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Circadian periodicity affects the type of ventricular arrhythmias and efficacy of implantable defibrillator therapies

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Abstract

Introduction: Factors influencing malignant arrhythmia onset are not fully understood. We explored the circadian periodicity of ventricular arrhythmias (VAs) in patients with implantable cardioverter and cardiac resynchronization defibrillators (ICD/CRT-D).

Methods: Time, morphology (monomorphic/polymorphic), and mode of termination (anti-tachycardia pacing [ATP] or shock) of VAs stored in a database of remote monitoring data were adjudicated. Episodes were grouped in six 4-h timeslots from 00:00 to 24:00. Circadian distributions and adjusted marginal odds ratios (ORs), with 95% confidence interval (CI), were analyzed using mixed-effect models and logit generalized estimating equations, respectively, to account for within-subject correlation of multiple episodes.

Results: Among 1303 VA episodes from 446 patients (63% ICD and 37% CRT-D), 120 (9%) self-extinguished, and 842 (65%) were terminated by ATP, 343 (26%) by shock. VAs clustered from 08:00 to 16:00 with 44% of episodes, as compared with 22% from 00:00 to 08:00 ($p < .001$) and 34% from 16:00 to 24:00 ($p = .005$). Episodes were more likely to be polymorphic at night with an adjusted marginal OR of 1.66 (CI, 1.15–2.40; $p = .007$) at 00:00–04:00 versus other timeslots. Episodes were less likely to be terminated by ATP in the 00:00–04:00 (success-to-failure ratio, 0.67; CI, 0.46–0.98; $p = .039$) and 08:00–12:00 (0.70; CI, 0.51–0.96; $p = .02$) timeslots, and most likely to be terminated by ATP between 12:00 and 16:00 (success-to-failure ratio 1.42; CI, 1.06–1.91; $p = .02$).

Conclusion: VAs did not distribute uniformly over the 24 h, with a majority of episodes occurring from 08:00 to 16:00. Nocturnal episodes were more likely to be polymorphic. The efficacy of ATP depended on the time of delivery.

KEYWORDS
cardiac resynchronization therapy, circadian periodicity, implantable cardioverter-defibrillator, remote monitoring, ventricular arrhythmias

1 | INTRODUCTION

Ventricular arrhythmias (VAs), such as ventricular tachycardia and ventricular fibrillation, are the leading causes of sudden cardiac death in Western countries.[1] Implantable cardioverter defibrillators (ICDs) significantly reduce mortality in primary and secondary prevention. However, current knowledge of factors associated with the onset of malignant arrhythmias is still incomplete. Population studies reported a temporal trend of VAs and sudden cardiac deaths,[2,3] but data were mostly derived from interviews and death certificates which may not allow assessing the exact time of arrhythmia onset. There are conflicting results on the circadian pattern of VA onset from population-based registries, small cohorts of ICD recipients,[4–8] and subanalysis of randomized clinical trials.[9–11]

We hypothesized that the same circadian periodicity known to influence several biological processes in humans may also include mechanisms underlying VA occurrence, their type, and even efficacy of ICD therapies. The identification of timeslots associated with a higher probability of VA onset might help programming the timing of antiarrhythmic drug administration and ICD therapies more effectively.

2 | METHODS

2.1 | Objectives

Our analysis aimed to: (1) explore circadian periodicity of VAs in patients implanted with an ICD or a cardiac resynchronization therapy defibrillator (CRT-D), who experienced at least one appropriately detected ventricular episode; (2) evaluate any relationship between circadian periodicity and main patient characteristics, morphology of arrhythmias, and efficacy of specific ICD therapy types (antitachycardia pacing [ATP], or shock).

The analysis was performed in the context of the Home Monitoring Expert Alliance (HMEA), an independent initiative providing a nationwide repository of data from remote monitoring of cardiac implantable electronic devices during ordinary medical practice.[12] We used data from the Home Monitoring system (BIOTRONIK), characterized by automatic daily transmissions of diagnostics data and validated per-episode intracardiac electrogram (IEGM) recordings.[13,14] The HMEA project was approved by competent Ethics Committees. All patients gave written informed consent before remote monitoring activation.

2.2 | Episode validation and data collection

Data relative to all device-detected VA episodes collected in the HMEA database were analyzed, including the pre-episode, detection, and posttherapy IEGM from available electrodes. For the present analysis, episode IEGMs were adjudicated by an independent panel of electrophysiologists blinded to patients' clinical data. Adjudicators had to assess ventricular origin and to report time of occurrence, mode of termination (shock, ATP, or self-termination), and morphology. A VA was classified monomorphic if it was characterized by a single stable morphology in all IEGM derivations during the whole episode record (up to first therapy if delivered); a VA showing any morphology change during recording was classified as polymorphic.[15] After filtering out episodes of non-ventricular origin, all adjudicated VAs were included in the analysis. Device programming and baseline patients' characteristics were retrieved, including cardiovascular history and pharmacological therapy at the time of implantation.

2.3 | Data analysis and statistics

Episode onsets were evaluated by generating 24-h distribution charts. Episodes were grouped according to time of their occurrence during six 4-h timeslots, from 00:00 to 24:00, in 24-h clock notation. Timeslots were further grouped as night slots (00:00–04:00 and 00:40–08:00); daytime slots (08:00–12:00 and 12:00–16:00); evening slots (16:00–20:00 and 20:00–24:00). The distribution of episodes was reported by percentage of episodes and by per-patient number of episodes occurring in each timeslot. Episodes were also evaluated by their morphology (monomorphic or polymorphic), and by type of termination: self-termination, by successful ATP, or shock delivery. Ventricular cycle at a time of device detection was also collected and reported.

To account for within-subject correlations in patients with multiple episodes, the distribution of episodes by timeslots was analyzed with linear-mixed models with random intercepts and slopes at the patient level: the number of episodes in each timeslot was set as the dependent variable, using the ordered rank of timeslots as independent linear and quadratic terms. Relative prevalence of polymorphic VAs in each predefined timeslots was assessed with Generalized Estimating Equations (GEE): we used an exchangeable correlation matrix with logit link function, reporting the marginal odds ratio (OR) with 95% confidence interval (CI) of polymorphic VA occurrence in one timeslot versus the others, adjusting by age, sex, ischemic cardiomyopathy, CRT, and diabetes mellitus. A similar method was used to estimate the likelihood of self-terminating VAs,

TABLE 1 Patients' characteristics

Number of patients	446
Follow-up duration (months)	33.8 (23.9–51.3)
Age (years)	70 (60–76)
Sex (female)	73 (16.9%)
CRT device	167 (37.4%)
LVEF (%)	30 (25–35)
NYHA Class II or III	399 (89.5%)
ICD indication	
Primary	351 (78.7%)
Secondary	95 (21.3%)
Comorbidities	
Hypertension	187 (41.9%)
Diabetes	70 (15.7%)
COPD	36 (8.1%)
Stroke/TIA	28 (6.2%)
Vascular disease	34 (7.6%)
Chronic kidney disease	49 (11.0%)
Structural heart disease	
Ischemic cardiomyopathy	197 (43.5%)
Nonischemic dilated cardiomyopathy	166 (37.3%)
Valvular disease	35 (7.8%)
Congenital disease	8 (1.7%)
Others	43 (9.6%)
History of atrial fibrillation	108 (24.2%)

Note: Data are expressed as median (interquartile range) or percentage.
Abbreviations: COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NYHA, New York Hear Association; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

as well as ATP success or shock delivery by the predefined timeslots. We also used GEE logit models to analyze the prevalence of polymorphic VAs in each timeslot by population subgroups: age class (>70 vs. ≤70 years), sex (female vs. male), coronary artery disease, CRT, diabetes mellitus, and history of atrial fibrillation.

For descriptive statistics, continuous variables were reported as median (interquartile range) or average ± standard deviation, when normally distributed; categorical variables as percentages of available data. Estimates of coefficients of fitted linear models (with standard errors between brackets) were also reported. The statistical significance level was set at $p = .05$. The analysis was performed with Stata software version 11.1SE (StataCorp).

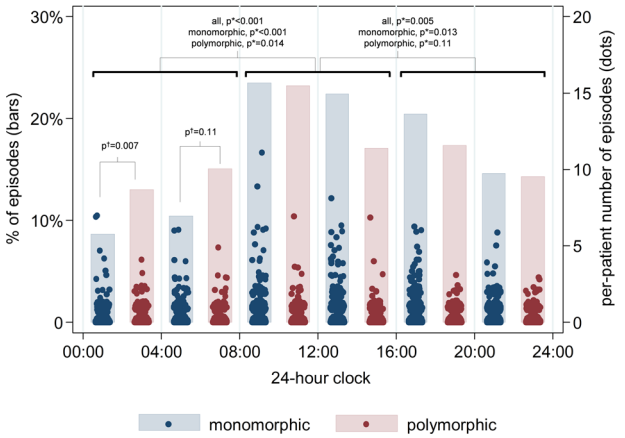

FIGURE 1 24-h distribution of onsets of monomorphic and polymorphic sustained ventricular arrhythmias. Bars denote relative percentages overall episodes (left axis); dots denote the number of episodes in each patient (right axis). Episodes were grouped according to time of their occurrence during six 4-h timeslots from 00:00 to 24:00 in 24-h clock notation: night slots (00:00–04:00 and to 04:00–08:00), daytime slots (08:00–12:00 and 12:00–16:00), and evening slots (16:00–20:00 and 20:00–24:00). *p* values marked with (*) refer to the results of mixed model analysis for the comparisons of daytime slots versus night and evening slots, for all episodes, and for monomorphic and polymorphic episodes, separately. *p* values marked with (†) refer to the results of generalized estimating equation analysis, to assess adjusted marginal risk for an arrhythmia to be polymorphic in each timeslot versus the other timeslots. Only significant or nearly significant values are shown

3 | RESULTS

3.1 | Patients' and episodes characteristics

Of the 1946 patients with an ICD or CRT-D device recorded in the HMEA database at the time of analysis, 446 had a total of 1303 true-positive VA episodes that were included in the analysis after adjudication. Baseline data of patients are summarized in Table 1. Data of 1410 device-years were analyzed, corresponding to a median follow-up of 33.8 (23.9–51.3) months. One hundred thirty-five patients (30%) had a single-chamber ICD, 144 (32%) a dual-chamber ICD, and 167 (37%) a CRT-D device. Indication to device implant was primary prevention in 351 patients (79%) and secondary prevention in 95 (21%) patients. The

TABLE 2 Circadian distribution of ventricular arrhythmias and cycle length by morphology

Timeslots	00:00–04:00	04:00–08:00	08:00–12:00	12:00–16:00	16:00–20:00	20:00–24:00	*p*
Monomorphic							
Episodes, *n* (%)	79 (8.7)	95 (10.4)	214 (23.5)	204 (20.5)	186 (18.8)	133 (14.6)	<.001[a]
Patients, *n* (%)	49 (11.0)	58 (13.0)	119 (26.7)	112 (25.1)	110 (24.7)	95 (21.3)	
Cycle length (ms)	314 ± 46	302 ± 38	311 ± 44	310 ± 43	312 ± 45	313 ± 42	.87[b]
Polymorphic							
Episodes, *n* (%)	51 (13.0)	59 (15.0)	91 (23.2)	67 (17.1)	68 (17.3)	56 (14.3)	<.001[a]
Patients, *n* (%)	37 (8.3)	44 (9.9)	69 (15.5)	52 (11.7)	60 (13.4)	45 (9.0)	
Cycle length (ms)	256 ± 33	262 ± 36	264 ± 41	269 ± 31	276 ± 36	263 ± 39	.019[b]
All							
Episodes, *n* (%)	130 (10.0)	154 (11.8)	305 (23.4)	271 (20.8)	254 (19.5)	189 (14.5)	<.001[a]
Patients, *n* (%)	76 (17.0)	91 (20.4)	170 (38.1)	148 (33.1)	158 (35.4)	131 (29.3)	
Cycle length (ms)	290 ± 46	286 ± 43	297 ± 47	299 ± 45	299 ± 46	297 ± 48	.14[b]

[a]Results of mixed model analysis of the number of episodes over timeslots, with random effects at patient level, and timeslot ranks as linear and quadratic terms; the significant *p* values denote nonuniform distribution with highest occurrence rate in the 08:00–12:00 and 12:00–16:00 timeslots.

[b]Results of linear-mixed model analysis of episode cycle lengths over timeslots. Polymorphic episodes exhibited a significant increasing trend ($p = .019$) from a minimum in the 00:00–04:00 timeslot up, to a maximum in the 16:00–20:00 timeslot.

majority of patients were male (83%) with a median age of 70 (60–76) years. Half of the patients had hypertension; other comorbidities were diabetes mellitus, chronic kidney disease, and hypercholesterolemia, with prevalence ranging from 19% to 29%. Ischemic cardiomyopathy was reported in 44%.

Despite registry-related heterogeneity, device detection settings showed limited interindividual variability: 85% of ventricular fibrillation detection zones ranged within 20 ms, (between 280 and 300 ms); 96% of devices had at least one additional detection zone for ventricular tachycardia (including monitoring zones), 80% of which were programmed within a 50 ms range (between 350 and 400 ms). A single ATP therapy for the fastest tachycardias and at least three ATP attempts in one of the slower detection zones were programmed before shocks in all patients.

The per-patient number of VA episodes ranged from 1 to 30. Of 190 (42.6%) patients with more than one episode, 94 (49.5%; or 21.1% of the 446 patients) had two episodes within the same or subsequent timeslot. Two patients experienced episodes that fulfilled the definition of an arrhythmic storm (≥3 sustained episodes with therapies within 24 h) which were included in the analysis. Among 1303 VA episodes, 911 (69.9%) were classified as monomorphic and 392 (30.1%) as polymorphic. Most episodes were terminated by ATP (842 [64.6%]) or shock (343 [26.3%], and the rest (118 [9.1%]) self-extinguished.

3.2 | Circadian analysis of ventricular arrhythmias

The circadian distribution of VA episodes is reported in Table 2 and graphically displayed in Figure 1, showing the per-patient number and the percentage of episodes occurring in each timeslot. The majority of episodes were observed in the daytime slots, between 08:00 and 16:00: 576 episodes (44.2%) in 255 patients (57.2%). The observation was statistically confirmed by mixed model analysis, where both linear (0.349 [standard error 0.049]) and quadratic (−0.045 [0.007]) coefficient estimates were significant ($p < .0001$ for both terms). Direct comparisons of night slots (from 00:00 to 08:00) and evening slots (from 16:00 to 24:00) versus daytime slots were also statistically significant ($p < .001$ for night vs. daytime; $p = .005$ for evening vs. daytime). Distributions did not differ significantly after grouping episodes by season, with mixed model analysis providing similar results for episodes occurring in spring-summer and fall-winter months (Figure S1).

A similar trend was observed in the groups of polymorphic and monomorphic VAs, with the latter more frequently occurring in the daytime versus night ($p < .001$) and evening ($p = .013$) slots. Polymorphic VAs were also more frequent from 08:00 to 16:00, however dependence on timeslots appeared slightly attenuated: comparison of episode frequency in daytime versus night slots was significant ($p = .014$), but a comparison between daytime and evening slots was not ($p = .11$). Also, the relative proportion of polymorphic versus monomorphic VAs was higher at night (13.0% vs. 8.7% [00:00–04:00 timeslot] and 15.0% vs. 10.4% [04:00–08:00 timeslot]), while it was inverted in all other timeslots.

TABLE 3 Adjusted marginal risks of episodes and device therapies by 24-h timeslots

Episode	Timeslot	Adjusted marginal OR (95% CI)	p
Polymorphic	**00:00–04:00**	**1.66 (1.15–2.40)**	**.007**
	04:00–08:00	1.36 (0.93–1.97)	.11
	08:00–12:00	0.93 (0.68–1.27)	.65
	12:00–16:00	0.86 (0.65–1.14)	.31
	16:00–20:00	0.83 (0.61–1.14)	.25
	20:00–24:00	0.84 (0.58–1.20)	.33
ATP-terminated	**00:00–04:00**	**0.67 (0.46–0.98)**	**.04**
	04:00–08:00	0.84 (0.60–1.19)	.34
	08:00–12:00	**0.70 (0.51–0.96)**	**.03**
	12:00–16:00	**1.42 (1.06–1.91)**	**.02**
	16:00–20:00	1.21 (0.86–1.69)	.28
	20:00–24:00	1.42 (0.99–2.04)	.06
Shock-terminated	00:00–04:00	1.39 (0.94–2.05)	.09
	04:00–08:00	1.21 (0.86–1.71)	.28
	08:00–12:00	**1.44 (1.06–1.95)**	**.02**
	12:00–16:00	**0.69 (0.51–0.94)**	**.02**
	16:00–20:00	0.81 (0.59–1.13)	.23
	20:00–24:00	0.71 (0.50–1.02)	.07

Note: The marginal risks and p values are the results of the analysis of logit GEE models, having the event in the first column as the dependent variable, and each timeslot as the independent variable. Age, sex, ischemic cardiomyopathy, CRT, and diabetes mellitus were included as adjusting covariates. A marginal OR > 1 (<1) indicates increased (decreased) probability of an event in a specific timeslot versus all the other timeslots. Polymorphic ventricular arrhythmias were 66% more likely to occur between 00:00 and 04:00; ATP was less likely to be effective in the 00:00–04:00 and 08:00–12:00 timeslots, and more likely between 12:00 and 16:00; conversely, risk of shock deliveries was higher in the morning slot and lower in the afternoon slot.

Abbreviations: ATP, antitachycardia pacing; CI, 95% confidence interval; CRT, cardiac resynchronization therapy; GEE, generalized estimating equations; OR, odds ratio.

At GEE analysis, the difference between monomorphic and polymorphic frequency in the 00:00–04:00 timeslot reached statistical significance; as listed in Table 3, the adjusted marginal risk of polymorphic VAs was 1.66 (CI, 1.15–2.4; $p = .007$) in the 00:00–04:00 timeslot, and 1.36 (CI, 0.93–1.97; $p = .11$) in the 04:00–08:00 timeslot. Marginal ORs in all other timeslots as well as all adjusting covariates, including ischemic cardiomyopathy, were not significant.

GEE analysis also showed that ATP therapies were more likely to be effective in the afternoon (i.e., timeslot 12:00–16:00,

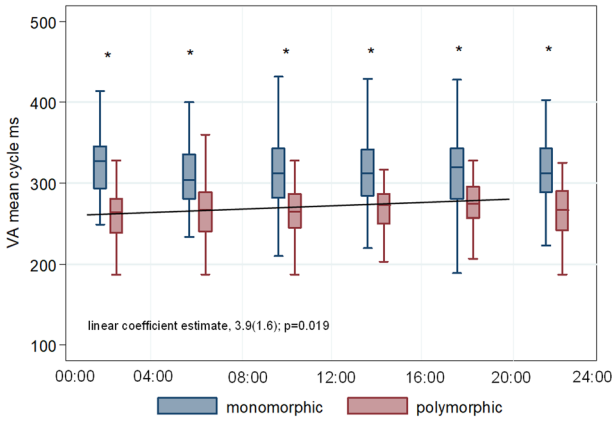

FIGURE 2 Boxplot of ventricular arrhythmia cycle length by morphology and timeslots. Ventricular tachycardia cycle length of polymorphic episodes significantly increased between 00:00–04:00 and 16:00–20:00 timeslots ($p = .019$). Asterisks denote $p < .001$ for comparisons between monomorphic and polymorphic

minimum of 256 ± 33 ms in the 00:00–04:00 timeslot, to a maximum of 276 ± 36 ms in the 16:00–20:00 timeslot (linear coefficient estimate, 3.9; standard error, 1.6; $p = .02$; Table 2).

4 | DISCUSSION

4.1 | Major findings

In our analysis, VA onsets did not distribute uniformly over the 24 h, with 44% of all episodes occurring between 08:00 and 16:00. The trend was statistically significant and common for both monomorphic and polymorphic arrhythmias. However, polymorphic VAs were prevalent at night, with 66% increased marginal risk for an arrhythmia to be polymorphic (i.e., more severe) in the 00:00–04:00 timeslot, as compared with all other timeslots. Consistently, episodes were less likely to be terminated by ATP therapy in that timeslot, as well as in the morning hours (08:00–12:00), when the risk for an episode to require a shock was higher. Conversely, ATP efficacy was maximum

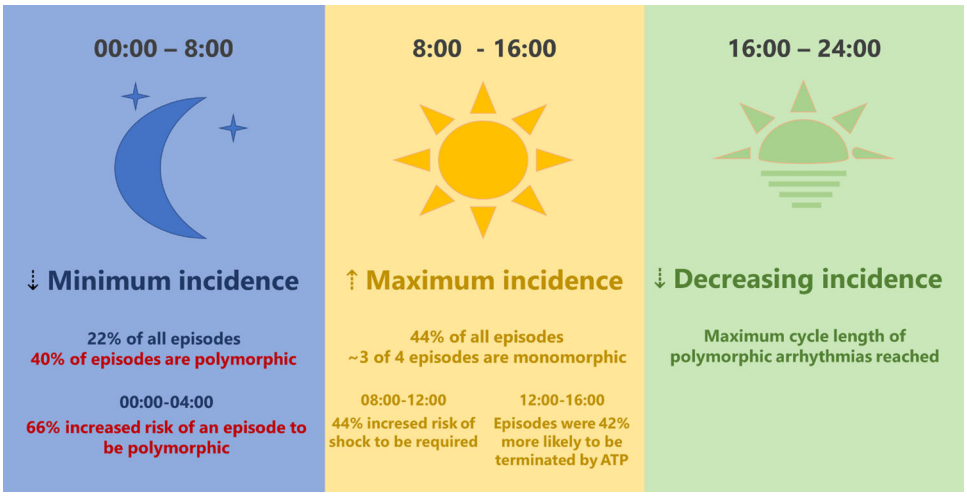

FIGURE 3 Circadian periodicity affects the type of ventricular arrhythmias and efficacy of implantable defibrillator therapies

with an adjusted marginal success-to-failure ratio of 1.42; CI: 1.06–1.91; $p = .02$ vs. all other timeslots), and ineffective at night (timeslot 00:00–04:00) and in the morning (timeslot 08:00–12:00), with an adjusted marginal success-to-failure ratio of 0.67 (CI, 0.46–0.98; $p = .04$) and 0.70 (CI, 0.51–0.96; $p = .03$), respectively. Consistently, shock delivery was 44% more likely to be required in the 08:00–12:00 timeslot ($p = .02$), and 31% more likely to be prevented by successful ATP in the 12:00–16:00 timeslot ($p = .02$).

Finally, polymorphic VAs had a shorter cycle length than monomorphic VAs (266 ± 37 vs. 316 ± 45 ms), with differences consistently significant across the six timeslots ($p < .001$ for all, Figure 2). Linear-mixed model analysis also showed a significant increasing trend of cycle length of polymorphic VAs, from a

in the early afternoon (between 12:00 and 16:00), with a 42% increased marginal success-to-failure ratio. The main findings of the study are summarized in Figure 3.

4.2 | Periodic variations in ventricular arrhythmias incidence

Remote monitoring of ICD and CRT-D devices provides a unique opportunity to observe the accurate 24-h distribution of VA onset. We supposed that VA timing is not randomly distributed, but could be related to other biological processes presenting similar 24-h periodicity. The human biological clock provides diurnal/nocturnal switch-like transitions of melatonin secretion[16] synchronized with the 24-h sun cycle.[17] This

synchronization regulates several human processes from gene expression to behavior. Also, fluctuations of sympathetic nerve activity on cardiomyocytes may lead to increased internal calcium concentration facilitating afterdepolarization.[18–20] Preclinical studies showed a circadian periodicity of cardiac potassium, sodium-ion channel gene expression,[21] and QT-interval duration. In the morning ventricular refractory periods are shorter,[22] favoring induction of VAs triggered by re-entry mechanisms.

The mechanisms underlying the relationship between the biological clock and circadian pattern of VA onset have not been fully understood. As a matter of fact, nonuniform 24-h episode distributions have also been reported in previous studies, albeit with some differences.[10] VA occurrence rate in ICD patient populations had been reported to be lower at night and higher in the morning already in studies dating back to the nineties.[4,5] However, these findings were based on diagnostics data of single-chamber devices with limited memory capacity as compared with contemporary technology. More recently, a subanalysis of the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial[9] confirmed a higher VA occurrence rate in the daytime hours, with a first peak in the morning. They also reported a second peak in the evening, which however was not clearly visible in our analysis as well as in an analysis pooling data from six previous studies on ICD or CRT-D devices conducted in the first decade of the 2000s.[11] Overall, previous analyses were based on diagnostic data stored in the device memories and retrieved at device interrogation. Despite a remarkable increase in device memory capacity during the last two decades, memory saturation and episode overwriting still cannot be excluded. Conversely, our analysis is based on remote monitoring data with daily automatic transmissions, ensuring virtually unlimited storage capacity. In addition, the level of remote monitoring coverage of the system we used[23] and the comprehensive information on arrhythmias it provides, further minimized the risk of underreporting.

We also differentiated between arrhythmia morphologies, which may have implications on the expected efficacy of scheduled therapies. The distinction between monomorphic and polymorphic was based on electrogram recordings available at device episode detection. Although variations in dynamic circuits and cycle length may arise during episodes starting as regular tachycardias, the distinction may help differentiate episodes with irregular cycles at the onset with obvious implications on the initiated therapies (ATPs or shocks) whose efficacy also showed circadian patterns in our analysis.

The 66% increased marginal risk for an arrhythmia to be polymorphic at night, as compared with daylight and evening timeslots, is a novel finding. During sleep (particularly during "rapid-eye-movement" [REM] sleep) the prevalent parasympathetic tone is interrupted by adrenergic tone peaks.[24] Our findings may be consistent with previous observations of more frequent malignant arrhythmias during REM sleep periods in dogs.[25] An overnight prolongation of QT/QTc intervals (and consequent increased risk of life-threatening arrhythmias) has been already reported in humans.[26]

4.3 | Clinical implications of ventricular arrhythmias timing and device therapies

Our findings may have both technical and clinical implications. Several studies showed that the clinical effects of accurate ICD programming go far beyond just the reliability of VA detection and treatment: patient quality of life, device longevity, and outcome are also concerned.[27,28] We observed higher marginal risks of polymorphic VAs and ineffective ATP at night, as well as a higher success-to-failure ratio of ATP in the afternoon. These findings might suggest preferring ATP attempts in daytime slots, particularly in the afternoon, and conversely limiting or even skipping them at night. We have also found that almost 50% of patients with a first VA occurrence had a recurrence within the same or subsequent timeslot. Therefore, a more aggressive intervention strategy may be worth considering during the eight hours following an episode. As these features are not available in current ICD generations, future device developments may include time-dependent programmability of the number of ATP attempts, or more flexible programming strategies based on the last episode timeslot.

On a more clinical note, the higher incidence of VAs from 08:00 to 16:00 or in the hours following a first occurrence may be a useful guide to individualize antiarrhythmic drug therapy on the patient's profile. Physicians might plan drug assumption favoring peak of blood drug concentration in the morning, or at the time of previous VA episode occurrence.

4.4 | Limitations

Our study was observational and retrospective and, therefore, it suffers from several limitations, including a lack of uniform procedures and device settings. However, data showed very limited heterogeneity in terms of arrhythmia detection programming, as reported above, and reflect current medical care in ordinary practice.

We also have no data relative to sleep apneas which may have potential implications for the reported finding of higher marginal risk of polymorphic VAs at night. This point deserves further investigation.

5 | CONCLUSIONS

Patients with ICD and CRT-D devices exhibited nonuniform distributions of VAs over the 24-hours. VAs, particularly monomorphic forms, clustered from 08:00 to 16:00; whereas nocturnal arrhythmias were more likely to be polymorphic. Efficacy of painless ATP therapies depended on time of arrhythmia onset.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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