Daily, weekly, monthly, and seasonal patterns in the occurrence of vasovagal syncope in an older population

Nynke van Dijk1*, Mardi C. Boer2, Tiziana De Santo3, Nicoletta Grovale3, Arnaud J.J. Aerts4, Lucas Boersma5, and Wouter Wieling2

1 Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, PO Box 22700, 1100 DE Amsterdam, The Netherlands; 2 Department of Internal Medicine, Academic Medical Centre, Amsterdam, The Netherlands; 3 Medtronic Italia, S.p.A., Italy; 4 Department of Cardiology, Atrium Medical Centre, Heerlen, The Netherlands; and 5 Cardiology Department, St Antonius Hospital, Heat Lung Centre, Utrecht, The Netherlands

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Aims The aim of this study was to assess the frequency of vasovagal episodes over the day, week, month, and seasons.

Methods and results This study was part of the multi-centre International Study on Syncope of Uncertain Etiology-2 (ISSUE-2), which included patients, aged 30 years or older, with severe neurally mediated syncope between June 2002 and July 2004. The Implantable Loop Recorder (ILR) was used to document the syncope-related ECG periods. For this study patients with recorded syncopal episodes after ILR-implantation was selected. At least one episode was documented in 106 patients. A higher number of episodes were documented during the morning than during other periods of the day ($P_{<0.01}$). There was no difference between various days of the week, episodes per month, or between seasons. There was no difference between age and gender groups, although elderly patients seemed to be responsible for the peak in the morning.

Conclusion A circadian pattern in the frequency of vasovagal episodes exists, with a peak in the morning. This is in accordance with reports of diurnal variations in blood pressure and heart rate. No difference was observed in syncope distribution between days of the week, months, or seasons.

KEYWORDS
Syncope; Vasovagal; Implantable loop recorder; Daily variation; Weekly variation; Seasonal variation

Introduction
Blood pressure (BP) and heart rate (HR) are regulated according to a circadian pattern.1,2 BP and HR are significantly lower at night than during the daytime,1,4 decline throughout the night and increase substantially at awaking.1 Possible explanations for BP and HR diurnal patterns include differences in physical activity3 and differences in activity of the autonomic nervous system between day and night.1–3 A circadian distribution has also been demonstrated for cardiovascular ischaemic events, with a peak between 6 am and noon.4,3

Since BP and HR vary in a circadian pattern, it could be that a circadian pattern also exists for inappropriate low BP responses. In patients with orthostatic hypotension due to autonomic failure, an inverse of the normal 24-h BP profile was observed with high BP at night6,7 and especially low BP in the morning, making patients more vulnerable to syncopal episodes in the morning. Whether this variation in the occurrence of syncopal episodes also exists in vasovagal patients is unknown, although one retrospective chart-study in young subjects, suggested a peak-occurrence in the morning.8

Although most vasovagal syncopal episodes are initiated by orthostatic stress, they can also occur in a supine position9,10 or even during sleep.11,12 Symptoms of these episodes include light-headedness, blurring of vision, and a feeling of generalized weakness. They are caused by systemic hypotension, leading to hypoperfusion of the brain due to a vasovagal response.10

But not only fluctuations in the frequency of vasovagal responses during the day, but also per day of the week, months, or even seasons have been suggested. In an earlier study a weekly pattern was suggested, while a slight predilection for the beginning of the week was recorded.13 However, in this study no quantitative results were reported. Furthermore, a high ambient temperature and heat acclimatization may affect the incidence of vasovagal syncope14 over the year.

The aim of the present study was to assess circadian variation of syncope frequency in adults over the day, testing the hypothesis that vasovagal syncope shows a peak frequency in the morning. Second aim was to assess
weekly, monthly, and seasonal patterns of the frequency of syncopal episodes.

Methods

This study was part of the International Study on Syncope of Uncertain Etiology-2 (ISSUE-2).15,16

Patients

All patients, aged 30 years or older, suspected of or diagnosed with neurally mediated syncope according to the guidelines published by the Task Force on Syncope of the European Society of Cardiology17 were eligible for inclusion.15 Only patients who had experienced three or more syncopal episodes in the last 2 years and had a severe clinical presentation of syncope requiring treatment initiation were included in this study. Patients with high likelihood of carotid sinus syndrome, cardiac syncope, symptomatic orthostatic hypotension, subclavian steal syndrome, or loss of consciousness different from syncope (such as epilepsy, psychiatric episodes of loss of consciousness) were not included.

Protocol

The ISSUE-2 was a multi-centre, prospective, observational study. The main objective was to verify the value of the implantable loop recorder (ILR) in assessing the mechanism of syncope and the efficacy of the ILR-guided therapy after syncope recurrence.15,16 Patients were enrolled at 63 European and American centres, between June 2002 and July 2004. Data were collected by local investigators and sent to an independent clinical research organization (RDES SL, Barcelona, Spain) via a dedicated Internet website. This organization maintained the database, issued data-clarification forms, and assisted by Medtronic clinical monitors, verified source documents.

The study was approved by the institutional review boards and signed informed consent was obtained from each patient at the time of enrolment.15,16 The ILR was used to document, quantify, and classify the syncope-related ECG periods. Arrhythmias were automatically detected by the ILR and stored. In addition, patients could activate the ILR and store the heart rhythm in case of symptoms of (pre)syncope. Furthermore, time and date of all (pre)syncopal events were collected. Follow-up was performed every 3 months, for a maximum of 24 months or until study ending.

For this study, the recordings were used to assess diurnal, weekly, and seasonal patterns in the occurrence of vasovagal syncope. In many patients with a syncope-recurrence after implantation of the ILR, the recorder was removed to start ILR-guided therapy according to study protocol.16 Registration and occurrence of further episodes were thus dependent on the treatment the patient received. Therefore, only the first documented syncopal episode after ILR implantation was used for the analysis of the distribution of episodes.

For this study only patients with one or more recorded syncopal episodes after ILR implantation were selected. Patient characteristics, time and date from the episodes, and type of syncopal events were retrieved from the database.

Analysis

All episodes were classified according to time of day (h), weekday, month of the year, and season.

Numerical data were graphically assessed for normality. Normal distributed data were expressed as mean (SD). Non-normal distributed data were expressed as median (quartiles). Categorical data were expressed as percentage of the total group of patients. Patients were divided into two age groups based on the median age, to assess the influence of age on the pattern of the episodes.

Time of day was divided into hours and into four periods, morning (6 am to noon), afternoon (noon to 6 pm), evening (6 pm to midnight), and night (midnight to 6 am) and compared with uniform occurrence (expected count of 25% of all patients in each group) using a $\chi^2$ test. Documented responses were divided into five possible categories by an endpoints committee: normal sinus rhythm, bradycardia, asystole, tachycardia, or other.15,16 Differences in these responses per daily period were assessed using a $\chi^2$ test.

Results

During the 2-year inclusion period 442 patients were eligible for inclusion in ISSUE-2.15,16 An ILR was implanted in 417 patients, as 25 patients or their physicians refused the implant. Of these patients, 36% ($n = 143$) had at least one syncopal recurrence. This episode was documented by ECG in 106 patients. Twenty-five patients had normal sinus rhythm during the episode and five bradycardic, 56 asystolic (median duration 12 s; range 3–90), 16 tachycardic, and two other responses were recorded (Figure 1). These 106 patients were included for this analysis (Figure 1). Baseline characteristics of the included patients are shown in Table 1. Median age of the patients was 69 years. This age was used as a cut-off point to assess the influence of age on the pattern of episodes.

Figure 2 shows the frequency distribution of syncope-episodes over the day, with striking peaks during the morning. Comparison of daily periods with expected uniform occurrence showed a statistical significant difference ($P < 0.01$) between the morning and other daily periods. The frequency of episodes in daily periods between age and gender groups was not statistically different ($P = 0.332$ and $P = 0.727$, respectively), although...
elderly patients seem to be mainly responsible for the peak in the morning (Figure 3). There was no difference in the type of syncopal responses over the day ($P = 0.813$).

As shown in Figure 2, syncopal episodes occurred at night as well. We recorded eight nocturnal (midnight to 6 am) episodes; five asystolic responses, and three times normal sinus rhythm. These episodes occurred in three women and five men with ages ranging from 46 to 87. Nocturnal episodes were most frequent ($n = 3$) between 5 and 6 am.

Figure 4 shows syncope distribution during the week. There is no difference between the days of the week, or between weekdays and weekend days. Weekly distribution is not different between age ($P = 0.646$) and gender groups ($P = 0.120$).

The distribution of syncopal episodes per month (Figure 5) shows no differences between the various months or seasons. Seasonal frequency distributions were not significantly different between age ($P = 0.763$) and gender groups ($P = 0.624$). Median time between implantation and the event was 83 days (quartiles 25–217). Time until event did not differ per season in which the ILR was implanted ($P = 0.461$).

**Discussion**

This study shows that a clear circadian variation in the frequency of syncopal episodes exists, with a striking peak in the morning, while there is no variation over days of the week, months of the year, seasons, or between older and younger patients or men and women.

Evidence of a day–night pattern in BP and HR is abundant.$^{1–5,18,19}$ The results of this study confirm our hypothesis that diurnal variation exists in syncopal episodes, based on these variations in BP and HR. These results confirm the retrospective results of Mineda et al.$^8$ in a younger patient group (mean age 37 years), who demonstrated a circadian pattern of vasovagal syncope, with two thirds of the total episodes occurring between 6 am and noon. In other studies,

**Table 1** Baseline characteristics

| Characteristics                        | n = 106 |
|----------------------------------------|---------|
| Age, mean (SD)                         | 67 (14) |
| Male gender (%)                        | 44      |
| Syncope events—history                |         |
| Syncopes, median (quartiles)          | 6 (4–10) |
| Syncopes—last 2 years, median (quartiles) | 4 (3–6) |
| Interval between first and last episode, median year (quartiles) | 6 (4–13) |
| Age at first syncope, mean (SD)       | 57 (18) |
| History of presyncope (%)             | 41      |
| Hospitalization for syncope (%)       | 53      |
| Injuries related to fainting (%)      | 65      |
| Major injuries (fractures, brain concussion) | 22      |
| Minor injuries (bruises, etc.)        | 52      |
| No warning at the onset of the attack (last and/or previous episode) (%) | 52      |
| Typical vasovagal/situational presentaion (last and/or previous episode) (%) | 36      |
| Atypical presentation (uncertain) (%) | 64      |
| Tilt testing: performed (%)           | 89      |
| Positive of performed                 | 40      |
| Cardioinhibitory or mixed of performed| 26      |
| ATP test: performed (%)               | 49      |
| Positive of performed                 | 31      |
| Normal electrocardiogram (%)          | 86      |
| No structural heart disease (%)       | 87      |
| Medical history (%)                   |         |
| Cardiac disease                       | 13      |
| Hypertension                          | 45      |
| Any neurological disease              | 9       |
| Diabetes                              | 9       |
| Any therapy at the time of enrolment (%) | 45      |
| Antihypertensive                      | 32      |
| Psychiatric                           | 11      |
| Antiarrhythmic                        | 6       |
| Others                                | 9       |

**Figure 2** Circadian distribution of vasovagal episodes.
Head-Up Tilt (HUT)-positive paediatric syncope patients showed significantly more syncopal episodes in the morning, compared with HUT-negative syncope patients. Although there are important differences in autonomic BP and HR regulation between young and elderly patients, these differences did not result in a different pattern between age groups in our study. Autonomic responses of elderly subjects to orthostatic stresses are reduced, which could result in more syncopal episodes. In addition in patients with orthostatic hypotension due to autonomic failure, an inverse of the normal 24-h BP profile was observed with high BP at night—and especially low BP in the morning. Both nocturnal polyuria and a redistribution of body fluid are mechanisms underlying the pronounced decreases in BP after prolonged recumbency at night. Although we observed a trend towards more
episodes of elderly patients in the morning this did not reach statistical significance when comparing periods of the day.

Another remarkable feature is the occurrence of syncope at night. Although vasovagal syncopal episodes seem unlikely to happen in a supine position, cases of vasovagal episodes at night or even during sleep have been reported.\(^\text{11,12}\) In these cases the patient usually wakes up because of feeling faint, often with abdominal discomfort, and loses consciousness in bed or immediately upon standing. Some patients reported having nightmares before the episode.

Proposed mechanisms for syncope interrupting sleep included asymmetrical slow wave activity in the cortex, changes between stages of sleep and nightmares, inhibiting sympathetic outflow.\(^\text{11}\) However, in case of transient loss of consciousness at night, causes such as epilepsy\(^\text{22–24}\) and cardiac syncope (Stokes Adams attack,\(^\text{25}\) Brugada,\(^\text{26,27}\) long QT-syndrome\(^\text{28}\)) should be excluded first. Especially, LQTS patients are more likely to have events during rest or sleep than during exercise.\(^\text{29}\) Other diagnostic possibilities include sleep apnoea, panic attacks, sleep paralysis, and hypoglycaemia.

In this study, there was no difference between weekdays. This is in concordance with one previous publication.\(^\text{13}\) Although work-related stressors might affect the susceptibility to vasovagal syncope, this was not found in this population. In a younger population, with more working subjects, differences between week and weekend days might however be present.

Heat acclimatization appears to have a remarkable influence on tilt tolerance\(^\text{14}\) and warm environments are mentioned as one of the most common triggers for vasovagal episodes.\(^\text{30,31}\) In this study, no significant difference in distribution of syncope was found between months or seasons of the year. Adaptations to lifestyle by subjects in warmer periods, and the limited variation in temperature in some countries between seasons, could be explanations for this lack of difference. Furthermore, it might be that only more acute changes in temperature, like entering a warm space or sauna, instead of more continuous high temperature levels to which subjects can adapt, are triggers for vasovagal episodes.

This study has several limitations. For the analysis only the first recurrent episode was used for analysis. Although the inclusion period consisted of two full years, a variation in inclusion frequency over the year could have influenced the number of patients at risk per month of the year and thereby the seasonal pattern. Furthermore, the episodes were not documented by ECG in 37 subjects. Since exact time and dates of the episodes in these subjects were not available, they were left out of the analysis. Since their episodes were not automatically registered by the ILR, their responses probably were different (no bradycardia or asystole) from the included group of patients. The results of this study might have been different in this group.

Secondly, data were collected in a group of severely affected older group of patients with presumed vasovagal syncope. Whether these results are also applicable to less severely affected younger patients, needs to be studied.

This study shows a distinct circadian pattern in the frequency of vasovagal syncope. There is a striking peak in frequency of vasovagal episodes in the morning, which consists mainly of elderly patients. This is in accordance with reports of diurnal variations in BP, HR, and diurnal shifts in cardiac autonomic balance. There is no difference in syncope distribution between days of the week, months, or seasons.

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Conflic of interest: N. G. and T. D. S. are employees of Medtronic Italia, S.P.A., Italy.

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