How to unblur the vasovagal evidence?

Thijs, R.D.; Fedorowski, A.

Clinical Autonomic Research (2023) 33:5–7
https://doi.org/10.1007/s10286-022-00915-9

EDITORIAL

How to unblur the vasovagal evidence?

Roland D. Thijs[1,2] · **Artur Fedorowski**[3,4]

Received: 5 December 2022 / Accepted: 5 December 2022 / Published online: 20 December 2022

Keywords Syncope · Norepinephrine · Norepinephrine transporter · Autonomic nervous system

Vasovagal syncope (VVS) is the most frequent, yet poorly understood, cause of transient loss of consciousness (TLOC). It affects up to 40% of the general population [1]. VVS has generally benign long-term prognosis and efficient first-line treatments, especially in younger individuals with sporadic attacks preceded by typical prodromes [1]. Simple interventions like explanation of VVS mechanism, education, life-style measures including dietary interventions (e.g. increased fluid and salt intake) and counterpressure manoeuvres appear to be effective in the majority of cases [1]. Despite these facts, the distressing presentation and frequent failure to establish the correct diagnosis fuels the high rate of emergency department visits, in-flight emergencies, hospital admissions and loads of tests with low clinical utility [2, 3]. Moreover, there is ample evidence emphasising the impact of VVS on daily living mainly due to high rates of anxiety and physical injury [2]. Nevertheless, in view of its frequent occurrence, the minority in whom these measures fail is still substantial. The prevalence of those with five or more vasovagal episodes during their life amounts to 5% of the general population [4]. For those with recurrent VVS attacks, often associated with trauma, and negative social or occupational consequences, the evidence supporting management is still rather blurry as we still have no well-defined treatment pathways for those who do not respond to first-line VVS interventions. Most pharmacological interventions are supported by class II recommendations, with the best evidence for use of midodrine and fludrocortisone against recurrent VVS (Fig. 1) [1, 5]. For a highly selective group of well-documented cases aged 40 years and older with dominant cardioinhibitory VVS, there is evidence for dual-chamber cardiac pacing [1].

The knowledge gap for the work-up of complex VVS comes as no surprise as it may be explained by several factors. First, VVS could be considered an orphan condition. While most orphan diseases are extremely rare, VVS is common but owes its orphan status to the subspecialisation of hospital care. The two main specialties involved in the outpatient TLOC evaluation: neurology and cardiology tend to focus on epilepsy or arrhythmias as a cause of TLOC. Often patients are evaluated by excluding the unlikely, less frequent cause and discharged with a "you-do-not-have" syndrome. Second, the burden and frequency of refractory VVS tend to be underestimated, thus making it difficult to obtain funding for further research. As a result, only a limited number of RCTs have been performed although refractory VVS is more prevalent than epilepsy or arrhythmias [1]. Third, performing such trials is a complex task as VVS is characterised by a strong placebo response. This effect is mainly driven by expectation effect and in part by natural variability (e.g. due to randomness of the events). Regression to mean seems to be of minor importance [6]. Fourth, VVS is extremely heterogeneous. Although VVS is often labelled as "simple faint", the full story turns out to be more complex. Even if we simplify VVS by focussing on hemodynamic patterns of those with tilt-induced and often nitroglycerine-provoked VVS, we face diverse responses particularly regarding the occurrence and strength of cardioinhibition [7].

How could we accelerate the evidence-based treatments for VVS? Modulating the autonomic system to prevent VVS is challenging especially for those in whom non-pharmacological treatments fail. The major difficulty lies in the fact that the instances are sporadic and often unpredictable.

✉ Roland D. Thijs
r.d.thijs@lumc.nl

1 Department of Neurology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands

2 Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands

3 Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden

4 Department of Medicine, Karolinska Institute, Stockholm, Sweden

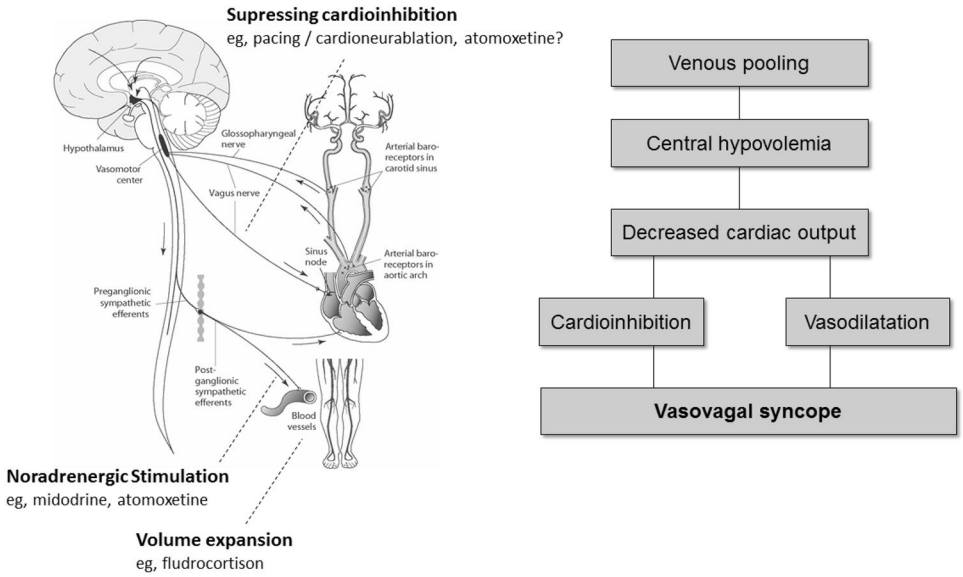

Fig. 1 Key treatments for vasovagal syncope [1, 5] and their impact on the vasovagal cascade [7]

Interventions should suppress the vasovagal reflex or provide an instant response early in the vasovagal cascade. Supressing the vasovagal reflex should predominantly focus on counteracting the central hypovolemia. A gradual decline of stroke volume seems to be the very first sign that precedes the decrease in heart rate and total peripheral resistance in VVS induced by head-up tilt [7]. The challenge for drug interventions is that it should be of sufficient strength to prevent the sporadic autonomic storm without negatively impacting the autonomic control in between events, e.g. by inducing hypertension or fluid retention. Invasive procedures, e.g. cardioneuroablation, face the same challenge: the reflex should be effectively supressed while preserving normal autonomic control. Responsive treatment strategies are complicated by the need of a reliable trigger to administer the intervention and would need instant efficacy. Regrettably, the hypotensive warning signs are often not recognised or too brief particularly among elderly subjects. Alternatively, sensors could help to detect incipient (cardioinhibitory) VVS at an earlier stage, like declining stroke volume or change in myocardial contractility, as especially designed for pacemaker based on close-loop system with seemingly good efficacy [8]. However, further clinical evidence is required also to understand the physiological roots and the outcome in mixed or predominantly hypotensive VVS.

In this issue, Sheldon et al. report real-world data on atomoxetine in a small cohort of 12 subjects with severe and recurrent VVS managed at a tertiary Syncope Unit [9]. Atomoxetine is an interesting drug for refractory VVS. It is a selective norepinephrine transporter inhibitor that prevents reuptake of norepinephrine from the synapse, thereby increasing norepinephrine levels in peripheral noradrenergic fibres [10]. It has a FDA approval for the treatment of attention deficit hyperactivity disorder and a class II recommendation for the treatment of neurogenic orthostatic hypotension [1]. In autonomic failure, it may capitalise on residual sympathetic outflow to combat orthostatic hypotension. Interestingly, atomoxetine does not augment blood pressure in healthy subjects [10]. This contrasts with midodrine which exerts a clear pressor response. Midodrine effectively reduces the likelihood of VVS but also carries the risk of developing supine hypertension [11]. Consequently, atomoxetine could be an attractive alternative for VVS prevention as it does not impact the blood pressure in between attacks. It is thought that the peripheral increase of norepinephrine is counteracted by a central, clonidine-like sympatholytic effect [10]. Indeed, a comparative study in central vs. peripheral causes of autonomic failure reported a more marked antihypotensive effect in those with central autonomic failure [12]. In the context of VVS, atomoxetine might shift the balance between central vs. peripheral sympathetic outflow, causing peripheral dominance while not affecting the net overall outflow.

A double-blind proof of principle study in 56 adults with VVS showed that atomoxetine prevented tilt-induced syncope by about half, mainly by blunting reflex bradycardia and counteracting the final fall in cardiac output [13]. This effect has been confirmed by similar experiments using other norepinephrine transporter inhibitors, including reboxetine and sibutramine [14]. While tilt table data are useful to examine hemodynamic properties, lower scores of tilt-provoked VVS following a drug intervention cannot reliably predict clinical efficacy [15]. We, therefore, need real-world data, ideally with randomised controlled design. Here, Sheldon et al. propose a novel method using the Poisson distribution to value simple clinical observations. The Poisson distribution is a calculus that is used to model the probability of the occurrence of discrete and sparse events. A

famous example is the report by Ladislaus von Bortkiewicz (1868–1931) who applied the Poisson distribution to evaluate the number of Prussian cavalrymen killed by horse kicks [16]. The figures perfectly fitted the expected numbers, thus demonstrating randomness and ruling out external factors like training year or cavalry corps. Sheldon et al. applied the same cavalry calculus and described the clinical response to atomoxetine as a collection of $n = 1$ studies [9]. Seven out of twelve subjects significantly improved, two did not improve, and three did not faint but had a too brief follow-up to detect significance. Interestingly, no subjects developed new hypertension. Instead, three subjects developed manageable dyspepsia or nausea and two others withdrew due to intolerable headache or worsened depression. The clinical and physiological data, thus, provides some support for the use of atomoxetine as an off-label alternative for refractory VVS. Fortunately, the proof of the pudding for the first-line use is on its way with the recently launched Prevention of Syncope Trial VII (POST7, NCT05159687). Meanwhile, we can strengthen our clinical observations with the cavalry calculus to explore new potentially valuable additions to our ammunition and ask ourselves whether more (norepinephrine) is less (faints) in vasovagal syncope.

Declarations

Conflict of interest RDT received research support from Medtronic, the Human Measurement Models Programme co-funded by Health ~ Holland, Top Sector Life Sciences & Health and ZonMw under grant agreement 114025101 (Brain@Home), Michael J Fox Foundation, Epilepsie NL and received speaker or consultancy fees from Theravance Biopharma, Arvelle, Medtronic, Xenon, Zogenix, UCB, NewLife Wearables and Novartis. AF has received speaker and consultancy fees from Medtronic Inc., Biotronik, Finapres Medical Systems, and ArgenX BV.

References

1. 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
2. Sun BC (2013) Quality-of-life, health service use, and costs associated with syncope. Prog Cardiovasc Dis 55(4):370–375
3. Borges do Nascimento IJ, Jerončić A, Arantes AJR, Brady WJ, Guimarães NS, Antunes NS, CarimJunior G, Marcolino MS (2021) The global incidence of in-flight medical emergencies: a systematic review and meta-analysis of approximately 1.5 billion airline passengers. Am J Emerg Med 48:156–164
4. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG (2006) Syncope in migraine: the population-based CAMERA study. Neurology 66(7):1034–1037
5. Ballantyne BA, Letourneau-Shesaf S, Raj SR (2021) Management of vasovagal syncope. Auton Neurosci 236:102904
6. Sahota I, Sheldon R, Pournazari P (2014) Clinical improvement of vasovagal syncope in the absence of specific therapies: the Seinfeld effect. Cardiol J 21(6):637–642
7. van Dijk JG, van Rossum IA, Thijs RD (2021) The pathophysiology of vasovagal syncope: novel insights. Auton Neurosci 236:102899
8. Sutton R, de Jong JSY, Stewart JM, Fedorowski A, de Lange FJ (2020) Pacing in vasovagal syncope: physiology, pacemaker sensors, and recent clinical trials-precise patient selection and measurable benefit. Heart Rhythm 17(5 Pt A):821–828
9. Sheldon RS, Seifer C, Parkash R, Sandhu R, Hamzeh R, Raj S. Atomoxetine for suppression of vasovagal syncope. Clin Auton Res. https://doi.org/10.1007/s10286-022-00905-x
10. Biaggioni I (2017) The pharmacology of autonomic failure: from hypotension to hypertension. Pharmacol Rev 69(1):53–62. https://doi.org/10.1124/pr.115.012161. (**PMID:28011746; PMCID:PMC6047298**)
11. Lei LY, Raj SR, Sheldon RS (2022) Midodrine for the prevention of vasovagal syncope: a systematic review and meta-analysis. Europace 24(7):1171–1178. https://doi.org/10.1093/europace/euab323. (**PMID:35025999; PMCID:PMC9301979**)
12. Shibao C, Raj SR, Gamboa A, Diedrich A, Choi L, Black BK, Robertson D, Biaggioni I (2007) Norepinephrine transporter blockade with atomoxetine induces hypertension in patients with impaired autonomic function. Hypertension 50(1):47–53
13. Sheldon RS, Lei L, Guzman JC, Kus T, Ayala-Paredes FA, Angihan J et al (2019) A proof of principle study of atomoxetine for the prevention of vasovagal syncope: the Prevention of Syncope Trial VI. Europace 21:1733–1741
14. Lei LY, Raj SR, Sheldon RS (2020) Pharmacological norepinephrine transporter inhibition for the prevention of vasovagal syncope in young and adult subjects: a systematic review and meta-analysis. Heart Rhythm 17:1151–1158
15. 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
16. von Bortkiewicz L (1898) Das Gesetz der kleinen Zahlen [The law of small numbers]. B. G. eubner, Leipzig, p 23