Modification of the Circadian Pattern of Ventricular Tachyarrhythmias by Beta-Blocker Therapy

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Summary

Background: Sudden cardiac death exhibits a circadian variation and predominantly occurs during morning hours. Beta-adrenergic antagonists have shown to blunt this morning peak. However, previous reports studying the effects of beta blockers on the circadian variation did not analyze the underlying cause of sudden cardiac death. It thus remains unclear whether ventricular tachyarrhythmias are influenced by beta-blocker therapy.

Hypothesis: This study tested the hypothesis that beta-blocking agents blunt the morning peak of life-threatening ventricular tachyarrhythmias.

Methods: In 87 patients who were treated and monitored with an implantable cardioverter defibrillator, the circadian distribution of ventricular tachyarrhythmias terminated by appropriate shocks was analyzed and compared in those receiving beta blockers versus those not receiving beta-blocker therapy.

Results: Tachyarrhythmic episodes in the absence of beta-blocker therapy ($n = 344$) exhibited a circadian variation with a distinct morning peak (16, 38, 28, and 18% of episodes at 0–6, 6–12, 12–18, and 18–24 h, respectively, $p < 0.001$). In contrast, tachyarrhythmic episodes during beta-blocker therapy ($n = 104$) were equally distributed over time (22, 27, 24, and 27% of episodes at 0–6, 6–12, 12–18, and 18–24 h, respectively, $p = 0.95$). The circadian distribution of episodes

was significantly different in patients with and those without beta blockade ($p < 0.05$).

Conclusion: Beta-adrenergic antagonists influence the circadian distribution of malignant ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. The blunted morning peak of tachyarrhythmic events during beta blockade supports the hypothesis that a sympathetic surge is involved in the circadian pattern of malignant arrhythmias.

Key words: ventricular tachyarrhythmia, beta-blocker therapy, circadian variation, implantable cardioverter defibrillator

Introduction

Sudden cardiac death predominantly occurs during morning hours.^{1–4} A similar circadian variation has recently been reported for malignant ventricular tachyarrhythmias monitored and treated by implantable cardioverter defibrillators (ICDs).^{5–10} The observation of an increased electrical vulnerability of the heart during the morning provides the opportunity for better understanding of the underlying mechanisms that may trigger life-threatening arrhythmias and sudden cardiac death. A surge in sympathetic tone and an augmentation of the sympathetic/vagal balance have been discussed as possible pathophysiologic mechanisms for the increased morning incidence of arrhythmias and sudden death.^{11–13} These concepts have been indirectly supported by a study which showed that beta-adrenergic antagonists are able to blunt the morning peak of sudden cardiac death.¹⁴ In that study, however, the underlying arrhythmia causing sudden death was not analyzed.¹⁴ It thus remains unclear whether the effect of beta blockers on the circadian variation was related to a true morning blunt of malignant tachyarrhythmias, or whether a higher proportion of bradyarrhythmia and asystole, which have been shown to occur without a morning peak,¹⁵ could have resulted in a more even distribution of sudden deaths in the beta-blocker group of that trial.

The purpose of our study was to determine the effects of beta-blocker therapy on the circadian variation of malignant ventricular tachyarrhythmias. To accomplish this, we ana-

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lyzed and compared the circadian distribution of appropriate shock episodes in patients with ICDs receiving beta-blocker therapy versus those not receiving such a therapy. These patients survive recurrent episodes of life-threatening tachycardias and ventricular fibrillation due to ICD discharges and are able to report the time and circumstances of events. Our aim was to test the hypothesis that beta-blocking agents blunt the morning increase of recurrent tachyarrhythmic episodes.

Methods

Study Population

Of 159 consecutive patients treated with an ICD in our institution, all patients with spontaneous and appropriate ICD discharges were included. The follow-up was performed every 2 months or immediately after a spontaneous shock episode and included a physical examination, an interview regarding current medication, and a test of the ICD memory. Patients were asked to keep a precise record of the time and circumstances of subjectively perceived ICD discharges. This record was used to determine the timing of shock episodes in patients with ICDs not capable of recording the precise time of device therapy [Ventak P (CPI Inc., St. Paul, Minn.) and PCD 7217 (Medtronic Inc., Minneapolis, Minn.)]. However, most devices implanted during the study [Ventak PRx1, PRx2, PRx3, P2, P3 (all CPI), PCD 7219 Jewel (Medtronic), and Guardian ATP3 (Telectronics, Englewood, Colo.)] provided a record of the time of ICD therapy.

Shock Episodes

Spontaneous ICD discharges were categorized as appropriate or inappropriate. Appropriate shocks were those assumed to have terminated life-threatening ventricular tachycardias or ventricular fibrillation. Shocks assumed to be triggered by supraventricular tachyarrhythmias were classified as inappropriate shocks. The classification was based on stored electrograms,¹⁶ RR interval analyses of the ICD printout,¹⁷ and on clinical symptoms prior and during a shock.¹⁸ An appropriate shock was defined as an ICD discharge that terminated (1) tachyarrhythmias with wide complexes and a different QRS configuration which was documented in stored electrograms¹⁶ in patients with a PRx2 ($n = 7$), PRx3 ($n = 5$), P2 ($n = 5$), P3 ($n = 3$), PCD 7219 Jewel ($n = 18$), and Guardian ATP3 ($n = 1$); (2) tachyarrhythmic events with pre-shock RR intervals that varied < 80 ms^{16, 17} in patients treated with a Ventak PRx1 ($n = 16$) and a PCD 7217 ($n = 20$); and (3) clinical symptoms such as palpitations, nausea, dizziness, light-headedness, and syncope^{16, 18} in patients treated with a Ventak P (no arrhythmia documentation available) ($n = 12$). Shocks that could not be clearly categorized were counted as inappropriate for the purpose of this study. Tachyarrhythmic episodes terminated by antitachycardiac pacing were not included because the cycle length of these episodes is usually higher compared with rapid tachyarrhythmias which are terminated by shock therapy and

which more likely represent aborted sudden death. In addition, patients are often unaware of these episodes and cannot report the precise time. To avoid a distortion of the circadian variation by single patients who experienced several appropriate shocks within a short period of time, frequent shocks were included as one shock episode. A shock episode was defined as a tachyarrhythmic event with a single or recurrent shock release that was considered to have ended when the patient was free of symptoms and further shocks for at least 1 h.

Data Analysis and Statistics

The circadian pattern of spontaneous appropriate shock episodes in patients on beta-blocking agents at the time of the shock was compared with the diurnal pattern of episodes occurring in patients without beta blockade. Patients on sotalol, a beta-adrenergic and potassium-channel antagonist¹⁹ were included in the group of patients on beta blockers. The frequency of appropriate shock episodes was plotted as a function of time of the onset of episodes based on hourly intervals. The chi-square goodness-of-fit test was used to test the diurnal variation of shock episodes for equal distribution in both groups. Characteristics of patients with and without beta blockade were compared using the chi-square test and the unpaired Student's *t*-test. All values were expressed as mean $\pm$ standard deviation. Differences were considered statistically significant for p values < 0.05 .

Results

In 99 of the 159 patients (62%), 552 spontaneous shock episodes were observed during a mean follow-up of 26 ± 15 months (range 2–58 months). Twelve patients (8%), in whom only inappropriate shock episodes occurred, were excluded from the analysis. The remaining 87 patients (55%) had 461 appropriate shock episodes of which 13 could not be related to the exact time of onset. Thus, a total of 448 episodes was included in the analysis of the circadian variation. Of these shock episodes, 104 (23%) occurred in patients on beta-blocker therapy and 344 episodes (73%) in patients without beta blockers.

At the time of the first and most subsequent shock episode, 18 patients were on beta-blocker medication. Ten patients received metoprolol (50–200 mg daily) and eight patients sotalol (160–480 mg daily). Characteristics of these patients versus those without beta-blocker therapy at the time of the first shock episode are shown in Table I. In both groups, most patients were male and had a history of aborted sudden death due to ventricular fibrillation or rapid ventricular tachycardia. The underlying heart disease was coronary artery disease in the majority of cases. There was a trend toward a lower age and a higher ejection fraction in patients on beta blockers; however, these differences were not significant. During follow-up, 10 patients in the group without initial beta-blocker therapy received sotalol ($n = 5$) or metoprolol ($n = 5$). Shock episodes occurring in these patients while on beta-blocker medication

TABLE I Characteristics of 87 patients with and without beta-blocker therapy

	Patients on beta blockers	Patients without beta blockade
No. of patients	18	69
Age (years)	53.3 ± 17.2	58.4 ± 10.2
Gender (%)		
Male	17 (94)	56 (81)
Female	1 (6)	13 (19)
Heart disease (%)		
Coronary artery disease	12 (67)	41 (59)
Dilated cardiomyopathy	2 (11)	20 (29)
Right ventricular dysplasia	2 (11)	1 (2)
Valve replacement	0 (0)	4 (6)
No structural heart disease	2 (11)	3 (4)
Ejection fraction (%)	39.9 ± 10.9	33.8 ± 15.0
Indication for ICD (%)		
Successful resuscitation (VT/VF)	14 (78)	51 (74)
Sustained symptomatic VT	4 (22)	18 (26)
Arrhythmia documentation in ICDs (%)		
Stored electrograms	7 (39)	32 (46)
RR interval analysis	8 (44)	28 (41)
No arrhythmia documentation	3 (17)	9 (13)

Values are given as mean ± standard deviation.

Abbreviations: VF = ventricular fibrillation, VT = ventricular tachycardia, ICD = implantable cardioverter defibrillator.

were included in the analysis of episodes during beta blockade. Thus, a total of 28 patients were on beta-blocker therapy at some time during follow-up.

Figure 1 depicts the circadian variation of shock episodes in patients with and without beta blockade. Shock episodes in patients on beta blockers (Fig. 1A) occurred almost equally distributed without a peak at any time of the day ($p = 0.95$). During the 6-h intervals 0–6, 6–12, 12–18, and 18–24 h, the distribution of shock episodes was 22, 27, 24, and 27%, respectively. In contrast, the diurnal distribution of episodes in

patients without beta blockade (Fig. 1B) showed a clear circadian pattern with a distinct morning peak and a smaller peak during late afternoon ($p < 0.001$). In this group, 16, 38, 28, and 18% of episodes occurred during the 6-h intervals 0–6, 6–12, 12–18, and 18–24 h, respectively. The circadian distribution of episodes differed significantly in patients with and without beta blockade ($p < 0.05$).

Discussion

The present study analyzed the influence of beta-adrenergic antagonists on the circadian variation of sustained ventricular tachyarrhythmias terminated by defibrillator discharges in a population of 87 patients with ICDs. In support of our hypothesis we found that patients on beta-blocker therapy exhibited an almost even distribution of shock episodes. In contrast, patients without beta-blocking agents had a clear circadian variation with a distinct morning peak and a minor peak during late afternoon.

Circadian Pattern of Ventricular Tachyarrhythmias

A circadian variation of malignant arrhythmias necessitating ICD therapy has been reported previously.^{5–10} Most of these studies demonstrated a significant peak between 6 A.M. and noon.^{5–7, 10} Our data on the diurnal distribution of episodes in patients without beta-blocking agents are consistent with these reports. The episode distribution is also comparable to reports on the onset of sudden cardiac death.^{1–4} Analyzing the electrocardiograms of semiautomatic defibrillators used by the emergency rescue team, a similar pattern was found for the onset of ventricular fibrillation.¹⁵ A morning increase in the incidence of premature ventricular beats²⁰ and sustained ventricular tachycardia²¹ has also been reported. Thus, ventricular arrhythmias ranging from premature ventricular contractions to sustained, life-threatening tachyarrhythmias, ventricular fibrillation, and sudden cardiac death exhibit a circadian variation with an increase during morning hours. This diurnal pattern is comparable to the onset of myocardial infarction,^{22, 23} ischemia,²⁴ and other acute cardiovascular diseases.^{13, 25}

FIG. 1 Circadian variation of shock episodes in patients with (A) and without (B) beta blockade. Shock episodes during beta blockade (A) occurred almost equally distributed over time. In patients without beta blockade (B), a circadian pattern of shock episodes was present with a distinct morning peak and a smaller peak during late afternoon.

Influence of Beta Blockers on the Circadian Variation

Several studies have shown that patients receiving beta-adrenergic antagonists exhibit no morning increases of myocardial ischemia and acute myocardial infarction.²²⁻²⁴ An attenuation and a blunted morning peak of ventricular ectopies in patients receiving sotalol have also been described.²⁶ However, there is only one study by Peters *et al.*¹⁴ which analyzed the influence of beta blockers on sudden cardiac death. The authors compared the time of onset of sudden cardiac death in patients receiving propranolol and those receiving placebo in the Beta-Blocker Heart Attack Trial (BHAT).¹⁴ In their analysis, the authors found a distinct morning increase of sudden deaths in patients without propranolol, whereas in patients on propranolol the midmorning peak of sudden cardiac death was blunted.¹⁴

The results of the present study are consistent with those findings reported by Peters *et al.*¹⁴ That study, however, was limited due to the fact that results were relying on eyewitnesses to determine the timing of sudden cardiac death and, more important, that no information of the underlying cause of sudden death was available in most patients. Since asystole as the primary cause of sudden cardiac death is almost equally distributed over time,¹⁵ a higher proportion of bradyarrhythmia and asystole in the propranolol arm of BHAT could have resulted in a more even distribution of sudden deaths. Therefore, our findings provide the first evidence that the circadian variation of potentially life-threatening ventricular tachyarrhythmias is substantially modified by beta-adrenergic blockade.

Study Limitations

(1) This study was performed in patients who had experienced previous episodes of ventricular tachyarrhythmias or aborted sudden death and who were treated with an ICD. These patients may not represent the normal population of those dying from sudden death. Thus, a selection bias cannot be completely excluded. However, the advantage of studying circadian patterns in this patient population is that patients survive episodes of rapid ventricular tachycardias or ventricular fibrillation due to ICD shock therapy and are able to report circumstances and the time of such events. In addition, new generation ICDs provide the precise time of life-threatening tachyarrhythmic events in the ICD memory.

(2) Data on the influence of sleep-wake patterns were not available. This may be of importance since the relative risk of sudden death has been shown to be higher within the first 3 h after awakening.²⁷

(3) We included both patients on metoprolol and those on sotalol (an antiarrhythmic drug with additional class 3 antiarrhythmic activity¹⁹) in the beta-blocker group because there was no difference in the circadian pattern of tachyarrhythmic events between the two subgroups. However, the number of shock episodes within each subgroup was relatively small. Larger patient populations should be studied to provide further evidence that sotalol and pure beta blockers exhibit the same effects on the circadian variation of tachyarrhythmic events.

Conclusion

The blunted morning peak of ventricular tachyarrhythmias by beta-blocker therapy supports the hypothesis that the circadian variation of tachyarrhythmias and sudden death is due to a morning surge in sympathetic tone resulting in an elevation of plasma catecholamine levels, heart rate, and blood pressure.^{12, 24} An augmentation of the sympathetic/vagal balance indicated by an increase in the ratio of the low- to the high-frequency components of heart rate variability may also play a role.^{11, 13} Beta-adrenergic antagonists which alter these conditions may therefore cause a more even diurnal distribution of the onset of malignant arrhythmias, sudden death,¹⁴ and other acute cardiovascular diseases.²²⁻²⁴ Recently, however, Middlekauff and Sontz²⁸ reported that sympathetic nerve activity is not higher during the morning (when sudden death occurs most frequently) compared with that in the afternoon (when sudden death incidence is lower). The authors suggest that an exaggerated morning end-organ responsiveness to catecholamines may be involved in the circadian pattern of acute cardiovascular diseases, but not an enhanced morning sympathetic outflow. Further studies need to address this issue.

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