive patients were studied. In 12 patients, repetitive baseline measurement of TWA revealed stable alternans voltage ($V_{alt}$) values (9.1 ± 5.8 $\mu$V vs. 8.5 ± 5.7 $\mu$V, p = NS). After drug administration, $V_{alt}$ decreased by 35% with metoprolol (7.9 ± 6.0 $\mu$V to 4.9 ± 4.2 $\mu$V; p < 0.001) and by 38% with sotalol (8.6 ± 6.8 $\mu$V to 4.4 ± 2.3 $\mu$V; p = 0.001). In eight patients with positive TWA at baseline, repeated measurement revealed negative test results. |
| **CONCLUSIONS** | In patients prone to sudden cardiac death, there is a reduction in TWA amplitude following the administration of antiadrenergic drugs. This result indicates that TWA is responsive to the pharmacologic milieu and suggests that, to assess a patient's risk of spontaneous ventricular arrhythmia, the patient should be tested while maintaining the pharmacologic regimen under which the risk of arrhythmia is being assessed. This applies particularly for beta-blocker therapy. (J Am Coll Cardiol 2001;38:2013–9) © 2001 by the American College of Cardiology |

Microvolt-level T-wave alternans (TWA) that is not visibly apparent on the electrocardiogram (ECG) can be detected during atrial pacing or during submaximal exercise, resulting in modest heart rate increases in patients with ventricular arrhythmias but not in control subjects (1). Assessment of TWA is increasingly used to stratify patients with heart disease for their risk of sudden arrhythmogenic death (2–5). Pastore and associates (6) recently demonstrated in a series of elegant experiments using high-density optical mapping techniques that there is a close link between TWA and the underlying mechanism of reentry. According to this mechanism, above a critical threshold heart rate, action potentials from neighboring cells alternate with opposite phase that greatly amplifies spatial dispersions of repolarization, which, in turn, form the substrate for unidirectional block and re-entry.

The influence of the autonomic nervous system on TWA is incompletely understood. Whereas previous investigations provided evidence for a role of the sympathetic limb in eliciting TWA (7), recent observations by Kaufman et al. (8) suggest that sympathetic activation is not mandatory for the occurrence of arrhythmogenic TWA. Similarly, only sparse data exist on the modulating effects of antiarrhythmic drugs on TWA (9,10). From a clinical perspective, however, these issues are of particular importance because most patients at risk for serious ventricular arrhythmias are treated with antiadrenergic drugs and many are receiving antiarrhythmic drugs, which prolong ventricular repolarization. Accordingly, the present prospective study was designed to evaluate specifically the effects of metoprolol, a pure beta-blocker, and sotalol, a beta-blocker with additional class III antiarrhythmic effects (11), on microvolt-level TWA in patients prone to sudden cardiac death.

## METHODS

**Patient population.** Consecutive patients who were referred to the arrhythmia service of the J.W. Goethe Uni-

**Abbreviations and Acronyms**

CAD = coronary artery disease
ECG = electrocardiogram/electrogardiographic
EP = electrophysiologic
ERP = effective refractory period
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
RV = right ventricular
TWA = T-wave alternans
$V_{alt}$ = alternans voltage
VF = ventricular fibrillation
VT = ventricular tachycardia

versity, Frankfurt, Germany, for evaluation of ventricular tachyarrhythmias were eligible for participation if they had one of the following: an episode of survived out-of-hospital cardiac arrest; documented sustained monomorphic ventricular tachycardia (VT); syncope in the presence of significant organic heart disease; or of nonsustained VT and reduced left ventricular function in the setting of chronic coronary artery disease (CAD). All patients had undergone extensive noninvasive and invasive diagnostic evaluation to establish the underlying heart disease. Patients were excluded if they had evidence of active ischemia, were in atrial fibrillation, or if a permanent pacemaker had previously been implanted. Patients receiving chronic amiodarone treatment were also excluded. All patients gave informed consent prior to enrollment in the study.
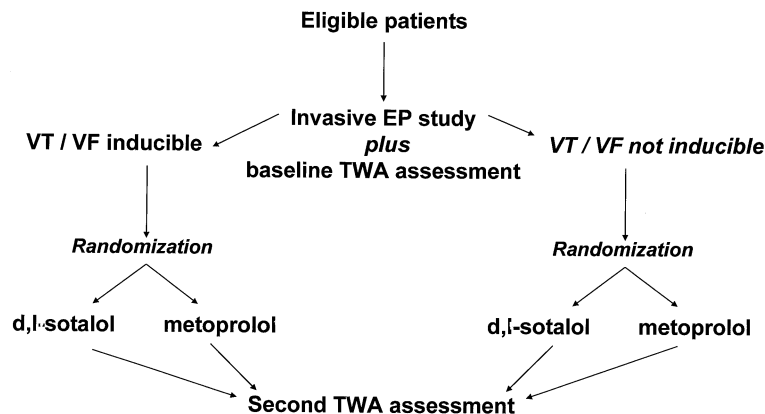
**Study protocol.** ELECTROPHYSIOLOGIC STUDY. Previously administered antiarrhythmic drugs and beta-blockers were withheld for at least 5 half-lives prior to electrophysiologic (EP) study. Three multipolar electrode catheters were positioned via the right or left femoral vein in the high right atrium, the right ventricular apex and the His bundle region. Programmed ventricular stimulation was performed according to a standardized protocol at two different sites (right ventricular [RV] apex; RV outflow tract) at basic cycle lengths of 600, 500 and 430 ms using one to three extrastimuli. The results of the EP study were defined as positive if sustained monomorphic VT or ventricular fibril-

lation (VF) was repeatedly induced. According to these results, patients were assigned to two different randomization strata (Fig. 1).

**Assessment of TWA.** For assessment of microvolt TWA, the spectral method described by Smith et al. (12) was applied using the system CH2000 (Cambridge Heart, Bedford, Massachusetts). This measurement has been described in detail elsewhere (13,14). Because of the low-amplitude nature of TWA, particular attention was paid to ensure adequate signal quality during TWA recording. Standard ECG leads along with the Frank orthogonal (XYZ) configuration were utilized. Multicontact silver–silver chloride electrodes specifically designed for noise reduction (HiRes, Cambridge Heart) were used. The TWA was measured using atrial stimulation at increasing heart rates of from 90 to 130 beats/min. Each pacing cycle length was maintained for at least 3 min. The TWA was defined as positive if the TWA voltage ($V_{alt}$) was >1.9 $\mu$V (at rest 1.0 $\mu$V) with the alternans ratio K—a measure of TWA significance—being >3.

**Measurement of TWA voltage.** The TWA recordings were interpreted by one of the investigators (T. K.) who was unaware of the patient's history, the drug administered, inducibility, or the sequence of TWA recordings. The magnitude of TWA voltage ($V_{alt}$) in individual patients was measured as follows: TWA spectra were printed (Fig. 2) and the two recordings of each patient compared as to the quality of the recordings at different corresponding heart rates. The $V_{alt}$ was measured at the highest common heart rate by picking the highest amplitude from the TWA trend summary of baseline and on-drug recordings. Because TWA amplitude is usually most pronounced in the precordial leads $V_2$ through $V_4$, these leads were selected for $V_{alt}$ determination.

**Assessment of TWA reproducibility.** Intraindividual reproducibility of TWA measurements during baseline was assessed in 12 randomly selected patients. These patients underwent two repetitive baseline TWA assessments 30 min apart from each other prior to randomization to drug treatment.

Eligible patients

Invasive EP study
*plus*
baseline TWA assessment

VT / VF inducible ← → *VT / VF not inducible*

*Randomization*                    *Randomization*

d,l-sotalol    metoprolol          d,l-sotalol    metoprolol

Second TWA assessment

**Figure 1.** Study protocol. EP = electrophysiologic; TWA = T-wave alternans; VF = ventricular fibrillation; VT = ventricular tachycardia.

**A**



**B**
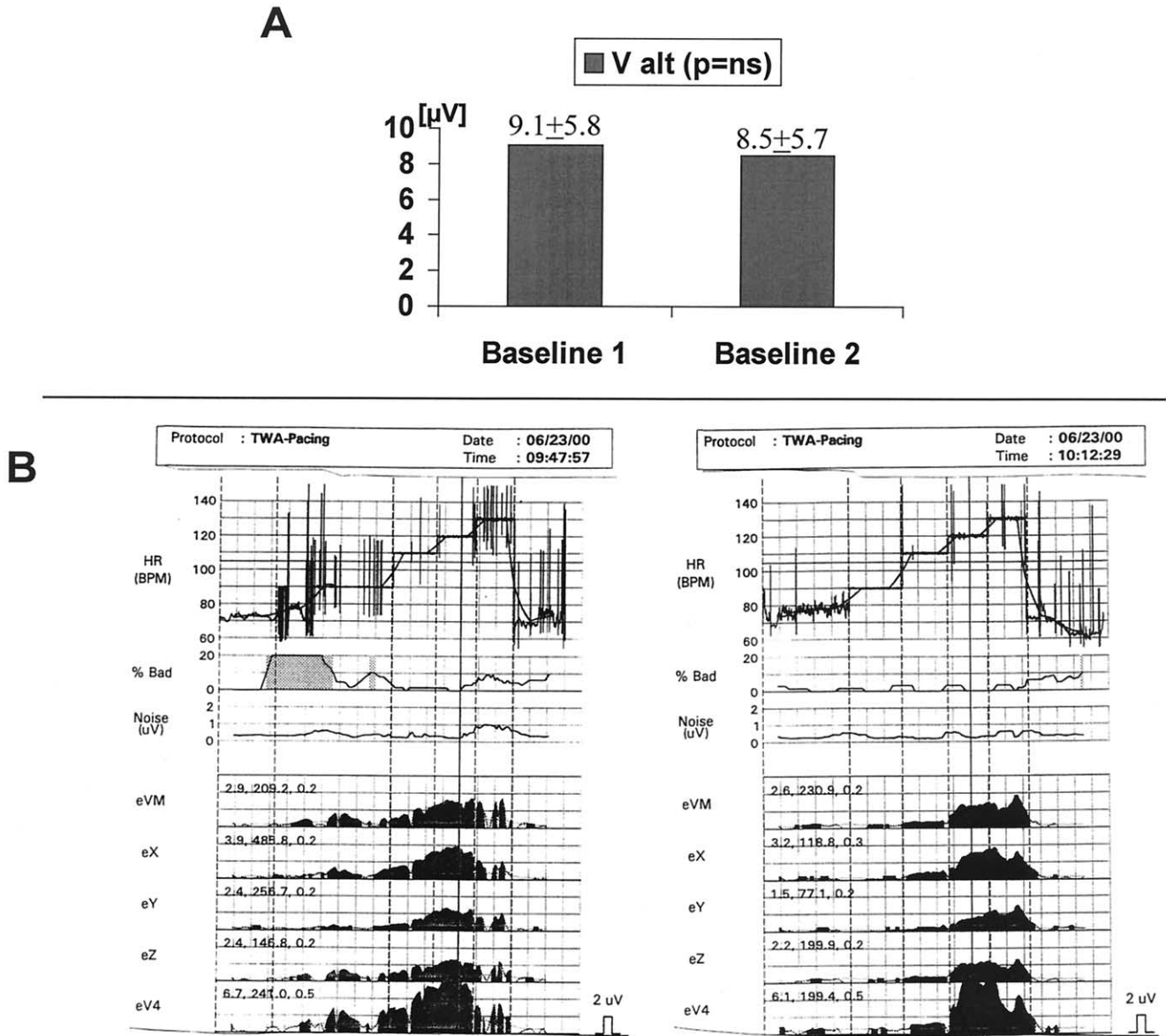


**Figure 2.** Reproducibility of T-wave alternans (TWA) analysis. **(A)** TWA amplitudes (alternan voltage [$V_{alt}$]) at two repetitive drug-free baseline measurements in 12 patients. **(B)** Representative TWA recordings in a patient with stable TWA amplitudes ($V_{alt}$) at repetitive drug-free measurements (NS = not significant). BPM = beats per minute; HR = heart rate.

**Randomized intervention.** After completion of baseline measurements, patients were randomized in a double-blind fashion to either metoprolol or *d,l*-sotalol treatment. Randomization was performed in two separate strata according to inducibility at EP testing (Fig. 1). Study drug was administered intravenously over 5 min at a dose of 1 mg/kg sotalol or a dose of 0.1 mg/kg metoprolol. On-drug TWA measurement was started 10 min after the end of drug infusion. Resting heart rate and ventricular effective refractory period (ERP) were also determined for comparison with baseline values.

**Statistical analysis.** Differences within and between (interaction) the two treatment groups with regard to the changes in heart rate, ERP, and TWA amplitude were performed using the two-way repeated measures analysis of variance

(Statistical Package for Social Sciences [SPSS], version 7.0). Mean values and standard deviations are given. A p value $<0.05$ was defined as statistically significant.

## RESULTS

**Baseline characteristics.** A total of 65 patients (mean age $61 \pm 10$ years; left ventricular ejection fraction [LVEF] $37 \pm 13\%$) were included in the study. Of these, 11 had to be excluded from the final data analysis for the following reasons: high incidence of spontaneous ventricular extrasystoles during atrial stimulation preventing accurate TWA determination in seven patients; increase in Wenckebach point after drug administration excluding comparison of TWA at corresponding heart rates in two patients; and

**Table 1.** Patients' Demographic Data

|  | N (%) |
|---|---|
| Age (yrs) | 61 ± 10 |
| Male gender | 47 (87%) |
| LVEF (%) | 37 ± 13 |
| CAD | 38 (70%) |
| Indication for EP study |  |
|    Ventricular fibrillation | 17 (30%) |
|    Sustained VT | 16 (30%) |
|    Nonsustained VT | 11 (20%) |
|    Syncope | 10 (19%) |
| EP inducible (%) | 29 (54%) |
| TWA positive (%) | 48 (89%) |

CAD = coronary artery disease; EP = electrophysiologic; LVEF = left ventricular ejection fraction; TWA = T-wave alternans; VT = ventricular tachycardia.

occurrence of sustained VT during baseline TWA testing in two patients. Accordingly, this report is based on analysis of the data obtained in 54 patients. Of these, 38 patients (70%) had CAD, whereas 16 (30%) had nonischemic cardiomyopathy (Table 1).

**Results of EP testing and baseline TWA assessment.** Sustained VT or VF was induced in 29 of 54 patients (54%), specifically in 25 of 38 patients (66%) with CAD and in 4 of 16 patients (25%) with nonischemic cardiomyopathy (p = 0.01). Overall, TWA was positive in 48 patients (89%). The incidence of a positive TWA was not significantly different in patients with documented VT/VF (32/34 patients; 94%) compared to those with a history of nonsustained VT or syncope (16/20 patients; 80%; p = 0.11). Except for one inducible patient, all patients (97%) were TWA positive. In noninducible patients, the prevalence of a positive TWA was lower, with 20 of 25 patients (80%; p = 0.06, compared to inducible patients). Baseline $V_{alt}$ (8.7 ± 7.1 $\mu$V vs. 7.7 ± 5.4 $\mu$V; p = 0.56) and TWA onset heart rate (96 ± 10 beats/min vs. 100 ± 11 beats/min; p = 0.63) were similar in both inducible and noninducible patients. Repeated baseline TWA testing was performed in 12 randomly selected patients whose demographic characteristics were comparable to those of the entire study cohort. The TWA amplitude was comparable between both tests (mean $V_{alt}$ 9.1 ± 5.8 $\mu$V vs. 8.5 ± 5.7 $\mu$V; p = 0.2; Fig. 2). A representative example of repetitive drug-free TWA measurements is shown in Figure 2.

**Effects of metoprolol and *d,l*-sotalol on TWA.** Of the 54 patients, 25 received metoprolol and 29 *d,l*-sotalol. Both drugs resulted in a comparable decrease in resting heart rate (metoprolol: 79 ± 12 beats/min to 67 ± 10 beats/min; sotalol: 75 ± 12 beats/min to 60 ± 9 beats/min; p < 0.01 for both comparisons). Ventricular ERP increased significantly from 244 ± 26 ms to 276 ± 36 ms (p < 0.001) in patients treated with sotalol and from 237 ± 25 ms to 257 ± 31 ms (p = 0.002) in patients receiving metoprolol. These changes in heart rate and ERP were comparable within the two treatment groups (p = 0.67 and p = 0.31, respectively).

In 8 of 48 patients with positive baseline TWA, the TWA turned negative after drug administration; five patients had received metoprolol, and three had received sotalol. Baseline $V_{alt}$ was lower in these eight patients as compared to those who remained TWA positive after beta-blockers (4.1 ± 1.4 $\mu$V vs. 9.2 ± 6.7 $\mu$V; p = 0.026). Administration of beta-blockers in these patients reduced $V_{alt}$ below 2 $\mu$V. Four of these patients (50%) had inducible VT/VF compared to 23 of 40 (56%) patients in whom TWA remained positive after drug administration (p = 0.71). All six patients with a negative TWA at baseline remained negative after drug administration.

A significant decrease in $V_{alt}$ occurred after drug administration in the entire patient population (8.4 ± 6.4 $\mu$V to 4.7 ± 3.3 $\mu$V; p < 0.001) as well as in the subgroup of patients with CAD (8.2 ± 6.8 $\mu$V to 4.5 ± 3.5 $\mu$V; p < 0.001). The decrease in $V_{alt}$ was comparable in patients receiving metoprolol (7.9 ± 6.0 $\mu$V vs. 4.9 ± 4.2 $\mu$V; p < 0.001) and in those treated with sotalol (8.6 ± 6.8 $\mu$V vs. 4.4 ± 2.3 $\mu$V; p = 0.001). A representative example of drug-induced reduction in $V_{alt}$ is shown in Figure 3. The heart rate at which TWA became detectable was similar at baseline and on-drug assessment in both study groups (metoprolol 94 ± 8 beats/min vs. 95 ± 7 beats/min; p = 0.86; sotalol: 99 ± 10 beats/min vs. 98 ± 12 beats/min; p = 0.83). The observed changes in $V_{alt}$ and onset heart rate were comparable within the two treatment groups (p = 0.905 and p = 0.602, respectively).

## DISCUSSION

The major finding of this prospectively designed study is that the cardioselective beta-blockers metoprolol and sotalol, which additionally prolongs ventricular repolarization, exert comparable effects on TWA. Both substances reduce overall TWA amplitude when measurements are compared to drug-free baseline assessment. However, TWA amplitude remained well above the conventionally defined level of significance (1–5). Importantly, only few patients become TWA-negative after short-term drug administration. Another finding worth emphasizing is that repeated measurements of microvolt TWA yielded comparable results. These findings have implications both with respect to the underlying EP mechanism of TWA and for the clinical usefulness of TWA determination to stratify patients for their risk of ventricular tachyarrhythmias and sudden cardiac death.

**Sympathetic nervous system and TWA.** There are conflicting reports in the literature on the role of the sympathetic nervous system in triggering TWA. One of the first observations related to this issue was reported in 1975 by Schwartz and Malliani (7), who described the case of a nine-year-old girl with the idiopathic long QT syndrome who repeatedly showed macroscopic TWA during episodes of sympathetic excitation. In the same report, experimental findings in vagotomized cats were described. In these animals, TWA could be elicited during stimulation of the left stellate ganglion. Subsequently, several similar observa-
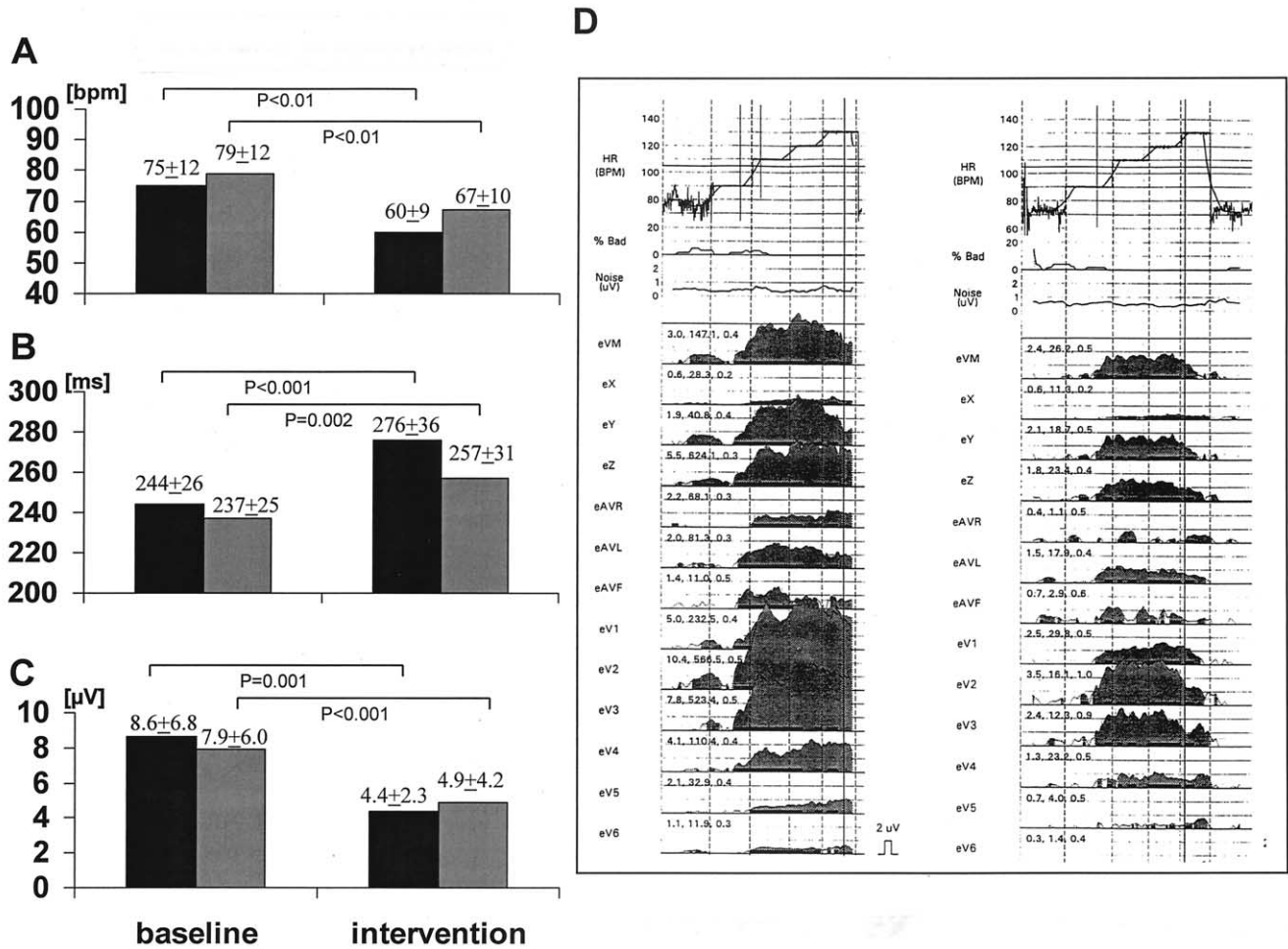
**Figure 3.** (A) Changes in heart rate following drug administration. (B) Changes in ventricular effective refractory periods following drug administration. (C) Changes in T-wave alternans (TWA) amplitude following drug administration ($V_{alt}$) in patients with *d,l*-sotalol (**dark bars**) and metoprolol (**gray bars**). (D) Representative example of a patient with a significant decrease in $V_{alt}$ in nearly all electrocardiographic leads following administration of *d,l*-sotalol (**left**: before drug administration; **right**: after drug administration). BPM = beats per minute; HR = heart rate.

tions in patients afflicted with the long QT syndrome were reported (15). These experimental findings along with the clinical observations led to the hypothesis that increases in sympathetic activity may play a critical role in triggering TWA as a precursor of malignant ventricular tachyarrhythmias.

In a recent and careful study in patients referred for EP testing, Kaufman et al. (8) measured TWA at identical pacing cycle lengths with and without isoproterenol in 14 patients. Five patients with a history of sudden cardiac death were noninducible at EP testing; in two of these, TWA increased significantly during adrenergic stimulation. In another two patients, beta-adrenergic stimulation induced TWA that was not already present at baseline (8). The investigators concluded from their observations that there is only a modest contribution of adrenergic tone to the occurrence of microvolt TWA in most patients.

In contrast to the report of Kaufman et al. (8), all patients enrolled in the present study had a history of documented or suspected malignant ventricular arrhythmia. Administration of antiadrenergic drugs resulted in a significant decrease in

TWA amplitude in all patients. Of note, however, only a few patients became TWA-negative after infusion of beta-blockers. From these observations, therefore, it appears tempting to speculate that, at least in some patients prone to sudden cardiac death, sympathetic activation plays a role in triggering the occurrence of discordant alternans in diseased regions of the myocardium. This hypothesis accords with findings demonstrating regional differences in sympathetic activation in patients after myocardial infarction (16,17).

The findings of the present prospective randomized study are further supported by preliminary observations reported on modulation of TWA by autonomic influences (18). The effects of selective sympathetic (esmolol, n = 17) or parasympathetic (atropine, n = 17) blockade on TWA were examined in 34 patients with inducible sustained VT. The $V_{alt}$ decreased with both sympathetic and parasympathetic blockade, but this decrease was more impressive with beta-blockade. Specifically, $V_{alt}$, measured in the vector magnitude lead, decreased from 2.2 ± 1.9 μV to 1.3 ± 1.9 μV (p < 0.05) with esmolol, resulting in a decrease of TWA sensitivity for prediction of EP results, from 71% to

35% (p = 0.08) (18). In contrast to our study, however, the baseline $V_{alt}$ was 2.2 $\mu$V, which is just above the predefined positivity level of 1.9 $\mu$V. In the present study, baseline $V_{alt}$, measured in the precordial leads, which tends to have a greater magnitude, averaged 8.4 $\mu$V, and TWA sensitivity decreased only from 88% to 72% (p = 0.06) with beta-blockers.

Finally, the well-appreciated benefits of beta-blocker therapy in preventing sudden arrhythmogenic death support the notion of a modulating effect of antiadrenergic therapy on triggers for ventricular tachyarrhythmias such as TWA (19).

**Prolongation of ventricular repolarization by antiarrhythmic drugs and TWA.** Despite the fact that assessment of microvolt-level TWA is increasingly used for risk stratification (2–5,20), to the best of our knowledge only one prospective study deals with the effects of antiarrhythmic drugs on TWA in patients with structural heart disease (10). Kavesh et al. (10) evaluated the effects of procainamide on TWA in 24 patients with inducible sustained VT at baseline and after acute drug loading. The magnitude of TWA amplitude decreased from 0.6 ± 0.8 $\mu$V to 0.3 ± 0.4 $\mu$V during sinus rhythm, from 2.0 ± 1.6 $\mu$V to 0.7 ± 0.7 $\mu$V during pacing at 100 beats/min, and from 3.0 ± 2.0 $\mu$V to 1.7 ± 1.8 $\mu$V during pacing at 120 beats/min (p < 0.001). This resulted in a decrease in the sensitivity of TWA for induction of sustained VT from 87% to 60% at a heart rate of 120 beats/min (10). It is again important to note that the mean TWA amplitude reported in that trial was markedly lower than that measured in the present study.

The only study dealing with the effects of class III antiarrhythmic drugs on TWA is a retrospective analysis evaluating the prevalence of TWA in relationship to amiodarone usage in patients with implantable cardioverter-defibrillators (ICDs) (9). In that study, Groh et al. (9) reported that a positive TWA was found only in 1 of 9 ICD patients (11%) treated with amiodarone as compared with 14 of 22 (64%) patients without antiarrhythmic drug therapy. During follow-up, the presence of TWA predicted future appropriate ICD therapy for ventricular tachyarrhythmias (9).

In our study, the decrease in TWA amplitude observed after sotalol administration was comparable to that following metoprolol infusion. This suggests that the effect of sotalol on ventricular repolarization is less important in terms of modulating TWA, at least during short-term administration.

**Clinical implications.** The observations from this prospective study have a number of important implications for the clinical use of TWA determination for risk stratification in patients with structural heart disease. First, there is a good intraindividual reproducibility of TWA assessment in the absence of beta-blockers or antiarrhythmic drugs. Second, in agreement with previous studies (2–5,13), there is a patient-specific heart rate threshold at which micro-

volt TWA becomes detectable. In patients with significant organic heart disease, this threshold is about 90 to 110 beats/min. Third, in patients at high risk for ventricular tachyarrhythmias, such as the ones enrolled in our study, TWA is usually measurable even in the presence of antiadrenergic medication. This prospective study, in conjunction with the earlier studies cited above (8–10), indicates that TWA is responsive to the pharmacologic milieu. In particular, we find here that beta-blockers tend to reduce TWA; beta-blockers are also known to reduce risk of spontaneous ventricular arrhythmia. Because cardioactive drugs may alter TWA and may also modulate susceptibility to spontaneous ventricular arrhythmias, it would seem to make most sense to perform TWA testing for purposes of risk stratification while maintaining the ongoing pharmacologic milieu of the patient. When the pharmacologic milieu of the patient is altered, TWA testing should be repeated to determine whether TWA status is altered.

A specific issue arises in this regard with respect to beta-blockers. T-wave alternans testing is most commonly performed noninvasively during stress testing. One effect of beta-blocker therapy is to limit the peak heart rate that may be achieved by a patient during exercise stress. Initially, a stress TWA test was interpreted to be negative if the criteria for positivity were not met and significant TWA was documented not to be present for at least 1 min at a heart rate of at least 105 beats/min (e.g., see Gold et al. [3]). Patients on beta-blockers frequently cannot attain a heart rate of 105 beats/min for this period of time and, thus, if not meeting the criteria for positivity, would be classified as indeterminate. For this reason, beta-blockers would be withheld for 24 h prior to TWA testing (3). The present study demonstrates that testing patients on beta-blockers is feasible, with only a few patients turning TWA-negative after the drug.

In a recent study of heart-failure patients without prior history of ventricular arrhythmias (5) we prospectively determined not to withhold beta-blockers; accordingly, we prospectively modified the criteria for negativity to also include patients who did not meet the criteria for positivity, who had a maximal stress test achieving a maximum heart rate of at least 80 beats/min, and who had no significant alternans for at least 1 min at a heart rate within 5 beats/min of their maximum rate. None of the patients classified as negative by this criterion subsequently sustained a ventricular tachyarrhythmic event. These results also suggest that beta-blockers may reduce arrhythmic risk both via a direct myocardial effect and also by blocking an arrhythmogenic increase in heart rate.

**Study limitations.** The present study must be interpreted in the face of certain limitations. Because of obvious logistic reasons, we used only acute drug administration to assess changes in TWA. This, of course, does not necessarily imply that the same or similar changes can be observed during prolonged administration of beta-blockers or sotalol. A second potential limitation is the fact that we did not

examine the effects of class I antiarrhythmic drugs. However, the use of this class of substances in patients with structural heart disease and serious ventricular arrhythmias has markedly decreased as the result of numerous prospective studies, including the Cardiac Arrhythmia Suppression Trial (21–23).

**Conclusions.** In patients with a history of documented or suspected ventricular tachyarrhythmias, there is a reduction in TWA amplitude following the administration of antiadrenergic drugs such as metoprolol and *d,l*-sotalol. This indicates that TWA is modulated—at least in some patients—by sympathetic activity. The fact that TWA is responsive to the pharmacologic milieu—as is the risk of spontaneous ventricular arrhythmias—suggests that for purposes of risk stratification TWA ought to be determined without alteration of the patient's ongoing pharmacologic regimen.

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## REFERENCES

1. Costantini O, Drabek C, Rosenbaum DS. Can sudden cardiac death be predicted from the T wave of the ECG? A critical examination of T-wave alternans and QT interval dispersion. Pacing Clin Electrophysiol 2000;23:1407–16.
2. Estes NAM, Michaud G, Zipes DP, et al. Electrical alternans during rest and exercise as predictors of vulnerability to ventricular arrhythmias. Am J Cardiol 1997;80:1314–8.
3. Gold MR, Bloomfield DM, Anderson KP, et al. A comparison of T-wave alternans, signal-averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol 2000;36:2247–53.
4. Hohnloser SH, Klingenheben T, Li YG, Zabel M, Petermans J, Cohen RJ. T-wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers. J Cardiovasc Electrophysiol 1998;12:1258–68.
5. Klingenheben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. Lancet 2000;356:651–2.
6. Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999;99:1385–94.
7. Schwartz PJ, Malliani A. Electrical alternation of the T wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. Am Heart J 1975;89:45–50.
8. Kaufman ES, Mackall JA, Julka B, Drabek C, Rosenbaum DS. Influence of heart rate and sympathetic stimulation on arrhythmic T-wave alternans. Am J Physiol 2000;279:H1248–55.
9. Groh WJ, Shinn TS, Engelstein EE, Zipes DP. Amiodarone reduces the prevalence of T-wave alternans in a population with ventricular tachyarrhythmias. J Cardiovasc Electrophysiol 1999;10:1335–9.
10. Kavesh NG, Shorofsky SR, Sarang SE, Gold MR. The effect of procainamide on T wave alternans. J Cardiovasc Electrophysiol 1999;10:649–54.
11. Hohnloser SH, Woosley RD. Sotalol. N Engl J Med 1994;331:31–8.
12. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ. Electrical alternans and cardiac electrical instability. Circulation 1988;77:110–21.
13. Hohnloser SH, Klingenheben T, Zabel M, Li YG, Albrecht P, Cohen RJ. T-wave alternans during exercise and atrial pacing in humans. J Cardiovasc Electrophysiol 1997;8:987–93.
14. Rosenbaum DS, Albrecht P, Cohen RJ. Predicting sudden cardiac death from T wave alternans of the surface electrocardiogram: promise and pitfalls. J Cardiovasc Electrophysiol 1996;7:1095–111.
15. Goldman DS, Zareba W, Moss AJ. Malignant T-wave alternans. Circulation 2000;102:e46–7.
16. Barber MJ, Mueller TM, Henry DP, Felten SY, Zipes DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. Circulation 1983;67:787–96.
17. Zipes DP, Wellens HJJ. Sudden cardiac death. Circulation 1998;98:2334–51.
18. MacMurdy KS, Kirk MM, Cooklin M, Shorofsky SR, Gold MR. The effect of selective autonomic blockade on T wave alternans (abstr). Circulation 1999;100 Suppl:2683.
19. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;5:335–71.
20. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994;330:235–41.
21. Echt DS, Liebson PR, Mitchell B, et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781–8.
22. The Cardiac Arrhythmia Suppression Trial II investigators. Effect of the antiarrhythmic agent moricizine in survival after myocardial infarction. N Engl J Med 1992;327:227–33.
23. Mason JW for the Electrophysiologic Study versus Electrocardiographic Monitoring investigators. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. N Engl J Med 1993;329:452–8.