Analysis of rhythm variation during spontaneous cardioinhibitory neurally-mediated syncope. Implications for RDR pacing optimization: an ISSUE 2 substudy

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Background Little is known of the variations of the heart rate during spontaneous cardioinhibitory neurally-mediated syncope. Their knowledge has both academic and practical implications for the optimization of rate drop response (RDR) pacing mode.

Method and results We describe variations of the rhythm occurring during 48 syncopal episodes documented by implantable loop recorder. The presyncopal phase of 18 s (interquartile range 9–65) was characterized by a fall in heart rate from 83 ± 20 bpm to maximal bradycardia or (multiple) asystolic pauses which lasted a median of 19 s (10–30). The recovery phase lasted 22 s (7–52). The total duration of the cardioinhibitory reflex was 85 s (47–116). We then calculated the potential increase in benefit that an optimally programmed drop rate detection could provide compared with a reference Lower Rate detection. Compared with Lower Rate detection (defined as two consecutive beats at 40 bpm), drop rate detection (assumed to be drop size = 20 bpm, detection window = 1 min, and drop rate = 50 bpm) would have been able to introduce intervention pacing, a median of 5.7 s (interquartile range = 2.5–10.4) earlier in 28 cases (58%).

Conclusion Cardioinhibitory neurally-mediated reflex varies widely from a few seconds to some minutes. In our data the total duration was <2 min. Optimal RDR programming, being potentially able to anticipate the detection of the cardioinhibitory reflex by a few seconds, could provide an increase in benefit for cardiac pacing therapy in prevention of syncope.

KEYWORDS Syncope; Diagnosis; Electrocardiography; Implantable loop recorder; Pacing; Cardioinhibition; Rate drop response

Introduction While there is much knowledge of what occurs during tilt-induced neurally-mediated syncope, little is known of the variations of heart rhythm during spontaneous cardioinhibitory neurally-mediated syncope. The increasing use of implantable loop recorders in patients with neurally-mediated syncope offers the opportunity to obtain complete electrocardiographic documentation of the spontaneous cardioinhibitory reflex involved in this syndrome in a sufficient number of patients to describe the characteristics of the reflex and to suggest practical interventions. The analysis of such episodes allows optimizing rate drop response (RDR) settings for permanent cardiac pacing therapy. Although the RDR feature was developed from theoretical calculations and observation of tilt-induced episodes of syncope, RDR programming in clinical practice has mostly been empirical.

In this study, we used the International Study on Syncope of Uncertain Etiology 2 (ISSUE 2)1 database in order: (i) to describe the characteristics of the cardioinhibitory reflex responsible of neurally-mediated syncope; (ii) to suggest suitable RDR programming based on these observations; and (iii) to test the programming using a RDR model on the ISSUE 2 population by measuring its potential benefit.

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Methods

We analysed the variations of rhythm, which occurred at the time of 48 syncopal episodes [48 patients, mean age 67 ± 13 years, 52% males, history of five (interquartile range 4-8) episodes of syncope per patient], documented by implantable loop recorder among 72 patients affected by cardioinhibitory neurally-mediated syncope participating in ISSUE 2. Analysed episodes were those in which there was a recording of the full episode, including presyncope and recovery phase and ≥1 asystolic pauses of >3 s duration or bradycardia <50 bpm for >10 s at the time of syncope. Each episode was classified as class 1 (asystole) or class 2 (bradycardia) of the ISSUE classification. Episodes with minimum heart rate <50 bpm and those with incomplete recording or with important artefacts that prevented interpretation were excluded.

Heart rate variations

Each episode was printed on paper at paper speed 25 mm/s and analysed by three investigators (MB, RS, WW). The following parameters were defined and calculated:

(a) Presyncopal (rate decrease phase) was calculated from the time of highest heart rate increase (peak rate) or, when absent, the beginning of heart rate decrease to the time of minimum heart rate or beginning of asystolic pause/s.

(b) Syncopal phase was the time duration of minimum heart rate (type 2) or the total duration of asystolic pause/s (type 1), which were likely to correlate with the maximum severity of symptoms.

(c) Recovery phase was the time needed to recover baseline heart rate from bradycardia.

(d) The sum of the duration of the above phases was defined as total duration of the cardionhibitory reflex.

RDR simulation

In the digitized loop recorder ECGs from the syncopal episodes, R-waves were manually annotated by one of us (SL). RR intervals were calculated from the R-wave annotations. These RR intervals were used as inputs to the Medtronic Inc., Kappa RDR detection algorithm.

The Medtronic RDR is a pacemaker feature designed to provide high-rate pacing therapy when a potential syncope or presyncope episode is detected. The algorithm, which detects the potential syncope and presyncope events, has been described by Johansen et al. Detection has two methods. Low-rate detect method will trigger high-rate pacing therapy if a programmable number of consecutively paced beats at the low rate are detected. Drop detect method will trigger high-rate pacing therapy if the ventricular rate falls by a programmable size (drop size) and ends below a programmable threshold (drop rate), within a programmable detection window (Figure 1). In the pacemaker, these two detection methods may be selected individually or simultaneously.

For this study, the algorithm was simulated using Matlab (The Mathworks, Natick, MA, USA). We were not able to deliver pacing because of the retrospective nature of this analysis. Therefore, we estimated where low-rate pacing would occur, which we termed the introduction of pacing. We used the device default of two consecutive paced or slow beats for the detection criteria in our simulations. An isolated single slow beat such as one following a premature ventricular complex would not yield a pacing response, while two consecutive paced beats were simulated for an isolated slow beat with interval more than twice that of the low rate. Two consecutive paced beats were also simulated for two consecutive slow beats, where the first beat would have occurred slower than the low rate and the second occurred after a second simulated paced beat at the low rate.

We then evaluated the best RDR programmable features to be effective in the majority of these episodes. The best values of the drop detection parameters (drop size, detection window, and intervention duration) were defined as those able to identify 80% of the episodes based on the manual evaluation described earlier.

Then, we evaluated which would have been the best average RDR programmable features able to work effectively in the majority of these episodes. To do this, the best average values of the drop detection parameters (drop size, detection window, and intervention duration) were defined as those able to identify 80% of the episodes based on the manual evaluation described earlier.

Figure 1 Schematic representation of simulation parameters with Drop detection in a patient with a bradycardiac type 2 event. Pacing starts when heart rate drops by 20 bpm (drop size) within 1 min (detection window) to a value of heart rate of 50 bpm for two consecutive beats (drop rate). Both drop size and drop rate criteria must be met for intervention pacing. Pacing intervention is set at 90 bpm. Intervention duration is not shown. Drop rate detection: detects relative heart rate drops of a pre-determined size. Drop Size: size of the relative heart rate drop. Drop Rate: rate must be at or below this rate for two consecutive beats. Detection Window: maximum time window used to determine drop size. Intervention rate: pacing rate. Intervention duration: duration of high-rate pacing.
duration) were assumed to be those able to identify 80% of the episodes, each based on the manual evaluation described earlier.

Finally, the modelled RDR detection was applied to each recording in order to calculate how much earlier the drop detection method would intervene with respect to a reference low-rate detection method. The improvement in time to trigger intervention rate pacing was the measure of potential benefit.

**Results**

**Heart rate variations**

Of 48 analysed episodes, 33 were asystolic and 15 bradycardiac. Among those asystolic, 20 were classified as type 1A (sinus arrest), 7 as type 1B (sinus bradycardia plus AV block), and 6 as type 1C (sudden onset AV block). The episodes were characterized by a fall in heart rate from 83 ± 20 bpm to maximal bradycardia or (multiple) asystolic pauses. The longest pause in each episode had a median duration of 13 s (interquartile range 5–20); 2–10 sequential pauses occurred in 23 cases, giving a median duration of asystolic pauses in the syncopal phase of 19 s (interquartile range 10–30) (Table 1).

The duration of the presyncopal phase (rate decrease phase) ranged widely from 0 s (in 5 type 1C episodes of sudden onset AV block) to several minutes (max 8), in some type 1A episodes of progressive sinus bradycardia followed by asystole. On average, the rate decrease phase was quite short being a median of 18 s. In eight cases, there was marked oscillation of heart rate before asystole suggesting autonomic imbalance.

Also, the recovery phase ranged widely from 0 s to several minutes (median 22 s). Overall, the total duration of the cardioinhibitory reflex ranged from 8 to 556 s (median 85 s).

**Simulation assumptions**

The proposed RDR parameters are listed in the Table 2 and Figure 1.

**Estimated RDR effect**

Compared with a low-rate detect method (defined as two consecutive beats at ≤40 bpm), drop detect method (aforementioned) triggered intervention pacing earlier by a median of 5.7 s (interquartile range —5.1—10.4) in 28 cases (58%); in four of these, an intervention would not have taken place with respect to standard hysteresis (Table 1 and Figure 2). Early detection was more frequent in recordings with only bradycardia than in those with asystolic pauses and in recordings with asystolic pauses of type 1A and 1B than in those with 1C (80, 56, and 17%, respectively, P = 0.03, χ² test) (Figure 3). In type 1C, the drop detect method was able to detect earlier only when asystolic AV block was preceded by a period of 2:1 AV block at a rate >40 and <50 bpm. Figures 4, 5, 6, and 7 show four explicable cases.

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**Table 1** Heart rate variations during spontaneous cardioinhibitory neurally-mediated syncope and estimated RDR values (according simulation assumptions)

<table>
<thead>
<tr>
<th>Measured data</th>
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<tbody>
<tr>
<td>Median duration of pre-syncopal phase (interquartile range), s</td>
<td>18 (9–65)</td>
<td>19 (10–30)</td>
</tr>
<tr>
<td>Max heart rate at the beginning of pre-syncopal phase, bpm (SD)</td>
<td>83 ± 20 range 54–140</td>
<td>22 (7–52)</td>
</tr>
<tr>
<td>Longest pause (27 episodes), (interquartile range), s</td>
<td>13 (5–20)</td>
<td>85 (47–116)</td>
</tr>
<tr>
<td>Total duration of asystolic phase (including 23 episodes with multiple pauses), median (interquartile range), s</td>
<td>20 range 54–140</td>
<td></td>
</tr>
<tr>
<td>Median duration of recovery phase (interquartile range), s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total duration of cardioinhibitory reflex, median (interquartile range), s</td>
<td></td>
<td></td>
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<tr>
<td>RDR data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median drop size from maximum heart rate to 50 bpm (interquartile range), bpm</td>
<td>30 (20–40)</td>
<td></td>
</tr>
<tr>
<td>Drop size 80% of episodes, bpm</td>
<td>≥20</td>
<td></td>
</tr>
<tr>
<td>Detection window 80% of episodes, s</td>
<td>&lt;71</td>
<td></td>
</tr>
<tr>
<td>Estimated intervention duration 80% of episodes, s</td>
<td>&lt;56</td>
<td></td>
</tr>
<tr>
<td>Estimated introduction of intervention pacing with drop detection:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases with early introduction of pacing, %</td>
<td>28 (58%)</td>
<td></td>
</tr>
<tr>
<td>Advance detection time, all cases of earlier introduction, median (interquartile range), s</td>
<td>—5.3 (—2.4—6.8)</td>
<td></td>
</tr>
<tr>
<td>Advance detection time, type 1A and 1B (n = 15) median (interquartile range), s</td>
<td>—4.2 (—1.54—5.6)</td>
<td></td>
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<tr>
<td>Advance detection time, type 1C (n = 1) median, s</td>
<td>—6.8</td>
<td></td>
</tr>
<tr>
<td>Advance detection time, type 2 (n = 12) median (interquartile range), s</td>
<td>—5.7 (—5.14—10.4)</td>
<td></td>
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</table>
Discussion

The spontaneous cardioinhibitory reflex

Given the sufficient number of observations, the present study is able to describe the range of electrocardiographic characteristics of the spontaneous cardioinhibitory neurally-mediated reflex. In general, the reflex varied widely from a few seconds to several minutes. In most cases total duration was <2 min. When present, asystolic pauses were prolonged and usually multiple (up to 10 sequential pauses), resulting in a prolonged duration of the asystolic phase. The long duration of the asystolic reflex forms a strong background to the potential beneficial effect of pacing therapy, as was observed in the ISSUE 2 study.1

On average, the pre-syncopal phase was quite short as also was the recovery prompt. The observed durations of the rate decrease phase (average of 18 s) was shorter than that observed during tilt-induced neurally-mediated syncope which, in a systematic evaluation,4 ranged from 1.6 min with nitroglycerine challenge to 3.0 min with passive tilt. Conversely, the rate decrease duration of the spontaneous episodes was consistent with the duration of the prodromal symptoms in tilt studies, which was, on average, 1 min before the onset of syncope.5,6 The short duration of spontaneous episodes is consistent with the clinical features of the ISSUE 2 population characterized by older patient age, unpredictable episodes of syncope with absence of prodrome in many. It is possible that a longer rate decrease phase could be present in younger patients affected by classical vasovagal syncope.

Development of a suitable RDR programme

Rate drop response was based on observation of the cardioinhibitory reflex.7 Initial experience suggested benefit of its use over simple rate hysteresis.8 In studies of pacing vs. controls,9–11 the RDR programme was arbitrarily left to investigator decision. No randomized controlled data on its efficacy in comparison with rate hysteresis have been reported. Moreover, in those studies as well in clinical practice, pacing intervention at high-programmed rates (i.e. 110 bpm) frequently caused patient’s discomfort.

We developed an objective RDR programme-based observations of spontaneous cardioinhibitory neurally-mediated syncopal episodes. Drop size, detection window, and intervention duration were actually calculated from these observations in order to be effective in 80% of cases. The values of the other parameters necessary for simulation were arbitrarily defined based on current knowledge. Drop rate was set at 50 bpm and low rate at 40 bpm as a compromise between early detection of a cardioinhibitory reflex and the need to

Table 2 Simulation parameters

<table>
<thead>
<tr>
<th>Detection options</th>
<th>Drop detection and low-rate detection</th>
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<tbody>
<tr>
<td>Drop detection</td>
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<tr>
<td>Drop size</td>
<td>20 bpm</td>
</tr>
<tr>
<td>Drop rate</td>
<td>50 bpm</td>
</tr>
<tr>
<td>Detection window</td>
<td>1 min</td>
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<tr>
<td>Intervention rate*</td>
<td>90 bpm</td>
</tr>
<tr>
<td>Intervention duration**</td>
<td>1 min</td>
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<tr>
<td>Low-rate detection</td>
<td></td>
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<tr>
<td>Low&lt;er) rate</td>
<td>40 bpm</td>
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<tr>
<td>Confirmation beats</td>
<td>2</td>
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</table>

* These parameters were predefined based on the literature (not calculated) (see text).
** Not relevant for this study.

Drop detection: detects relative heart rate drops of a pre-determined size. Drop size: size of the relative heart rate drop. Drop rate: rate must be at or below this rate for two consecutive beats. Detection window: maximum time window used to determine drop size. Intervention rate: pacing rate. Intervention duration: duration of high-rate pacing. Low-rate detection: it detects heart rate that falls to a user-defined lower rate (similar to ‘hysteresis’-like algorithms); it intervenes when lower rate pacing occurs for two consecutive beats (confirmation beats).

Figure 2 Predicted advance of drop detection compared with standard hysteresis at 40 bpm mode [low<er) rate detection]. In the simulated model, an earlier introduction of pacing ranging from 2 s to 200 s occurred in 24 patients. In a further four patients pacing occurred only with drop detection, as their lower rate was always >40 bpm and never activated standard hysteresis.
avoid false-pacing intervention due to non-reflex bradycardic episodes. Indeed, data from the literature of prolonged electrocardiographic monitoring in 183 healthy subjects\(^{12}\) showed that the minimum daily heart rate was 53 ± 8 bpm in males and 56 ± 7 bpm in females; only 2.5% of males had a minimum heart rate <40 bpm and the lowest heart rate in females was 42 bpm; pauses >2 s were present in 2% of subjects, whereas no subjects had pauses >3 s. In a study of 50 healthy elderly individuals,\(^{13}\) the minimal observed heart rate was 42 bpm (mean 57 ± 9) during sleep and 50 bpm (mean 64 ± 9) when awake. In another study of 98 healthy subjects >60-years-old,\(^{14}\) the minimal heart rate was 53 ± 7 bpm. In subjects older than 80 years\(^ {15}\) sleep rates <50 bpm occurred in 14% but sinus pauses >2 s were never observed.

Therefore, in the absence of a drop rate detection algorithm, a hysteresis trigger rate of 50 bpm would probably result in many false-positive detections, since this value is
above the lower 95% confidence interval of normal subjects. Simple hysteresis at 40 bpm, i.e. the lower rate detection, should be very specific as heart rate \( < 40 \text{ bpm} \) was very unusual in healthy adults in the earlier mentioned studies\(^\text{12-15} \) and was effectively used in a previous pacing study.\(^\text{16} \) Furthermore, two consecutive beats (confirmation beats) were required in order to avoid detection by a single cycle longer than that value (for instance premature beats). Intervention rate was set to 90 bpm, in order to provide the maximum haemodynamic benefit while avoiding symptomatic perception of higher pacing rates.\(^\text{16} \) A study has shown that pacing at an intervention rate of 90 bpm was never perceived by patients, whereas it caused palpitations in 80% of cases when set to 110 bpm.\(^\text{17} \)
Benefit of RDR programme

The drop detection algorithm we developed was compared with standard hysteresis at 40 bpm. This latter has been validated in neurally-mediated syncope patients in a previous study.17 Compared with standard hysteresis, the RDR programme would have been of potential benefit, on average, in 58% of episodes, whereas in the remainder this function would have been overcome by standard hysteresis. As expected, the benefit was greater in the cases with prolonged pre-syncopal phase than in those without. Apart from some exceptions, earlier detection occurred only a few seconds in advance. Whether this short time would have had clinical utility to avoid or limit symptoms is uncertain. However, two considerations are relevant. The first is that a sudden cessation of cerebral blood flow for 6–8 s has been shown to be sufficient to cause complete loss of consciousness18 and, therefore, the earlier introduction of pacemaker therapy probably due to an associated vasodepressor reflex; whether the RDR programme would have limited symptoms is yet unproven. This hypothesis will be validated prospectively in ISSUE 3 randomized study.19

Conclusion

Cardioinhibitory neurally-mediated reflex varies widely from a few seconds to some minutes with a total duration <2 min in most cases. Optimal RDR pacemaker programming, being potentially able to introduce dual-chamber pacing a few seconds earlier in many cases, might provide increased benefit of cardiac pacing therapy.

References