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Review

Vagus nerve stimulation and heart rate variability: A scoping review of a somatic oscillatory signal

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HIGHLIGHTS

- Achieving "healthy" HRV (heart rate variability) is not necessary for the therapeutic benefits of VNS (vagus nerve stimulation) in treating drug-resistant epilepsy.
- Decreases in frequency domain parameters may be useful to pre-operatively screen VNS responders from VNS non-responders.
- Transient HRV changes after VNS may imply the presence of other mechanisms responsible for the therapeutic effects of VNS.

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ABSTRACT

The goal of this review is to synthesize the literature on vagus nerve stimulator (VNS)-related changes in heart rate variability (HRV) in patients with drug-resistant epilepsy (DRE) and assess the role of these changes in seizure relief. A scoping literature review was performed with the following inclusion criteria: primary articles written in English, involved implantable VNS in humans, and had HRV as a primary outcome. Twenty-nine studies were retrieved, however with considerable heterogeneity in study methods. The overall depression in HRV seen in DRE patients compared to healthy controls persisted even after VNS implant, indicating that achieving "healthy" HRV is not necessary for VNS therapeutic success. Within DRE patients, changes in frequency domain parameters six months after VNS implant returned to baseline after a year. The mechanism of how VNS reduces seizure burden does not appear to be significantly related to alterations in baseline HRV. However, the subtlety of sympathetic/parasympathetic signaling likely requires a more structured approach to experimental and analytic techniques than currently found in the literature.

Abbreviations: Avg, average; BP, blood pressure; DRE, drug resistant epilepsy; ECG, electrocardiogram; EMU, epilepsy monitoring unit; F, female; HF power, absolute power of the high frequency band (0.15–0.4Hz); Hr, hours; HR, heart rate; Hz, hertz; LF power, absolute power of the low frequency band (0.04–0.15Hz); LF/HF, ratio of LF to HF power; M, male; Mins, minutes; mo, month; MSE, mean slope entropy; n/a, not applicable; NN, number of normal sinus beats; NS, no significant change; pNN50, successive heartbeat intervals that exceeds 50ms divided by the number of RR interval; RMSDD, root mean squared of the difference between successive NN intervals; SD, standard deviation; SD1, poincaré plot standard deviation perpendicular to the line of identity; SD2, poincaré plot standard deviation along the line of identity; SDNN, standard deviation of normal sinus beats; SDANN, standard deviation of the average of normal sinus beats; SDSD, standard deviation of the difference between successive NN intervals; VLF power, absolute power of the very low frequency band (0.0033–0.04 hz); VNS, vagus nerve stimulator.

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Contents

1. Introduction

Implantable vagus nerve stimulators (VNS) are a well-established treatment strategy for drug-resistant epilepsy (DRE) (Ji et al., 2019), defined as epilepsy that is refractory to treatment with two or more anti-seizure medications (ASMs) of different mechanisms (Kwan et al., 2009). After VNS implantation only around 60 % of patients experience some degree of seizure reduction, with less than 10 % of these patients achieving true seizure freedom (Boon et al., 2009). Despite being a common treatment option for DRE, the exact mechanism of how VNS reduces the intensity and frequency of seizures is still unclear.

VNS sends electrical stimulation both afferently to the brain and efferently to multiple parasympathetic ganglia located in the epicardium and the atrial and ventricular septum of the heart (Capilupi et al., 2020). In the peripheral nervous system VNS afferently stimulates the vagus, projecting to the nucleus tractus solitarius which then goes on to activate various subcortical and cortical brain regions, such as the cholinergic basal forebrain (Bowles et al., 2022). Consistent data suggests that patients with epilepsy have lower than normal heart rate variability (HRV), and that dramatic decrements in postictal (Naritoku et al., 2003) and baseline HRV (Evangelista et al., 2023) are associated with increased risk of sudden unexpected death in epilepsy (SUDEP). Although VNS is associated with a decreased risk for SUDEP (Ryvlin et al., 2018) the underlying mechanism of how VNS reduces this risk is unclear, as is how HRV is related, if at all.

Given these correlations and less than ideal seizure outcomes, HRV and VNS has been increasingly popular in epilepsy research over the past 10–20 years. Within this growing body of literature there is significant heterogeneity in not only study methods but also outcome measures, so comparing the findings of these studies proves statistically challenging. A statistically rigorous metanalysis in 2021, restricting their comparison to pre- to post-surgical HRV outcomes, found no significant changes in HRV after VNS implant (Wu et al., 2021). While rigorous, that metanalysis included only one-third of available studies investigating VNS effects on HRV in patients with epilepsy and, due to its methodology, did not comment on many HRV variables that may be beneficial to understand in wider context moving forward. We believed that a scoping review would allow for a wider comparison of study outcomes, and a more descriptive synthesis of the current literature.

2. Methods

2.1. Selection criteria

Two of the authors (CW, IM) independently vetted articles based on the following eligibility criteria. Articles needed to include *all* the following criteria to be included in this review: implantable VNS device, human subjects only, HRV as primary outcome, and primary research article published in English.

2.2. Search strategy

The following online databases were used in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (Page et al., 2021a, Page et al., 2021b): PubMed, Web of Science, EMBASE, and Cochrane Library. Search terms were modified to accommodate each database's format, but overall modeled the following format: ("Heart rate variability" OR HRV OR "heart period variability") AND ("Vagus Nerve Stimulation" OR "vagal nerve stimulation" OR VNS) AND

(seizure OR epilepsy). After combining articles from each database, duplicate articles were removed. Next, two of the authors (CRW, IM) reviewed the remaining abstracts based on the selection criteria indicated in *section 2.1*. The final database search was completed on January 14, 2024. Backwards citation chaining was performed as needed via Google Scholar.

2.3. Data extraction

Two authors (CRW, IM) abstracted data from the final list of retrieved articles. HRV definitions and the respective abbreviations are listed as follows (HRV abbreviations, units, and definitions in table format can be found in *Supplemental* Table 1 for easy reference*)*:

Time Domain: heart rate (*HR*), normal-to-normal RR interval (*NN*), standard deviation of NN (*SDNN*), the number of adjacent NN intervals that differ from each other for more than 50 ms divided by the total number of RR intervals in 50sec (*pNN50*), standard deviation of the average NN interval for each 5 min segment of a 24hr ECG recording (*SDANN*), average of the SDNN (*SDNN Index*), root mean squared of the differences in successive RR intervals (*RMSDD*), relative standard deviation of differenced in successive RR intervals (*SDSD*)
Frequency Domain: power of the high frequency band between 0.15–0.4 Hz (*HF power*), power of the low frequency band between 0.04–0.15 Hz (*LF power*), ratio of LF power to HF power (*LF/HF*), power of the very low frequency band between 0.0033–0.04 Hz (*VLF power*), power of HR oscillations throughout the day (*total power)*
Non-linear Domain: poincaré plot standard deviation perpendicular to the line of identity (*SD1*), poincaré plot standard deviation along the line of identity (*SD2*), fractal correlation coefficients alpha and beta (*alpha* and *beta*, respectively), and multi-slope entropy area under the curve (*MSE 1–20*)

Demographic information, VNS settings, electrocardiogram (ECG) methodology, and applied statistics were also abstracted from each article. Article quality was assessed using criteria published by Rutka et al. (Rutka, 2016) (see Table 1*)*.

3. Results

3.1. Literature search

The final search across all databases retrieved a total of 182 unique studies. Based on the inclusion criteria detailed in section 2.1, 28 studies were included in this review. Backward citation chaining identified one additional article, resulting in a total of 29 studies. Fig. 1 outlines this article selection process in detail.

Table 1
Quality Assessment Criteria.

Evidence Level	Description
I	Randomized control trial (RCT), OR meta-analysis of randomized trials with homogenous results
II	Prospective therapeutic comparative studies, OR meta-analysis of Level II studies or Level I studies with inconsistent results
III	Retrospective cohort study, OR case-control study OR meta-analysis of Level III studies
IV	Case series
V	Case report, OR expert opinion, OR personal observation

Criteria to categorize research articles based on study methods and the corresponding quality of evidence. Obtained from the original editorial published by Rutka et al in 2016 for the Journal of Neurosurgery (Rutka, 2016).

Of these 29 articles, 20 had category II levels of evidence; three retrospective patient analyses which fell under category III; four category IV case series; and two category V case reports (*see* Table 2*A)*. Of the six category III and IV reports, four investigated HRV and VNS implant specifically in pediatric patients (Gutiérrez-Maldonado et al., 2018, Koenig et al., 2008, Yang et al., 2020, Zaaimi et al., 2007). There were no articles containing category I levels of evidence.

3.2. Patient populations

The average sample size among studies was 21 ± 20 patients (*avg ± SD)*, with a range of 1–64 patients. Fourteen studies involved adult patients, nine had pediatric patients, while the other six drew from a mixture of both adult and pediatric populations (Table 2*B)*. The median number of male subjects was 7 (range 1–42) and female subjects was 5 (range 1–22) per study (Table 2*B)*.

3.3. Data collection specifics

In all patients VNS settings were optimized for seizure control prior to the onset of the study, and thus VNS settings were too widely variable to allow for any pooled analyses.

ECGs were obtained in the context of different activity conditions: in an epilepsy monitoring unit (EMU), at rest, or during normal daily activity. Only two studies (Frei and Osorio, 2001, Jansen et al., 2011) altered patient ASMs in the EMU and during ECG recording, whereas all other studies allowed patients to remain on their typical ASM regiment. The specific ASM patients were on prior to VNS were not mentioned in any of the studies included in this review.

Two of the retrieved studies did not provide any information on ECG activity conditions employed in their study (Galli et al., 2003, Jansen et al., 2011). Most HRV data was obtained from ECGs recorded over a 12–24 hour period, however four studies used collection times of 10-minutes or less (Table 2*A)*. It is generally accepted that, with the exception of HF/RMSDD/SDSD, most HRV parameters cannot be accurately estimated from shorter (i.e., 5–10 minutes) ECG segments (McNames and Aboy, 2006).

ECG sampling frequency dictates which HRV parameters can be drawn from a strip. A sampling frequency of 250 Hz is the lowest threshold to analyze frequency domain parameters (Kwon et al., 2018). Any lower frequency threshold restricts data to time domain parameters and those data compatible with Poincaré plots; a frequency greater than 500 Hz decreases the signal-to-noise ratio (Kwon et al., 2018). Ten of the studies included in this report did not report their ECG sampling frequency, ten studies reported a sampling frequency between 240–300 Hz, and eight used 500 Hz (table 2*A)*. Thus, fewer than 18 of 29 studies used a sampling frequency sufficient to provide analyses of frequency domain parameters. More detailed information on study characteristics can be found in Table 2*A*.

In regards to non-linear parameters, only 9 of the 26 studies investigated the effects of VNS on non-linear HRV parameters (ie SD1/2, alpha and beta coefficients, MSE1-20). The "VNS on vs off" was the only methodologic category that did not include any studies investigating non-linear parameters. However even within the other categories that did include non-linear analysis, these studies often looked into different parameters, making comparisons between studies not possible in many cases (see Table 3*A–E)*.

3.4. HRV results

Twenty-nine studies were retrieved through a comprehensive literature search using PubMed, Web of Science, EMBASE, and Cochrane Library. Overall, 15 papers fell into the post- vs pre-

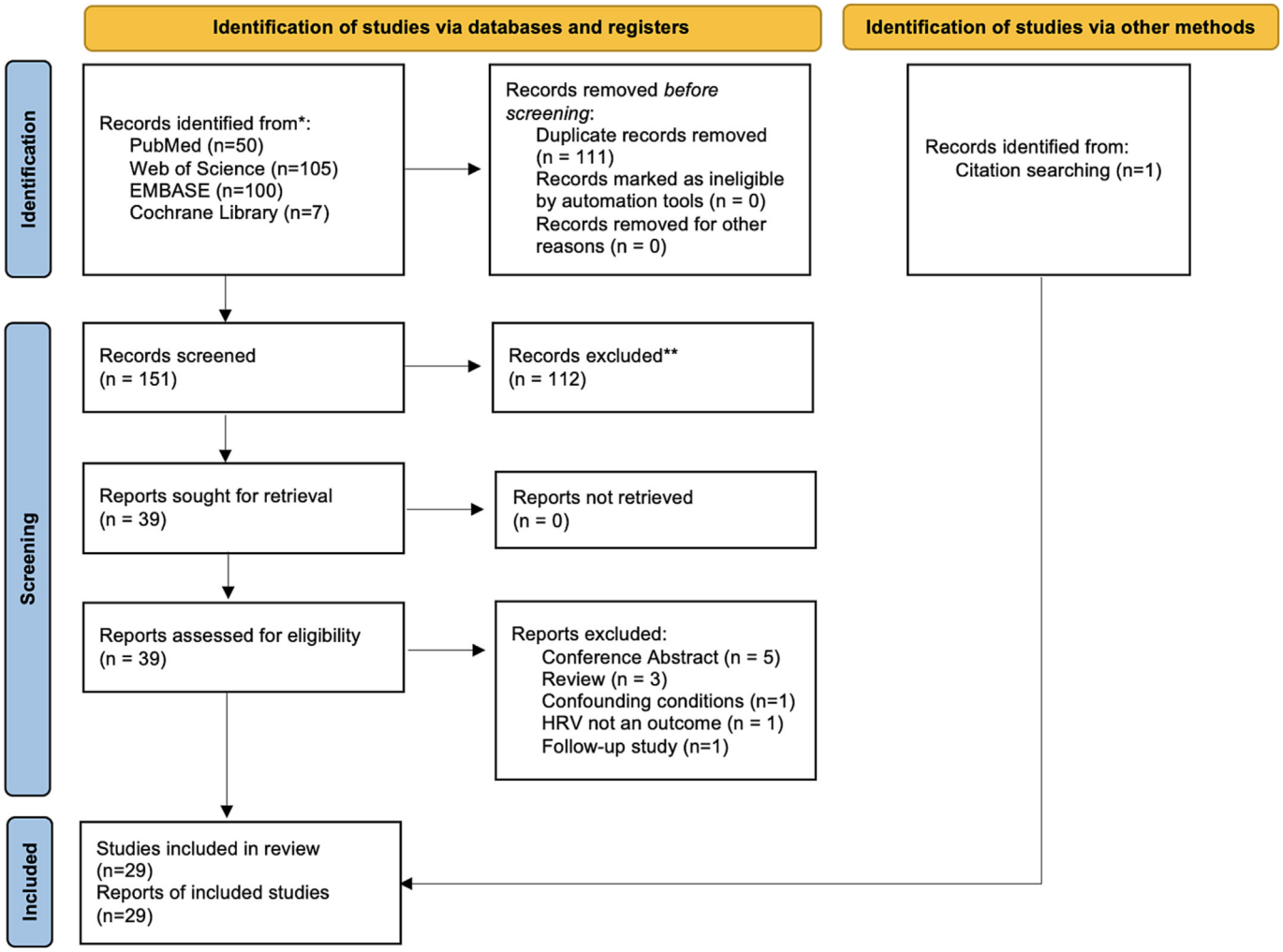

Fig. 1. PRISMA Flow Diagram. PRISMA flow diagram (Page et al., 2021a, Page et al., 2021b) of our literature search as of January 14, 2024. The arrows indicate the step-wise procedural flow of finding studies that met this study's inclusion criteria.

implant category, 8 in pre-implant vs control, 5 in post-implant vs control, 11 in VNS-on vs VNS-off, and 7 in the VNS responders vs nonresponders category. The main highlights from each category are included below, however for a more detailed depiction of the HRV findings in each category please see Table 3. Studies were divided into one of the follow categories based on methodologic approach:

1. ***Post- vs Pre-VNS implant***: HRV outcomes were compared before and after VNS implantation.
2. ***Pre-VNS Implant vs Control***: HRV outcomes were compared between matched controls and patients prior to VNS implantation.
3. ***Post-VNS Implant vs Control***: HRV outcomes were compared between matched controls and patients after VNS implantation.
4. ***VNS-on vs VNS-off***: HRV outcomes were compared between periods of VNS activity and inactivity in the same study subject.
5. ***VNS responders vs VNS non-responders***: HRV outcomes were compared between patients who experienced a ≥50 % reduction in seizure frequency (RSF) after VNS device implantation ("VNS responders") and patients who did not experience a ≥50 % RSF ("VNS-nonresponders").

The reader is invited to refer to Table 3 to see how many studies of a given design commented on a given HRV parameter.

3.4.1. Post- vs Pre- VNS implant

There were no significant differences seen in time domain parameters in post-VNS DRE patients compared to baseline. HF power was found to significantly changed up to one year post VNS-implant, however the directionality of this change conflicted between studies likely due to population size and study parameters (Galli et al., 2003, Hirfanoglu et al., 2018, Jansen et al., 2011, Kamath et al., 1992). LF power, a theorized marker for sympathetic activity, was elevated in DRE patients up to one year post-implant (Hirfanoglu et al., 2018, Kamath et al., 1992). In contrast to the clear ongoing therapeutic effects of VNS, changes in HF and LF power returned to baseline (regardless of magnitude and directionality) after one year post-implant (Garamendi et al., 2017, Hirfanoglu et al., 2018).

3.4.2. Pre-Implant vs control

Compared to healthy controls pre-implant DRE patients had significantly decreased time domain parameter measurements (Fang et al., 2021, Hirfanoglu et al., 2018, Liu et al., 2017, Liu et al., 2018a, Liu et al., 2018b) regardless of sleep-wake cycle, which supports existing evidence that DRE patient have depressed HRV (Shaffer and Ginsberg, 2017).

In terms of frequency domain parameters, HF/LF/total power were all consistently decreased in pre-implant DRE patients compared to health controls (Fang et al., 2021, Hirfanoglu et al.,

Table 2
Methodologic Characteristics.

2A) Study population and methodologic characteristics, including the number of study subjects, subject sex, age demographics of the study (ie pediatric vs adult vs combination of adult/pediatric VNS patients) ECG condition/duration/sampling rate, and level of evidence for each study (Rutka, 2016). *Abbreviations: ECG = electrocardiogram; EMU = epilepsy monitoring unit; F = female; Hr = hours; Hz = hertz; Min = minutes; n/a = not applicable; Sampling Rate = percentage (number/category total); M = male.*

	Subjects	Males/ Female	Age Demographic	ECG Conditions	ECG Duration	ECG Sampling Frequency	Level of Evidence
(Barone et al., 2007)	8	2 M/6F	Adult	Ambulatory	24 h	*n/a*	II
(Cadeddu et al., 2010)	10	6 M/4F	Adult and Pediatric	EMU	24 h	*n/a*	II
(Constantinescu et al., 2019)	5	1 M/4F	Adult	EMU	5 min	*n/a*	IV
(Constantinescu et al., 2020)	5	1 M/4F	Adult	EMU	20 min	*n/a*	IV
(Fang et al., 2021)	59	40 M/19F	Adult and Pediatric	Ambulatory	24 h	500 Hz	II
(Frei and Osorio, 2001)	5	4 M/1F	Adult	EMU	24 h	240 Hz	III
(Galli et al., 2003)	7	4 M/3F	Adult	*n/a*	24 h	250 Hz	II
(Garamendi et al., 2017)	15	13 M/2F	Adult	EMU	10 min	*n/a*	II
(Gutiérrez-Maldonado et al., 2018)	2	0 M/2F	Pediatric	EMU	n/a	500 Hz	V
(Hirfanoglu et al., 2018)	20	11 M/9F	Pediatric	EMU	24 h	*n/a*	II
(Hödl et al., 2020)	30	16 M/14F	Adult	EMU	48 h	256 Hz	II
(Hödl et al., 2021a)	26	13 M/13F	Adult	EMU	70 min	256 Hz	III
(Hödl et al., 2021b)	7	3 M/4F	Adult	EMU	80 min	256 Hz	III
(Jansen et al., 2011)	17	13 M/4F	Pediatric	*n/a*	24 h	*n/a*	II
(Kamath et al., 1992)	8	6 M/2F	Adult	EMU	45 min	500 Hz	II
(Koenig et al., 2008)	1	0 M/1F	Pediatric	EMU	*n/a*	*n/a*	V
(Liu et al., 2017)	64	42 M/22F	Adult and Pediatric	Ambulatory	24 h	500 Hz	II
(Liu, et al., 2018a)	64	42 M/22F	Adult and Pediatric	Ambulatory	24 h	500 Hz	II
(Liu, et al., 2018b)	63	42 M/21F	Adult and Pediatric	EMU	24 h	*500 Hz*	II
(Milosevic et al., 2011)	34	13 M/4F	Pediatric	EMU	50 min	250 Hz	II
(Pruvost et al., 2006)	10	4 M/6F	Pediatric	EMU	12 h	256 Hz	II
(Ronkainen et al., 2006)	42	24 M/18F	Adult	Ambulatory	24 h	*n/a*	II
(Schomer et al., 2014)	9	6 M/3F	Adult	Ambulatory	24 h	*n/a*	II
(Setty et al., 1998)	12	8 M/2F	Adult and Pediatric	EMU	17 min	500 Hz	II
(Stemper et al., 2008)	21	10 M/11F	Adult	EMU	12 h	300 Hz	II
(Verrier et al., 2016)	28	9 M/19F	Adult	EMU	24 h	*n/a*	II
(Yang et al., 2020)	2	1 M/1F	Pediatric	Ambulatory	24 h	500 Hz	IV
(Zaaimi et al., 2007)	10	4 M/6F	Pediatric	EMU	*n/a*	256 Hz	IV
(Zaaimi et al., 2009)	10	4 M/6F	Pediatric	EMU	12 h	256 Hz	II

2B) Data from all retrieved studies were divided into five categories based on study approach: post-vs pre-implant, pre-implant vs control, post-implant vs control, VNS-on vs off, and VNS responders vs nonresponders. The results of each row are reported in the following formats: Subjects = median(range); Sex = mean±standard deviation; Levels of Evidence, ECG Conditions, ECG Duration, and Sampling Rate= number of applicable studies in that column category (n)/total studies in that column category. *Abbreviations: Avg = average; ECG = electrocardiogram; EMU = epilepsy monitoring unit; Hr = hours; Hz = hertz; Mins = minutes; SD = standard deviation; VNS = vagal nerve stimulator.*

	Post- vs Pre-Implant	Pre-Implant vs Control	Post-Implant vs Control	VNS-on vs off	Responders vs Non-Responders
Subjects *[median(range)]*	17 (2–64)	51 (2–64)	34 (17–64)	10 (1–34)	59 (7–64)
Sex *[avg+SD]*					
male	18±17	27±17	21±13	6±5	30±16
female	11±9	15±9	12±9	4±3	17±7
Level of Evidence *(n/total)*					
II	11/15	7/8	5/5	7/11	6/7
III	1/15	0/8	0/5	1/11	1/7
IV	3/15	0/8	0/5	1/11	0/7
V	0/15	1/8	0/5	2/11	0/7
ECG Conditions *(n/total)*					
EMU	5/15	2/8	2/5	10/11	2/7
freely ambulatory	9/15	5/8	2/5	1/11	5/7
not provided	1/15	1/8	1/5	0/11	0/7
ECG duration *(n/total)*					
≥24 h	11/15	7/8	4/5	2/11	6/7
overnight	0/15	0/8	0/5	3/11	0/7
≤80 mins	4/15	0/8	1/5	3/11	1/7
not provided	0/15	1/8	0/5	3/11	0/7
Sampling rate *(n/total)*					
500 Hz	4/15	5/8	1/5	1/11	4/7
≤300 Hz	2/15	0/8	1/5	5/11	2/7
not provided	9/15	3/8	3/5	5/11	1/7

Table 3
HRV results based on category. Heart rate variability (HRV) results from each study in all five categories: post- vs pre-implant, pre-implant vs control, post-implant vs control, VNS-on vs off, and responders vs non-responders. HRV measurements are grouped based on parameter: Time Domain, Frequency Domain, and Non-Linear Domain parameters. HRV results from each study are represented by qualitative arrows, indicating overall trends since a unified analysis was not statistically possible. HF and LF can be quantified by three different units – ms2, nu (*), Hz (**) – and are labeled by asterisks accordingly in the tables below. If an HRV result was not recorded by a study, the corresponding grid on the table was left blank. Case reports (category IV/V) are denoted by "^" next to the author name. HRV Parameter Definitions by Domain Type with Abbreviations in Parentheses: ***Time Domain***: heart rate (HR), normal-to-normal RR interval (NN), standard deviation of NN (SDNN), the number of adjacent NN intervals that differ from each other for more than 50 ms divided by the total number of RR intervals in 50sec (pNN50), standard deviation of the average NN interval for each 5 min segment of a 24hr ECG recording (SDANN), average of the SDNN (SDNN Index), root mean squared of the differences in successive RR intervals (RMSDD), relative standard deviation of differenced in successive RR intervals (SDSD). ***Frequency Domain***: power of the high frequency band between 0.15–0.4 Hz (HF power), power of the low frequency band between 0.04–0.15 Hz (LF power), ratio of LF power to HF power (LF/HF), power of the very low frequency band between 0.0033–0.04 Hz (VLF power), power of HR oscillations throughout the day (total power). ***Non-linear Domain***: poincaré plot standard deviation perpendicular to the line of identity (SD1), poincaré plot standard deviation along the line of identity (SD2), fractal correlation coefficients alpha and beta (alpha and beta, respectively), and multi-slope entropy area under the curve (MSE 1–20).

***3A)* Post- vs Pre-Implant DRE Patients.** *Abbreviations and Symbols: BP = blood pressure; DRE = drug resistant epilepsy; mo = month; NS = no significant change; VNS = vagal nerve stimulator; ↑ = increase; ↓ = decrease;^= case report; * = nu; **=hertz.*

	Time Domain Parameters								**Frequency Domain Parameters**					**Non-Linear Domain Parameters**							
	HR	**NN**	**pNN50**	**SDNN**	**SDANN**	**SDNN Index**	**RMSDD**	**SDSD**	**HF Power *(ms2, *nu, **Hz)***	**LF Power *(ms2, *nu, **Hz)***	**VLF Power**	**Total Power**	**LF/ HF**	**SD1**	**SD2**	**Alpha**	**Beta**	**MSESlope 5**	**MSE Area 1–5**	**MSEArea 6–15**	**MSEArea 6–20**
(Kamath et al., 1992)																					
high stimulation	NS								↑**	NS**			↓								
low stimulation	NS								NS**	↑**			NS								
(Galli et al., 2003)																					
daytime (1mo)			NS		NS		NS		NS	NS	NS		NS								
daytime (2mo)			NS		NS		NS		NS	NS	NS		NS								
nighttime (1mo)			NS		NS		NS		NS	NS	NS		NS								
nighttime (2mo)			NS		NS		NS		↓	NS	NS		NS								
(Ronkainen et al., 2006)		NS		NS					NS		NS			NS	NS	NS	NS				
(Barone et al., 2007)		NS	NS	NS		NS	NS		NS	NS	NS		NS								
(Cadeddu et al., 2010)																					
daytime			NS	NS	NS	NS	NS	NS	NS	NS											
nighttime			↑	NS	NS	NS	↑	↑	NS	NS											
daytime BP zenith			NS	NS	NS	NS	NS	NS	↑	↓			↓								
(Jansen et al., 2011)																					
Stage-2 Sleep	NS	NS	NS	NS	NS		NS		↓*	↑*			NS								
Slow Wave Sleep	NS	NS	NS	NS	NS		NS		↓*	↑*			NS								
(Schomer et al., 2014)	NS								NS	↓			↓								
(Garamendi et al., 2017)																					
pre vs 6mo post									NS	NS			NS								
pre vs 12mo post									NS	NS			NS								
(Verrier et al., 2016)	NS								NS	NS			NS								
(Hirfanoglu et al., 2018)																					
combined post 6mo	↓		↑	↑	↑	↑	↑		↑	↑		↑	NS								
daytime post 6mo			↑	↑			↑		↑	↑		↑	NS								
nighttime post 6mo			NS	NS			↑		↑	↑		↑	NS								
combined post 12mo	NS		NS	↑	↑	NS	NS		NS	NS		↑	NS								
daytime post 12mo			NS	↑			NS		NS	↑		↑	NS								
nighttime post 12mo			NS	NS			NS		NS	NS		NS	NS								
(Liu et al., 2018a)																					
all DRE patients		NS	NS	NS			NS		NS	NS	NS		NS			NS	↓	NS		NS	
only VNS responders		NS	NS	NS			NS		NS	NS	NS	NS	NS					NS		↑	↓	NS
^(Constantinescu et al., 2019)																					
Valsalva							2↑														

Table 3 (*continued*)

***3A)* Post- vs Pre-Implant DRE Patients.** *Abbreviations and Symbols: BP = blood pressure; DRE = drug resistant epilepsy; mo = month; NS = no significant change; VNS = vagal nerve stimulator; ↑ = increase; ↓ = decrease;^= case report; * = nu; **=hertz.*

	Time Domain Parameters								Frequency Domain Parameters					Non-Linear Domain Parameters							
	HR	**NN**	**pNN50**	**SDNN**	**SDANN**	**SDNN Index**	**RMSDD**	**SDSD**	**HF Power *(ms2, *nu, **Hz)***	**LF Power *(ms2, *nu, **Hz)***	**VLF Power**	**Total Power**	**LF/ HF**	**SD1**	**SD2**	**Alpha**	**Beta**	**MSESlope 5**	**MSE Area 1–5**	**MSEArea 6–15**	**MSEArea 6–20**
deep breathing							2↓ 2↑ 2↓														
hand grip							2↑ 2↓		↓												
resting							2↑ 2↓														
standing							3↑ 1↓		NS												
^(Constantinescu et al., 2020)																					
Valsalva				↑			↑						↓	1↑ 4↓							
deep breathing				↑			↑		↑				↓	2↑ 3↓							
hand grip				↓					↓				↑	2↑ 3↓							
resting														1↑ 3↓ 1 NS							
standing				↓					↓				↑	2↑ 3↓							
(Hödl et al., 2020)				NS			NS		NS	NS											
^(Yang et al., 2020)	4↑ 6↓			6↑ 4↓			6↑ 3↓ 1 NS		6↑ 4↓	4 6↓↑		6↑ 4↓	4↑ 6↓	6↑ 3↓ 1 NS	6↑ 4↓						

***3B)* Pre-implant DRE vs Healthy Control.** *Abbreviations and Symbols: mo = month; NS = no significant change;↑ = increase; ↓ = decrease;^= case report; * = nu; **=hertz.*

	Time Domain Parameters								Frequency Domain Parameters					Non-Linear Domain Parameters							
	HR	**NN**	**pNN50**	**SDNN**	**SDANN**	**SDNN Index**	**RMSDD**	**SDSD**	**HF Power *(ms2, *nu, **Hz)***	**LF Power *(ms2, *nu, **Hz)***	**VLF Power**	**Total Power**	**LF/ HF**	**SD1**	**SD2**	**Alpha**	**Beta**	**MSESlope 5**	**MSE Area 1–5**	**MSEArea 6–15**	**MSEArea 6–20**
(Ronkainen et al., 2006)		↓		↓					↓	↓	↓			↓	↓	NS	NS				
(Jansen et al., 2011)																					
Stage-2 Sleep	↑	NS	NS	NS	NS		NS		↑*	↓*			NS								
Slow Wave Sleep	↑	NS	NS	NS	NS		NS		↓*	↑*			↑								
(Liu et al., 2017)		NS	↓	↓			↓		↓	↓	↑	↓	NS	↓	↓			□	□	□	□
^(Gutiérrez-Maldonado et al., 2018)		↓		↓			↑		↑	↓						↓					
(Hirfanoglu et al., 2018)																					
combined	↑		↓	↓	↓	↓	↓		↓	↓		↓	NS								
daytime			↓	↓			↓		↓	↓		↓	NS								
nighttime			↓	↓			↓		↓	↓		↓	NS								
(Liu et al., 2018b)		↓	↓	↓			↓		↓	↓	↓	↓	NS					↓	↓	↓	↓
(Liu et al., 2018a)		↓	↓	↓			↓		↓	↓	↓	↓	NS					↓	↓	↓	↓
(Fang et al., 2021)		↓		↓	↓		↓	↓	↓	↓	↓			↓	↓						

***3C)* Post-Implant DRE vs Healthy Control.** *Abbreviations and Symbols: mo = month; NS = no significant change; ↑ = increase; ↓ = decrease; * = nu; **=hertz.*

	Time Domain Parameters								Frequency Domain Parameters					Non-Linear Domain Parameters							
	HR	**NN**	**pNN50**	**SDNN**	**SDANN**	**SDNN Index**	**RMSDD**	**SDSD**	**HF Power *(ms2, *nu, **Hz)***	**LF Power *(ms2, *nu, **Hz)***	**VLF Power**	**Total Power**	**LF/HF**	**SD1**	**SD2**	**Alpha**	**Beta**	**MSESlope 5**	**MSE Area 1–5**	**MSEArea 6–15**	**MSEArea 6–20**
(Ronkainen et al., 2006)	□	↓	□	↓	□	□	□		↓	↓	↓	□		↓	↓	NS	NS				
(Jansen et al., 2011)	□												□								
Stage-2 Sleep	NS	NS	NS	NS	NS		NS		↑*	↓*			NS								
Slow Wave Sleep	NS	NS	NS	NS	NS		NS		↓*	↑*			↑								
(Milosevic et al., 2011)																					
Stage-2 Sleep	↑	↓	NS	NS	NS		NS		↓*	↑*			NS			NS					
Slow Wave Sleep	↑	↓	NS	NS	NS		NS		↓*	↑*			↑			NS					
(Hirfanoglu et al., 2018)	□			□					□	□		□									
control vs 6mo	↑	□	↓	↓	↓	↓	↓		↓	↓	□	↓	NS	□	□						
daytime control v 6mo		□	↓	↓			↓		↓	↓	□	↓	↓					□	□	□	□
nighttime control v 6mo		□	↓	↓	□		↓	□	↓	↓	□	↓	NS	□	□						
control vs 12mo	↑	□	↓	↓	↓	↓	↓		↓	↓		↓	NS			□					
daytime control vs 12mo			↓	↓			↓		↓	↓		↓	NS								
nighttime control vs 12mo	□		↓	↓			↓		↓	↓		↓	NS								
(Liu et al., 2018b)	□	NS	↓	↓			↓		↓	↓	↓	↓	NS					↓	NS	↓	↓

***3D)* VNS-on vs off.** *Abbreviations and Symbols: NS = no significant change; ↑ = increase; ↓ = decrease;^= case report; * = nu; **=hertz.*

	Time Domain Parameters									Frequency Domain Parameters					Non-Linear Domain Parameters							
	HR	**RSA**	**NN**	**pNN50**	**SDNN**	**SDANN**	**SDNN Index**	**RMSDD**	**SDSD**	**HF Power *(ms2, *nu, **Hz)***	**LF Power *(ms2, *nu, **Hz)***	**VLF Power**	**Total Power**	**LF/ HF**	**SD1**	**SD2**	**Alpha**	**Beta**	**MSESlope 5**	**MSE Area 1–5**	**MSEArea 6–15**	**MSEArea 6–20**
(Setty et al., 1998)			NS	NS				NS		NS	NS	NS										
(Frei and Osorio, 2001)	↓	□			2↑ 2↓					↓												
(Pruvost et al., 2006)			↓							↑	↑			NS								
^(Zaaimi et al., 2007)	5↑ 1↓ 4NS	□																				
^(Koenig et al., 2008)			↓	↓				↓		↓	↓	↓										
(Stemper et al., 2008)			NS							↑	↑											
(Zaaimi et al., 2009)		↓																				
(Milosevic et al., 2011)			NS							↓	↑			↑								
(Schomer et al., 2014)										NS	NS			NS								
(Garamendi et al., 2017)										NS	NS			NS								
^(Gutiérrez-Maldonado et al., 2018)	↓	□	↑	↑	↑			↑		↑	↑						□					

***3E)* VNS Responder vs Non-Responder.** *Abbreviations and Symbols: NS = no significant change; Responder50 = ≥50% seizure reduction after VNS; Nonresponder50 = ≤50% seizure reduction after VNS; ↑ = increase; ↓ = decrease; * = nu; **=hertz.*

	Time Domain Parameters								Frequency Domain Parameters					Non-Linear Domain Parameters							
	HR	**NN**	**pNN50**	**SDNN**	**SDANN**	**SDNN Index**	**RMSDD**	**SDSD**	**HF Power *(ms2, *nu, **Hz)***	**LF Power *(ms2, *nu, **Hz)***	**VLF Power**	**Total Power**	**LF/ HF**	**SD1**	**SD2**	**Alpha**	**Beta**	**MSESlope 5**	**MSE Area 1–5**	**MSEArea 6–15**	**MSEArea 6–20**
Pre-implant																					
(Ronkainen et al., 2006)		NS		NS					NS	NS	NS			↑	NS	NS	NS				
(Liu et al., 2017)		□	□		□		□	□	□	□	□			□							
responders vs nonresponders		NS	NS	NS	□		NS	□	NS	NS	NS	NS	NS	NS	NS						
nonresponders vs controls		↓	↓	↓	□		↓	□	↓	↓	↓	↓	↓	↓	↓						
(Liu et al., 2018b)																					
combined		NS	NS	NS			NS		NS	NS	NS	NS	NS					NS	↑	↑	↑
responders50 v nonresponders50		NS		NS	□				↑	↑	↑	↑	↓					NS	NS	NS	NS
(Liu et al., 2018a)		□	□	□	□		□	□	□	□	□	□	□	□							
responders vs nonresponders		NS	NS	NS	□		NS	□	NS	NS	NS	NS	NS	□							
nonresponders vs controls		NS	↓	↓	□		↓	□	↓	↓	↓	↓	NS	□							
(Hödl et al., 2020)									↓												
(Fang et al., 2021)																					
sleep		↑	↑		□		↑	↑	↑	↑	↑			↑	↑						
awake		↑	↑	NS	□		↑	↑	↑	↑	↑			↑	NS						
(Hödl et al., 2021b)		□	□		□	NS	□	□	□	□	□			□							
Post-implant																					
(Ronkainen et al., 2006)		↑	□				□		□					□							
(Liu et al., 2018a)																					
responders vs controls		NS	NS	NS			NS		NS	NS	NS	NS	NS					↓	NS	NS	NS
nonresponders vs controls		NS	↓	↓			↓		↓	↓	↓	↓	NS					NS	NS	↓	↓
(Hödl et al., 2020)									↓												

2018, Liu et al., 2017, Liu et al., 2018a, Liu et al., 2018b, Ronkainen et al., 2006), which has been associated with an increased risk for SUDEP (Evangelista et al., 2023). Respiratory-associated HRV parameters (RSA) in both adults and children tended towards less variability during deeper stages of sleep (Sowho et al., 2014), and these changes appear to be more pronounced in pediatric DRE patients compared to healthy age-matched controls (Jansen et al., 2011).

Multi-Slope Entropy (MSE) (Liu et al., 2018a), a non-linear approach to measure entropy, and SD1/SD2 (Fang et al., 2021, Liu et al., 2017, Ronkainen et al., 2006) were also found to be decreased in DRE patients compared to healthy controls, however the clinical application of these findings is still unclear (Liu and Wessel, personal correspondence 2022).

3.4.3. Post-Implant vs control

VNS did not alter the overall depression in time domain parameters (Hirfanoglu et al., 2018, Liu et al., 2018a, Ronkainen et al., 2006) or frequency domain parameters (Hirfanoglu et al., 2018, Liu et al., 2018a, Ronkainen et al., 2006) seen in post-implant DRE patients compared to healthy controls. One study noted that the LF/HF power ratio in post-implant pediatric patients was significant decreased shortly after VNS implant (*six months*) but became insignificant after time (*12 months*) without any associated changes in seizure burden (Hirfanoglu et al., 2018).

3.4.4. VNS-on vs VNS-off

Heart rate was the only time domain parameter that was found to be significantly decreased during periods of VNS stimulation (Frei and Osorio, 2001, Gutiérrez-Maldonado et al., 2018). Only pediatrics patients were found to have a decrease in RSA strictly within the limits of VNS-on periods during sleep (Zaaimi et al., 2009).

The way studies defined periods of VNS stimulation versus inactivity affected the outcome of frequency domain parameter results. Milosevic et al. was the only study that did not include details on VNS settings (Milosevic et al., 2011); the rest employed settings either based on each individuals patient's ideal therapeutic VNS settings (Frei and Osorio, 2001, Garamendi et al., 2017, Schomer et al., 2014, Zaaimi et al., 2007, 2009) or had VNS settings standardized across all patients (Gutiérrez-Maldonado et al., 2018, Koenig et al., 2008, Pruvost et al., 2006, Setty et al., 1998, Stemper et al., 2008). Of the five studies that standardized VNS settings, all had the frequency set to 20–30 Hz and had the VNS turned on ("VNS-on" period) for 30–60 seconds. One study had the time between electrical pulses set as low as 250 ms (Gutiérrez-Maldonado et al., 2018), two at 500 ms (Koenig et al., 2008, Pruvost et al., 2006), and the longest at 750 ms (Setty et al., 1998). The studies tended to vary in how long the VNS was off ("VNS-off" periods) in between VNS-on periods. VNS-off periods ranged from 108 seconds (Koenig et al., 2008) to 5 minutes (Setty et al., 1998, Stemper et al., 2008), with one study having VNS-off periods varying from 1-3 minutes (Pruvost et al., 2006).

Studies that standardized VNS settings across all subjects (30 Hz, 500 ms pulse width, 60 seconds VNS-on period) found HF and LF power to be increased during VNS-on periods 12–24 months after VNS implant (Pruvost et al., 2006, Stemper et al., 2008). However, studies that did not standardize VNS settings across patients found HF power to be decreased 12–24 months post-implant (Frei and Osorio, 2001, Milosevic et al., 2011).

3.4.5. VNS responders vs Non-Responders

After VNS implant, VNS responders had a significantly elevated NN compared to VNS non-responders (Ronkainen et al., 2006); this difference was not seen prior to VNS implant (Liu et al., 2017, Liu et al., 2018a, Liu et al., 2018b, Ronkainen et al., 2006).

No significant differences were seen in HF and LF power measurements between responders and non-responders in ambulatory ECG settings (Liu et al., 2017, Liu et al., 2018a, Liu et al., 2018b, Ronkainen et al., 2006), however when recorded in the EMU HF power, and thus HF band variability, was found to be increased in both pre- and post-implant VNS-responders only (Hödl et al., 2020). Also, LF and VLF power were found to be elevated in pre-implant VNS-responders who had greater than 50 % RSF after VNS implant (Liu et al., 2018b).

In terms of non-linear domain parameters, SD1 was consistently found to be increased in responders compared to non-responders (Fang et al., 2021, Ronkainen et al., 2006). VNS-responders presented with an increase in SD2 only while asleep (Fang et al., 2021), whereas during the day no significant difference in SD2 was seen between responders and non-responders (Fang et al., 2021, Ronkainen et al., 2006).

4. Discussion

The purpose of this review was to provide a wide look at how implantable VNS devices alter HRV in patients with DRE. There was significant heterogeneity between aims, methods, and data analysis in the studies we retrieved, and these differences made rigorous statistical meta-analysis difficult. Interestingly, we found that *any* HRV parameters that changed early after VNS implantation (particularly frequency domain parameters) tended to return to baseline within 12 months post-implant. We also note that the overall HRV depression seen in DRE patients prior to VNS did not change after implantation, despite increasing vagal stimulation as parameters were adjusted for seizure control (rather than with the primary endpoint of altering HRV).

4.1. HRV Post-Implant

It is generally accepted that HRV is decreased in DRE patients compared to their healthy counterparts (Baysal-Kirac et al., 2017), and in our review this was also appreciated across all domain parameters in the pre-implant vs control category. Surprisingly, this overall decrease in HRV compared to healthy controls persisted in DRE patients even after VNS implant (Hirfanoglu et al., 2018, Jansen et al., 2011, Liu et al., 2018b, Milosevic et al., 2011, Ronkainen et al., 2006), despite the anticipated overall increase in parasympathetic activity. This aligns with the notion that a left-sided VNS implant does not exert a profound influence on cardiac autonomics (Capilupi et al., 2020) and that improvements in HRV status are not a necessary condition for therapeutic seizure effects of VNS. The effects of VNS on HRV seem to disappear within a year post-implant while the reduction in seizure burden persists for far longer, suggesting that alterations in HRV are not an important biomarker for VNS efficacy.

4.2. SUDEP

After implantation VNS stimulates the peripheral vagus nerve in a pulsatile fashion which instead of permanently altering baseline HRV activity, as established by our review, it may instead provide therapeutic benefit via acute modulation of autonomic balance in the pre- and post-ictal phase. As a whole, pediatric DRE patients have been found to have a more robust decrease in RSA during sleep compared to healthy age-matched counterparts (Jansen et al., 2011), and during periods of VNS stimulation (ie VNS "on" period) they express a more robust improvement in RSA than other groups (Zaaimi et al., 2009). Improvements in HRV (ie increasing variability) has been associated with a reduced risk of SUDEP in human patients with epilepsy (Sivathamboo et al., 2021), and the

therapeutic effects of VNS may have more to do with that immediate control of systemic parasympathetic-sympathetic balance during the post-ictal phase rather than altering long-term/baseline HRV. For example, in this review we found that frequency domain parameters that were initially increased post-implant tended to return to baseline within 12 months, which was appreciated in both the post- vs pre-implant and post-implant vs control analyses. In other words, although the VNS does modulate certain linear parameters, these effects do not vary with the therapeutic effects on seizure frequency.

However, there is still a strong association between VNS therapy and a decreased risk of SUDEP, with patients who experience SUDEP being less likely to have undergone VNS implant than non-SUDEP counterparts (Evangelista et al., 2023). A 2023 review by Evangelista et al found that most patients with SUDEP tended to experience focal temporal lobe epilepsy (TLE) (Evangelista et al., 2023), a region of the brain that, along with the insular cortex, plays a large role in the cortical component of central autonomic signaling (Cechetto, 2014). Likewise, autonomic dysfunction secondary to aberrant synchronization of these cortical regions is closely associated with an immediate increase in the risk of SUDEP (Evangelista et al., 2023). The effects of VNS on the synchronization of cortical activity may be more influential in reducing SUDEP risk than promoting peripheral parasympathetic predominance. VNS afferently stimulates nerves projecting to the nucleus tractus solitarius in the medulla, which then relays that signal to various subcortical and cortical brain regions (Bowles et al., 2022). It has been shown that VNS induces cortical stimulation largely through dose-dependent activation of cholinergic and noradrenergic modulatory pathways, which historically have been shown to play a role in regulating states of arousal (Bowles et al., 2022, Collins et al., 2021). During periods of VNS stimulation VNS responders tend to demonstrate global neural *de*synchronization, which likely helps mitigate epileptic activity by preventing the abnormal network synchronization seen with seizures and SUDEP. It is thought that abnormal synchronization is driven by cortical activation of basal forebrain-mediated cholinergic signaling pathway (Workewych et al., 2020).

4.3. Cognition

In humans, the immediate pre-ictal period is accompanied by an elevation in heart rate, LF/HF ratio, and the SD2/SD1 ratio that is not seen during the inter-ictal period (Behbahani et al., 2013). Given that heart rate variability and brain functioning involve the integration of information from a multitude of different homeostatic mechanisms (Francesco et al., 2012), non-linear parameters provide a way to capture nuances in these data that traditional linear analysis cannot (Young and Benton, 2015). For example, outside the field of epilepsy, a study looking at the relationship between HRV parameters and cognition function in healthy individuals found that that non-linear parameters were able to delineate certain sex-differences in heart rate complexity (parasympathetic predominance) that were more robust in females compared to males in regards to cognitive functioning, and that HR complexity (non-linear parameters) served as a predictive marker for cortisol levels in females but not males (Young and Benton, 2015). Previous work has shown sex differences in cardiac parasympathetic activity in female rats compared to males (Du et al., 1994), however the work by Young et al 2015 was the first to show that under healthy conditions non-linear HRV parameters could allow for more nuanced investigation into the mechanism behind changes in autonomic balancing in healthy adults that linear analysis innately miss (Young and Benton, 2015).

4.4. Autonomic balance

It has also been shown that after a seizure, post-ictal cardiac autonomic balance returns to baseline quicker in rats with a VNS in place than those without, *and* that this return to baseline occurs at a faster rate in male compared to female rats (Yaghouby et al., 2020). During the post-ictal state after convulsive seizures in rats, there is a mild but significant decrease in HRV, notably in measures of entropy (a nonlinear parameter), that resolves in during the inter-ictal state (Naritoku et al., 2003). These nonlinear domain changes are associated with an immediate increase in risk of cardiac complications during the post-ictal period; VNS might potentially serve to restore a more healthy autonomic balance in the post-ictal period (Darbin et al., 2002), something that is observed in post-operative deep brain stimulation (DBS) patients with DRE (Lorincz et al., 2023). We encourage future investigations to explore possible sex-differences via non-linear HRV parameters in epilepsy populations as this has yet, to our knowledge, been studied in DRE patients with an implantable VNS.

4.5. Limitations

A significant limitation to our understanding of VNS effects on HRV is the vast heterogeneity of study protocols, ECG conditions, and population demographics across studies. For instance, although 250 Hz is technically sufficient to detect frequency domain parameters, in ambulatory conditions this sampling frequency is likely far too low to detect meaningful changes in such an autonomically stimulating environment (ie compared to the EMU), especially given such conflicting HF and LF power readings based in sampling frequency (Hödl et al., 2020, Kamath et al., 1992, Ronkainen et al., 2006, Setty et al., 1998, Stemper et al., 2008, Yerdelen and Erol, 2013). We also were challenged with HRV data collected from ECGs of vastly different durations, limiting our ability to systematically compare findings between studies. In the field of cardiology, ultrashort (ie <5 min), short (ie 5-10mins), and 24hr ECG recordings are not interchangeable in terms of HRV measurements (Shaffer and Ginsberg, 2017), and these standardizations -- ie based on public access HRV standardization checklists (Catai et al., 2020)) – need to be carried over into the field of epilepsy research as well. Another limitation to this review is that the potential effects of ASMs on post-VNS HRV were not factored into our analysis, although some literature has suggested that certain ASMs could have an impact on HRV (Dono et al., 2022, Hallioglu et al., 2008).

4.6. Conclusion

This review hopefully has highlighted how delicate autonomic signaling is and how slight protocol changes can have significant effects on results. Future explorations of HRV require a rigorous and standardized methodology to understand these signals more clearly. Also, it would be of benefit to more thoroughly delineate HRV patterns after VNS implant within different epilepsy syndromes, as one study noted that focal seizures tended to respond better to VNS than mixed types (Liu et al., 2018a), as well as immediate changes in HRV during the immediate pre-ictal/post-ictal states in DRE patients. We highly encourage any future work on HRV in epilepsy pathophysiology or therapeutic mechanisms to incorporate the use of standardized non-linear analysis, thus allowing for a more nuanced investigation into HRV than the more traditionally obtained using more linear parameters.

In summary, our work has highlighted the methodologic variability amongst papers investigating the effects of VNS on HRV in DRE. Our findings support that of Wu et al. (Wu et al., 2021) that VNS does not cause robust changes in the autonomic functioning

of the heart after implant. However, after reviewing a greater breadth of the literature, we found that VNS does cause a transient increase in frequency domain parameters during the first six months post-implant, and that frequency domain parameters may have pre-operative potential to differentiate DRE patients that will have a more robust response to VNS implant from VNS non-responders. VNS is a valuable therapeutic tool and although changes in HRV do not seem to be the driving force behind the therapeutic benefit of VNS, there is still much to understand about how both HRV and VNS interact with the mechanisms driving DRE.

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Declaration of Interest

None of the authors have any reportable conflicts of interest.

Appendix A. Supplementary material

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