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Nocturnal Peak in Atrial Tachyarrhythmia Occurrence as a Function of Arrhythmia Burden

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Abstract

Introduction—We examined circadian periodicity of atrial tachyarrhythmias (AT/AF) in a large group of patients with implantable devices, which allow continuous collection of the event data over prolonged periods of time.

Methods and Results—A total of 16,130 AT/AF events were recorded in 236 patients (age: 63 ± 12 years, 27% female, 90% had a history of cardiovascular disease, 33% ischemic, LVEF: $49 \pm 18\%$) over a period of 12 months. To exclude interactions with therapy, the patterns of arrhythmia occurrence were examined for all events and for those episodes that were preceded by at least 1, 6, and 24 hours of sinus rhythm. To prevent biasing toward patients with more frequent episodes, the patterns of AT/AF onset were analyzed both in absolute and patient-normalized (i.e., divided by the total number of events in each patient) units per hour per patient and then summarized for the entire group. In patients with <4 AT/AF events, the onset times were randomly distributed over 24-hour period. However, as the number of AT/AF events increased, a nocturnal pattern of occurrence (determined by the occurrence of a trough around noon) gradually emerged and became highly statistically significant ($P < 10^{-4}$). The magnitude of nocturnal peak of AT/AF events was well explained by a single-exponential function ($R^2 = 0.97$, $P < 10^{-2}$).

Conclusion—Patients with more frequent atrial tachyarrhythmias are more likely to develop AT/AF at night. Knowledge of patient-specific circadian patterns of arrhythmia occurrence can be useful for personalized management of individuals with significant arrhythmia burden.

Keywords

atrial tachycardia; atrial fibrillation; autonomic nervous system; circadian; pacemaker

Introduction

All atrial tachyarrhythmias (atrial tachycardia/flutter and atrial fibrillation, AT/AF) are not created equal; they arise in various parts of atrial chambers interspersed by complex neurovascular structures, islands of fibrosis, and suddenly “erupting” triggers of enhanced

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automaticity.^{1,2} A variety of the 24-hour patterns of AT/AF initiation (including random, diurnal, nocturnal, and multimodal types) has been reported in different populations, but its principal mechanisms remain unexplained.^{3–13} The uncertainty, in a large part, stems from the technical difficulties of continuous data collection over prolonged time required to capture arrhythmic events (which can be rare or asymptomatic) and processing such prodigious amounts of data. Most studies of the circadian patterns of AT/AF have been limited to the information collected from ambulatory (Holter) ECG data⁵ or emergency phone calls.³ Although these investigations have provided important insights into the incidence of AT/AF, they could not systematically examine the determinants of various circadian patterns, due to the inability of tracking multiple arrhythmic events over prolonged periods of time. More recently, advances in the implantable device technology have opened a window of opportunity for long-term continuous data collection and accurate tracking of arrhythmic events.⁴

Thus, the goal of this study was to examine both the circadian periodicity of AT/AF and its determinants in a large cohort of patients with implantable devices. A better understanding of such determinants could be useful for optimization of arrhythmia prevention and management and may provide the basis for development of more efficient, patient-specific approaches.

Methods

Study Population and Patient Characteristics

Data for this study were obtained from the Jewel AF study that has been described in detail.^{14–17} Briefly, this multicenter study was conducted in 60 centers. A Jewel 7250 AF ICD (Medtronic, Minneapolis, MN, USA) was implanted in patients who had a clinical indication for the implantation of a ventricular ICD and at least 2 documented episodes of (symptomatic or asymptomatic) AF and/or AT in the year before implantation, with a 12-lead ECG documentation of at least 1 episode. Patients with chronic AF (unable to sustain sinus rhythm) were excluded. Ventricular therapies were enabled in all patients. Patients were followed up with routine device interrogations for up to 3 years; changes in antiarrhythmic drug therapy during the study period were discouraged.

Atrial Arrhythmia Detection and Discrimination Algorithm

The detection and discrimination algorithm implemented in the Jewel 7250 AF ICD has been described in detail.^{14–17} In short, the device discriminates AT from AF on the basis of 2 programmable detection zones, which may overlap. The nominal (factory) settings for the device include: (i) the 12-beat median atrial cycle length (ACL) for AF and AT equal to 100–270 ms and 170–320 ms, respectively; and (ii) the ACL regularity within the overlapping zone of 170–270 ms (i.e., the diagnosis of AT or AF is made if ACL is regular or irregular, respectively). These threshold values could be changed at the discretion of the treating physician.

Data Analysis

The demographic and clinical characteristics that were available for the studied patient population are shown in Table 1. To examine systematically the impact of these variables on the circadian patterns of AT/AF initiation, multiple analyses were required in the subsets obtained using various combinations of these patient characteristics. Clearly, the large number of possible subsets that could be generated using various cutoff values of these variables makes manual analysis unfeasible. In particular, dichotomizing the first 7 demographic and clinical variables (e.g., males vs females) would generate 128 subsets; furthermore, with multiple cutoff values (e.g., different frequencies of AT/AF events) the number of possible subsets would be even larger.

To obviate this problem, we have developed a suite of software routines (SQL, Microsoft, Redmond, WA; Matlab, Mathworks, Natick, MA, USA) that allows computationally efficient generation and systematic analysis of various data subsets. Monte Carlo simulations ($N = 10,000$ simulations for each statistical test) were performed to eliminate false-positive findings due to multiple comparisons. The software has been thoroughly tested using multiple side-by-side comparisons of both automatically and manually selected subsets using pairwise differences between the corresponding data entries. These tests were performed in 35 subsets (for some, randomly selected variables shown in Table 1). In all tests, the subsets selected using automatic and manual procedures have been found to be identical.

To prevent biasing of the results toward patients with more frequent episodes, the patterns of AF onset were analyzed both in absolute (number of AT/AF events per hour) and patient-normalized units (number of AT/AF per hour divided by the total number of AT/AF events in each patient over the follow-up period) in each patient and then summarized for the entire group, as shown in Figure 1.

For each binary variable shown in Table 1, the dataset was dichotomized into the subsets of patients with and without the corresponding variable (e.g., males vs females), and the circadian patterns of AT/AF in both subsets were compared. For nonbinary variables (e.g., age, LVEF), the data sets were divided into the 2 subsets (above and below the mean value), then into the 4 subsets (corresponding to 25, 50, 75, and 100% of the dataset), and finally into the 10% bins (e.g., LVEF < 50, 40, and 30%), and the circadian patterns of AT/AF were compared for all these subsets.

To examine the impact of AT/AF frequency, the analysis was performed in (i) the entire dataset and (ii) the subsets of patients with different cutoff values for arrhythmia frequency (<2, 3, 4, ..., maximum number of AT/AF per patient). Similarly, to estimate the impact of AT/AF duration, the analysis was performed in the subsets of AT/AF events of various durations (<30 seconds, 30 seconds, >1 minutes, >1 hour, >2 hours, etc.). In addition, the impact of medications was examined by performing the analyses in (i) the entire dataset, (ii) the subset of patients who had no changes in any medications during the follow-up period, and (iii) the subsets of patients with/without β -blockers, as well as each medication listed in Table 1.

The body mass index (BMI) was calculated as weight/height² (kg/m²). The presence and statistical significance of a 24-hour periodicity was tested using the cosinor analysis:¹⁸ $f(x) = a * \cos(2\pi x/24 + b) + c$ where the coefficients a, b, and c were computed using the nonlinear least-squares (Gauss–Newton) method. The goodness of fit was estimated using R², the statistical significance of the model (P-value) was tested using a zero-amplitude test.¹⁸ To minimize the effects of distributions that are different from normal, the comparisons of independent subgroups were carried out using the nonparametric Mann–Whitney *U*-test. Data were presented as the number of patients (% total) or as mean $\pm$ standard deviation (SD). In addition, the median values and 25–75% ranges are shown for nonparametric tests (which minimize possible biases for data distributions that are different from normal). Fisher's exact test was used to compare the number of patients on each medication in the studied group and in all patients with AT/AF (Table 1). $P < 0.05$ was considered significant.

Results

Patient Characteristics

A total of 16,130 AT/AF events were recorded in 236 patients (age: 63 ± 12 years, 27% female, 90% had a history of cardiovascular disease, 33% ischemic, LVEF: $49 \pm 18\%$) with implantable devices over a period of 12 ± 9 months (Table 1). There were no differences in clinical or demographic characteristics between the study group and all patients with AT/AF events (Table 1). The proportions of AT and AF events (classified by the device using the rate and regularity criteria¹⁵) were 65% and 35%; they occurred in 210 and 200 patients, respectively.

Patterns of Initiation of Paroxysmal Atrial Tachyarrhythmias

To assess the influence of the device's therapy on the pattern of AT/AF initiation, we compared the onset times for all 16,536 arrhythmic events and for those that were preceded by 1 hour, 6 hours or 24 hours of sinus rhythm (Fig. 1). In all these groups, paroxysmal AT/AF occurred 2–3 times more frequently at night than during the daytime, peaking around midnight and decreasing to a minimum around noon. The patterns of nocturnal predominance of AT/AF initiation (determined by the occurrence of a trough around noon) were similar when the mean frequency of the event initiation was examined in absolute (a.u.) and patient-normalized units to control for potential biasing toward patients with more frequent events. The patterns of AT/AF initiation could be approximated well by a single-cosine function ($R^2 = 0.73$, $P < 10^{-5}$) with a 24-hour period, further supporting the significance of 24-hour rhythmicity in the incidence of arrhythmic events. The patterns of arrhythmia initiation were similar for the subgroups of events classified by the device as AT and AF (Fig. 1; panels E, F).

Because changes in antiarrhythmic drug therapy and multiple sequential drug use could affect event rates, the patterns of AT/AF were also analyzed in a subset of patients who did not have changes in medication during the follow-up. The pattern of AT/AF events in this subgroup was similar to that in Fig. 1, confirming that the presence of nocturnal peak was unrelated to specific medications (data not shown).

The Impact of Arrhythmia Burden

To exclude interactions with device's therapy, 2413 AT/AF events that were preceded by at least 24 hours of sinus rhythm were selected for this subanalysis. The impact of AT/AF burden has been examined systematically for all subsets of patients with different AT/AF frequencies (<2, 3, 4, ..., the maximum number of AT/AF per patient), as shown in Figure 2. In patients with <4 AT/AF events, the onset times were randomly distributed over 24-hour period (72 patients, Fig. 2A). However, as the number of AT/AF events increased, a nocturnal peak of arrhythmia initiation gradually emerged and became highly statistically significant ($P < 10^{-4}$). This pattern was observed both in absolute and patient-normalized units. The magnitude of the nocturnal peak of AT/AF initiation was well explained by a single exponential function ($R^2 = 0.97$; $P < 10^{-2}$; Fig. 2B), with a steep, near-linear increase between 4 and 50 arrhythmic events ($R^2 = 0.86$, $P < 10^{-5}$ for a linear fit in that region of the graph). We note that the maximum number of AT/AF events per patient in the studied dataset was 119; however, only 7 patients had >50 AT/AF events (543 events for all 7 patients; Fig. 2C), which limited more detailed analysis of the circadian patterns in the subgroup of patients with >50 arrhythmic events.

The Impact of Demographic and Clinical Characteristics

The circadian patterns of AT/AF initiation were examined in the subsets of patients selected using the demographic and clinical characteristics listed in Table 1. A circadian pattern of arrhythmia initiation was present in patients who were of normal weight ($BMI < 25 \text{ kg/m}^2$; Fig. 3), those who were overweight ($BMI = 25\text{--}30 \text{ kg/m}^2$), and those who were obese ($BMI > 30 \text{ kg/m}^2$). This pattern was statistically significant both in patients with preserved and reduced systolic function (Fig. 4A). The circadian pattern was preserved in both males and females ($P < 10^{-5}$ and $P = 0.01$, respectively, Fig. 4B).

A pronounced circadian pattern of the AT/AF initiation (with a nighttime peak and daytime trough level) was observed both in younger (< 65 years old, $P < 10^{-5}$; Fig. 4C) and older patients (≥ 65 years old, $P < 10^{-4}$). This pattern was present in patients with and without coronary artery disease ($P = 0.01$ and $P < 10^{-5}$, respectively; Fig. 4D), regardless of the NYHA class, the presence or absence of structural heart disease or medications taken, including β -blockers ($P < 10^{-4}$ for all analyses listed above; Fig. 3D). There were no differences between the circadian patterns of AT/AF initiation for the events that occurred in the first 1, 2, 3, 6, 12, or 24 months compared to the entire 36-month period of monitoring (data not shown).

The Impact of Arrhythmia Duration

The circadian pattern of the AT/AF onset times, with a nighttime peak and daytime trough, was preserved and statistically significant in all studied subsets of arrhythmias of various durations (Fig. 3E). However, there was no significant circadian variation in the duration of AT/AF episodes when examined on a patient-by-patient basis.

Circadian Patterns of AT/AF Initiation in Individual Patients

A cosinor analysis of individual patients' data performed in those with ≥ 6 arrhythmic events confirmed that the proportion of patients with a significant ($P < 0.05$) 24-hour variation of

AT/AF onsets increased as a function of individual's AT/AF burden. Indeed, a circadian pattern of arrhythmia initiation was observed in 24% of patients with 6–11 episodes (55 patients), 37% of those with 12–50 episodes (49 patients) and 86% of those with >50 episodes (7 patients). Examples of pronounced 24-hour variation of AT/AF onset frequency in patients with a large number of arrhythmic episodes are shown in Figure 5.

As expected, the peak times of AT/AF occurrence exhibited some amount of patient-to-patient variability (Fig. 5). To examine the determinants of such variability, the peak times of AT/AF occurrence have also been examined in the subgroups of patients with different clinical and demographic characteristics. In all examined subgroups, the peak times of arrhythmia occurrence were similar. This suggests that the individual variability in the time of AT/AF occurrence could not be explained by the clinical or demographic characteristics available for this study.

Discussion

In patients with rare arrhythmias (<4 AT/AF episodes over the follow-up period), the events are distributed randomly over a 24-hour period. However, a nocturnal peak emerges in patients with more frequent AT/AF episodes and grows as a function of the total number of arrhythmias. This strong relationship between the nighttime peak of AT/AF initiation and total arrhythmia burden is present in both absolute and patient-normalized units. It is observed in patients of different age groups, genders, irrespective of the level of LVEF, presence of coronary artery disease and pharmacological treatment (including beta-blockers), as well as in the subsets of AT/AF of different duration.

The relationship between a nocturnal pattern of AT/AF and total arrhythmia burden was confirmed by the comparative analysis of the subgroups of patients with <4, 4–9 and 10–50 arrhythmias (Fig. 2A). Because the sample size of all 3 subgroups was similar (69–72 patients), the absence of a circadian pattern of arrhythmia initiation in those with <4 events, in contrast to those with 4–9 and 10–50 arrhythmias, could not be explained by the smaller sample size. In addition, the strong relationship between circadian pattern and the total arrhythmia burden was confirmed by the analysis of individual patient data (Fig. 5).

Previous Studies

To explain the differences in the circadian patterns of AT/AF reported in different populations, Gillis *et al.* have suggested that the 24-hour distributions are modulated by the disease burden (i.e., the frequency and duration of arrhythmias as well as the presence of structural heart disease).⁴ Our analysis supports and further extends this notion by showing that the most important determinant of the circadian pattern of AT/AF initiation (among all studied clinical and demographic characteristics) is the total frequency of arrhythmic events.

Interestingly, the nocturnal pattern of AT/AF events has been observed not only in humans, but also in nonprimate mammals. In particular, a similar pattern of AT/AF (with a 12-hour shift due to the nocturnal activity pattern in mice) has been also reported in a genetic mouse model of heart failure and arrhythmias.¹³ This suggests that the predominance of AT/AF

events during the period of rest (inactivity) involves the physiological mechanisms that have been evolutionally “conserved” and independent of species specifics.

Autonomic Nervous System Activity and Circadian Patterns of the AT/AF Initiation

A major role of the ANS in the initiation of AT/AF has long been recognized and supported by a number of experimental and clinical studies.^{9,19–23} However, despite its long history, the specific contributions of vagal and sympathetic ANS effects to the arrhythmogenesis, as well as the accuracy of estimating those effects in a clinical setting, are still being debated. Coumel has proposed to classify all AT/AF episodes as “vagal” or “sympathetic,” depending on the relative balance between the 2 systems.⁹ However, a recent large-scale clinical study, which included 5,333 patients with AF from 35 European countries, has demonstrated that a majority of arrhythmic events cannot be classified as purely sympathetic or vagal; only 6% and 15% had vagal and adrenergic trigger patterns, respectively.¹⁰ Nevertheless, this large-scale multicenter investigation has confirmed the most important clinical implication of Coumel's theory that β -blockers applied in patients with the vagal type of AT/AF may promote arrhythmogenesis and increase the frequency of arrhythmic events.¹⁰

Body Mass Index and Sleep-Disordered Breathing

A link between morbid obesity and obstructive sleep apnea has been well documented, although the exact physiological mechanisms remain debated.²⁴ In our study, however, the nocturnal pattern of AT/AF was similar in all patients, regardless of their BMI. This does not support the notion that obstructive sleep apnea is a primary factor determining a nocturnal pattern of arrhythmias, although we cannot rule out the potential role of central apnea, which is highly prevalent in this population.²⁵ Further research is necessary to delineate the impact of various forms of sleep-disordered breathing (SDB) on the nocturnal occurrence of arrhythmias. The central and obstructive SDB have been frequently observed in patients with nocturnal,²⁶ paroxysmal,²⁷ and chronic^{28,29} atrial fibrillation, although the temporal and causal links between the disordered breathing and arrhythmias remain to be determined.³⁰ SDB is common in patients with low LVEF (<40%),¹ who also have chronically elevated sympathetic and limited vagal activity.¹²

The potential role of short-term surges of parasympathetic activity that may occur during nighttime also requires further investigation.³²

Limitations

An absence of data on SDB, oxygen saturation and the level of vagal activity in the studied population did not allow further analysis of these plausible mechanisms of the nocturnal arrhythmia occurrence. Furthermore, the data presented here are from a selected group of patients with implantable devices; therefore, the findings might not be generalizable to a general population of patients with atrial tachyarrhythmias. The number of patients with >50 AT/AF events was relatively small (N = 7), which limited the analysis of circadian patterns in this subgroup. Further research is warranted to examine the reproducibility of our results in various groups of patients. Another important limitation is that device implantation and therapy could potentially interfere and modify the patterns of arrhythmia initiation. To

examine the impact of such confounders, we compared all 16,130 AT/AF episodes with the episodes that were preceded by at least 1, 6, and 24 hours of sinus rhythm (Fig. 1). In all 4 datasets, the patterns of AT/AF were similar to each other, showing a pronounced nocturnal peak. The patterns of arrhythmias were also similar in those patients who did not have changes in medication during the follow-up, confirming that the presence of nocturnal peak was independent of specific medication changes (data not shown).

The incidence of AT/AF events in some patients peaked at 8–10 pm and then declined (Fig. 5, patients #60, 86, and 136), which could reflect the effect of medication intake in the evening hours. However, the nocturnal trend was consistently present in patients with and without β -blockers, Ca^{2+} -channel blockers and other antiarrhythmic medications.

It is likely that some patients in our study had abnormal autonomic nervous system activity, which is typical for patients with ICD. Because the heart rate variability and other autonomic markers were not available to us, further research is needed to examine the relationship between autonomic activity and patterns of AT/AF.

Finally, the detection and classification of AT/AF events by the Jewel 7250 AF ICD device in previous studies was reasonably high (approximately, 90%).¹⁵ However, as previously acknowledged,¹⁵ some events classified by the device as AT may have been an AF, if a thorough electro-physiological evaluation could be conducted.^{15,33} Based on previous reports, we estimate that the number of such misclassified events is small (within 10%).¹⁵

Conclusion

A strong nocturnal peak of AT/AF initiation emerges as a function of total arrhythmia burden. Patients with more frequent arrhythmias are more likely to develop AT/AF at night, which suggests that nighttime physiological and/or pathophysiological events might be responsible for arrhythmia triggering. Therefore, evaluation of nighttime physiology, with particular attention to respiratory function, occurrence of sleep-disordered breathing and apnea is warranted in these patients. In addition, the analysis of autonomic nervous system activity, its potential instabilities and short-term surges of vagal activity, which may occur during the night, might be useful in this patient population. Identifying and mitigating these patient-specific promoters of arrhythmias could facilitate arrhythmia management, reduce the number of arrhythmic events and improve the quality of life in this group.

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Figure 1.

The mean frequency of onset times of all paroxysmal AT/AF events (panel A), events separated by 24 hours (panel B), 6 hours (panel C) and 1 hour of sinus rhythm (panel D); the mean frequency of the onset times of AT events (panel E) and AF events (panel F). To prevent biasing toward patients with more frequent episodes, the mean frequency of the events over the follow-up period was estimated in 1-hour intervals both in absolute (mean number of AT/AF events per hour [a.u.]) and patient-normalized units (number of AT/AF per hour divided by the total number of AT/AF events in each patient [n.u.]). A cosine function $f(x) = a \cdot \cos(2\pi x/24 + b) + c$ with the coefficients a , b , and c determined using nonlinear least squares (Gauss-Newton) has been fitted to the mean number of AT/AF events per hour (a.u.). The goodness of fit was estimated using R^2 , the statistical significance of the circadian patterns was tested using a zero-amplitude test. A sun symbol indicates noontime.

Figure 2.

Panel A: the mean frequency of the onset time of paroxysmal AT/AF grouped in 1-hour intervals over 24-hour period in absolute (mean number of AT/AF events per hour) units. The onset times for patients with 1–3 AT/AF events were distributed randomly over 24-hour interval. However, as the number of events gradually increased, a nocturnal peak slowly emerged and became highly pronounced. *For patients with 50–119 events, each point on the graph of the AT/AF frequency was rescaled (divided by 10), to show these data in the same reference frame together with the other patient groups which had lower event frequency. Panel B: the magnitude of the nocturnal peak of AT/AF onset times for each tracing shown in Panel A (i.e., range of circadian variation = max – min number of events) was approximated well ($R^2 = 0.97$, $P < 10^{-2}$) by a single exponential function shown at the top. Panel C: the number of AT/AF events versus the number of patients in the studied group. The P-values were calculated using the cosinor analysis and a zero-amplitude test (see Figure 1 legend for details).

Figure 3.

Patterns of initiation of AT/AF events in patients who were of normal weight (BMI < 25 kg/m²), who were overweight (BMI = 25–30 kg/m²; panel B), and who were obese (BMI > 30 kg/m²; panel C). Panel D: the impact of β -blockers on the mean frequency of the onset time of paroxysmal AT/AF grouped in 1-hour intervals over 24-hour period in absolute (mean number of AT/AF events per hour) units was examined in the subgroups of patients with and without these medications (all β -blockers combined, Table 1). Note that the circadian patterns were also examined for each medication listed in Table 1 separately (data not shown); in all these subgroups, the circadian patterns were similar to that shown in this figure. Panel E: the impact of arrhythmia duration on the mean frequency of the AT/AF onset times grouped in 1-hour intervals over 24-hour period in absolute (mean number of AT/AF events per hour) units was examined for VT/VF events lasting < 30 seconds, 30 sec to 1 hour, 1–2 hours, and > 2 hours; n is the number of patients in the corresponding subgroup. See Figure 1 legend for details.

Figure 4.

The impact of demographic and clinical characteristics on the mean frequency of the onset times of paroxysmal AT/AF grouped in 1-hour intervals over 24-hour period in absolute (mean number of AT/AF events per hour) units was examined in the subgroups of: (i) patients with LVEF < 40% versus those with LVEF ≥ 40% (panel A), (ii) males versus females (panel B), (iii) younger (<65 years old) versus older (≥ 65 years old) patients (panel C), and (iv) patients with versus without coronary artery disease (CAD) (panel D). The number of patients in each subgroup is shown in parentheses. The P-values were calculated using the cosinor analysis and a zero-amplitude test (see Figure 1 legend for details).

Figure 5.

Patterns of initiation of AT/AF events in 4 patients with frequent arrhythmic episodes (>50 events/patient). The line shows the cosine function fitted to the data points (dots) using the nonlinear least-squares (Newton–Gauss) method. The goodness of fit was estimated using R^2 ; the P-values were calculated using a zero-amplitude test (see Figure 1 legend for details). Note that the number of AT/AF events increased in the evening and night time.

TABLE 1

Clinical Characteristics of Patients with AT/AF Events

Clinical Characteristics	All Patients with AT/AF Events	Patients with AT/AF Preceded by 24 hours of SR [§]	P*
N (patients)	236	220	
Age (years)	63 ± 12	63 ± 12	0.7
Gender female (%)	27%	26%	0.9
Body mass index (kg/m ²)	29 ± 6	29 ± 6	1.0
History of cardiovascular disease (%)	90%	90%	1.0
Ischemic heart disease (%)	33%	33%	0.8
LVEF (%)	49 ± 18%	49 ± 18%	1.0
AT/AF events			
Total	16, 130	2413	
Mean/per patient ± std	70 ± 111	11 ± 16	
Median/25–75% range	25/9–82	6/3–12	
Follow-up (months)			0.7
Mean ± std	12 ± 9	12 ± 9	
Median/25–75% range	11/5–18	10/5–18	
Medications (%)			
Beta-blockers (all types combined)	89	90	1.0
Antiarrhythmic and rate control (All types combined)	100	100	1.0
Other	92	91	1.0

[§]SR = sinus rhythm.

* All patients versus patients with events preceded by 24 hours of SR.