Clinical Autonomic Research (2024) 34:17–19
https://doi.org/10.1007/s10286-023-01005-0

EDITORIAL

How low can you go: heart rate dynamics in between vasovagal syncope

Roland D. Thijs[1,2] · **Satish R. Raj**[3,4]

Received: 22 November 2023 / Accepted: 22 November 2023 / Published online: 23 December 2023
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany 2023

Keywords Deceleration capacity · Bradycardia · Cardioinhibition · Heart rate variability · Vasodepression · Hypotension

> If the flow of blood fails, and the colour alters, and the pulse becomes weak, stop the bleeding. Also, if yawning and stretching, hiccup, or nausea come on. Watch the pulse if the colour changes quickly and the flow is free, so as to be on guard against syncope.
>
> Ibn Sina (980–1037 CE) [1].

The gradual slowing of the pulse has always been recognized as a prominent sign in vasovagal syncope (VVS). For a long time in history this seemed the sole mechanism to explain the circulatory arrest in VVS. It was not until the discovery of the sphygmomanometer that vasodilatation was identified as a coinciding mechanism contributing to the fall in blood pressure (BP) in VVS. Sir Thomas Lewis's case observations in soldiers with an "irritable heart" marks this turning point [2]. His astute observations combined with beat-to-beat BP recordings uncovered attacks "in which the blood pressure sinks without a lowering of pulse rate, and the patient verges on unconsciousness whenever the pressure reaches certain low levels." Lewis concludes that the "cause of syncope is mainly vasomotor and not vagal" and redefined the term vasovagal in the context of syncope to emphasize the duality of the reflex.

✉ Roland D. Thijs
r.d.thijs@lumc.nl

1 Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

2 Department of Neurology, Leiden University Medical Centre, PO box 9600, 2300 RC Leiden, The Netherlands

3 Department of Cardiac Sciences, Libin Cardiovascular Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

4 Autonomic Dysfunction Center, Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

The emergence of new therapies for VVS sparked the interest in markers to detail the dominant mechanism at play [3]. Although some signs of cardioinhibition may be seen in nearly all cases, the relative impact of cardioinhibition declines with age with the most prolonged asystolic response among the younger individuals [4]. Refractory VVS cases with dominant vasodepressive subtypes could benefit from therapies aiming to expand plasma volume or to promote vasoconstriction while interventions targeting bradycardia may be considered in those with a dominant cardioinhibitory profile [5, 6]. These second-line therapies only apply to highly selected cases, as the majority appears to benefit from simple interventions like education about the vasovagal response and its natural history, life-style measures including dietary interventions, and counterpressure maneuvers [5, 6]. There are some data to suggest that even the encounter with an expert physician can be therapeutic [7].

Investigative strategies in vasovagal syncope

When considering more targeted second-line treatments the crucial question is how to be sure of the dominant mechanism at play? The most studied approach is to provoke symptoms during tilt table testing or carotid sinus massage (Table 1) [8]. Both tests are attractive as they offer simultaneous recordings of heart rate and continuous blood pressure, thus allowing to determine the relative timing and hereby to derive the presumptive mechanism. The disadvantage, however, is that the provocation itself may cause bias due to variation in test methodology.

Event recording, in which a monitor is placed to "capture" spontaneous attacks, has no such limitations, yet the need to await future attacks will delay management decisions [3]. Another drawback of event monitoring is that we can currently do this well for electrocardiographic (EKG) but not

Table 1 Investigative Strategies in Vasovagal Syncope

	Provocation needed	Dependent on test details	Clinical Truth for at least one spontaneous spell	Ability to identify dominant hemodynamic mechanism	Rapid or delayed answers
During spontaneous syncopal spells					
Implantable loop recorder	N	N	Y	N	Delayed
Wearable HR monitor	N	N	Y	N	Delayed
Wearable HR/BP monitor	N	N	Y	Y	Delayed
In-between syncopal spells					
Tilt table test	Y	Y	N	Y	Rapid
Carotid sinus massage	Y	Y	N	Y	Rapid
24-h ambulatory BP monitor	N	N	N	N	Rapid
24-h EKG monitor	N	N	N	N	Rapid

BP = blood pressure; HR = heart rate; EKG = electrocardiographic

for BP recordings, thus carrying the risk of falling in the same trap as in the years before the sphygmomanometer. Documenting asystole during a spontaneous event does not mean that it is the dominant mechanism, as the asystole may occur after vasodepression has already provoked loss of consciousness [9].

Another approach to uncover more hidden traits in subjects with VVS is to apply long-term recordings in between attacks. Ambulatory blood pressure monitoring (ABPM) in people with VVS and healthy controls revealed that having one or more daytime systolic BP drops < 90 mmHg is a distinct finding (specificity 94%) in VVS with a sensitivity of 29% [10]. The ABPM analogy could also be useful to identify cardioinhibitory traits in VVS using Holter recordings. The classical approach has been to use 24-h EKG to assess daytime/nighttime heart rate variability, but this never made it to the clinic because of poor predictive power and conflicting results. Selective quantification of relative sparse bradycardic events may be an alternative way to express heart rate metrics.

Heart rate decelerations

In this issue Li et al. examined the heart rate deceleration profiles in VVS [11]. They studied 24-h EKG recordings of 188 subjects with VVS of whom 129 had a positive head-up tilt test and compared them with 132 healthy controls. The overall deceleration capacity (DC) appeared to be higher in subjects with VVS than healthy controls. There were no differences observed in DC between those with positive and uneventful tilt table tests. The major driver for the overall increased DC in VVS consisted of a higher prevalence of frequent short-lasting deceleration runs in VVS. In contrast, the rare longer deceleration runs (episodes of 8 to 10 consecutive beat-to-beat HR) were more common among healthy controls. The two deceleration indices (overall higher deceleration capacity and lower amount of very long deceleration runs) had more discriminative power, where conventional heart rate variability parameters did not.

Interestingly, a recent study of the same group suggested that DC findings might help to predict treatment response to invasive cardioneuroablation (CNA) procedures in cases with refractory VVS [12]. The authors assessed DC at baseline in a cohort of patients undergoing CNA. The baseline DC appeared to be useful to discriminate between responders (no syncope recurrence) and non-responders, with higher DC values in responders. Nighttime DC had the highest predictive value. Noteworthily, any head-up-tilt variable (absence of symptoms or, if symptomatic, the classification of the hemodynamic response) failed to reliably separate responders from non-responders. It is likely that treating all cases with refractory VVS with CNA carries a huge risk of offering a wrong treatment in a "mainly vasomotor condition," thus probably explaining the low response rate. It is therefore vital that metrics like DC help improve case selection when considering invasive, and potentially harmful, treatments for refractory VVS.

How strong is the discriminative DC power as a diagnostic test? When comparing the daytime DC results with the ABPM findings, the specificity appears lower (74% vs. 94%), while sensitivity is higher (75% vs. 29%). While the report energizes the enthusiasm for DC as a more specific EKG marker than heart rate variability in VVS, there remain many questions. How reproducible is DC in syncope patients from day to day? Does DC discriminate VVS from other causes of syncope? Will DC be useful when performed in other syncope centers? Why is the DC only relevant for the shorter deceleration runs? What explains the increased prevalence of very long deceleration runs in healthy controls? We obviously need to develop more personalized treatments for patients with VVS. Deceleration capacity is a promising

candidate to phenotype VVS subtypes, but the proof of the pudding will need further multicenter validation studies.

Acknowledgements RDT is supported by the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, and reports grants from EU Pathfinder, Vriendenloterij, Michael J Fox Foundation, EpilepsieNL, The Netherlands Organisation for Health Research and Development (grant no. 843002707), and the Human Measurement Models Programme co-funded by Health~Holland, Top Sector Life Sciences & Health, and ZonMw under grant agreement 114025101 (Brain@Home). SRR has been supported by grants from the Canadian Institutes of Health Research (Ottawa, ON, Canada), Heart & Stroke Foundation of Canada (Ottawa, ON), Dysautonomia International, Standing Up to POTS, and the National Center for Advancing Translational Sciences (UL1 TR000445; Bethesda, MD, USA).

Declarations

Conflict of interest RDT reports personal fees from UCB, Theravarance, Novartis, Eisai, LivAssured, Xenon, Angelini, Zogenix, and Arvelle and grants from Medtronic and NewLife Wearables. SRR is a Consultant for Theravance Biopharma, Amneal Pharma, Servier Affaires Medicales, Regeneron, Antag Therapeutics, and Argenx BV. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Avicenna (980–1037) The Canon of medicine of Avicenna (1973) AMS press New York, p 507.
2. Lewis T (1932) A Lecture on vasovagal syncope and the carotid sinus mechanism. Br Med J 3723:873–876
3. Brignole M, Rivasi G, Fedorowski A, Ståhlberg M, Groppelli A, Ungar A (2023) Tests for the identification of reflex syncope mechanism. Expert Rev Med Dev 20:109–119
4. van Dijk JG, van Rossum IA, Thijs RD (2021) The pathophysiology of vasovagal syncope: novel insights. Auton Neurosci 236:102899
5. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A et al (2018) 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J 39:1883–1948
6. Ballantyne BA, Letourneau-Shesaf S, Raj SR (2021) Management of vasovagal syncope. Auton Neurosci 236:102904
7. Raj SR, Sheldon RS (2022) Vasovagal syncope needs the "expert touch." JACC Clin Electrophysiol 8:150–151
8. Thijs RD, Brignole M, Falup-Pecurariu C, Fanciulli A, Freeman R, Guaraldi P, Jordan J, Habek M, Hilz M, Traon AP, Stankovic I, Struhal W, Sutton R, Wenning G, Van Dijk JG (2021) Recommendations for tilt table testing and other provocative cardiovascular autonomic tests in conditions that may cause transient loss of consciousness: consensus statement of the European Federation of Autonomic Societies (EFAS) endorsed by the American Autonomic Society (AAS) and the European Academy of Neurology (EAN). Clin Auton Res 31(3):369–384
9. Saal DP, Thijs RD, van Zwet EW, Bootsma M, Brignole M, Benditt DG, van Dijk JG (2017) Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope. JACC Clin Electrophysiol 3(13):1592–1598
10. Rivasi G, Groppelli A, Brignole M et al (2022) Association between hypotension during 24 h ambulatory blood pressure monitoring and reflex syncope: the SynABPM 1 study. Eur Heart J 43:3765–3776
11. Li J, Sun W, Yang X, Tu B, Cai S, Hu F, Weng Z, Liu S, Lai Z, Zheng L, Yao Y (2023) Characteristics of deceleration capacity and deceleration runs in vasovagal syncope. Clin Auton Res. https://doi.org/10.1007/s10286-023-00989-z. (**in press**)
12. Tu B, Wu L, Hu F, Fan S, Liu S, Liu L, Ding L, Zheng L, Yao Y (2022) Cardiac deceleration capacity as an indicator for cardioneuroablation in patients with refractory vasovagal syncope. Heart Rhythm 19:562–569