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REVIEW ARTICLE

Heart rate variability modification as a predictive factor of sudden unexpected death in epilepsy: How far are we? A systematic review and meta-analysis

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Abstract

Background: Sudden unexpected death in epilepsy (SUDEP) is a sudden, unexpected death in people with epilepsy, with or without evidence of an epileptic seizure. The pathophysiological mechanism underlying SUDEP appears to be partly associated with an autonomic nervous system (ANS) dysfunction. Heart rate variability (HRV) analysis is a reliable, non-invasive method for detecting fluctuations in the ANS. In this systematic review we analyzed the data available in the literature on changes in HRV parameters in patients with SUDEP.

Methods: We carried out a systematic search of the literature to identify the quantitative variations of HRV in epileptic patients with SUDEP. The following databases were used: Pubmed, Google Scholar, EMBASE, and CrossRef. A pooled analysis was carried out, and the results obtained were compared using mean difference (MD). The review was registered on the PROSPERO platform (CRD42021291586).

Results: Seven articles were included, with a total of 72 SUDEP cases associated with altered HRV parameters. Generally, a reduction of SDNN (standard deviation of the RR intervals) and RMSSD (root mean square differences of successive RR intervals) was reported in most SUDEP patients. According to MD, the SUDEP patients showed no differences in time and frequency domain parameters compared to controls. However, a trend toward increased low frequency and high frequency ratio (LF/HF) was observed in the SUDEP patients.

Conclusions: HRV analysis is a valuable method for assessing cardiovascular risk and cardioautonomic impairment. Although a possible association between HRV variation and SUDEP has been reported, further studies are needed to assess the potential role of HRV modifications as a SUDEP biomarker.

KEYWORDS
biomarker, epilepsy, HRV, prevention, SUDEP

Giacomo Evangelista and Fedele Dono contributed equally to this work.

INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) refers to the death of seemingly healthy people with epilepsy (PwE), with or without the occurrence of a seizure [1]. The incidence of SUDEP in young adults (aged 20–45 years) is 27 times higher than sudden death in the general population [2,3]. Uncontrolled generalized tonic–clonic seizures (GTCS) are the most critical risk factor for SUDEP [4]. Epilepsy onset before 16 years of age and duration of disease longer than 15 years [4] are other well-known SUDEP risk factors [4-6].

Little is known about the possible pathophysiological pathways underpinning SUDEP onset. According to the literature, autonomic nervous systems (ANS) imbalance – leading to central hypoventilation or cardiac dysrhythmia [7-9] – seems to play a pivotal role. Hence, evaluating ANS functioning in PwE should be mandatory, especially in those with a high risk of SUDEP [10,11]. Several non-invasive assessments can be carried out to that aim, including blood pressure and heart rate variation tests during postural changes, Valsalva maneuvre [12], sudomotor functioning testing [13], or heart rate variability (HRV) evaluation [10,11]. The latter is an easy-to-make index of cardiac autonomic control [14]. It can be calculated on the basis of electrocardiogram (ECG) derivations of a standard electroencephalogram (EEG) recording [15]. The HRV represents the change in time intervals between successive heartbeats [16,17]. An increased HRV suggests vagal dominance over sympathetic components, while a decreased HRV reflects a reduced vagal output [14,18].

According to the literature, the decrease in HRV is associated with a higher risk of death for cardiovascular [19,20] and non-cardiovascular causes [21-25]. Recently, HRV has been evaluated in the SUDEP population with inconclusive results. Even though a decreased HRV has been shown to correlate with other SUDEP risk factors [26,27], some reports show that an increased HRV may also be associated with SUDEP [28]. Thus, the possible role of HRV evaluation in SUDEP risk management and prediction has yet to be understood.

This systematic review aims to analyze the available data on HRV parameter changes in patients with SUDEP underlying the possible role of HRV modification as a SUDEP predictive factor.

METHODS

Searching strategy and review organization

The research question was expressed according to the PICOS (Population, Intervention, Comparison and Outcomes) criteria (Table S1). In particular, we compared HRV parameters pooled data between SUDEP and pharmacoresistant epilepsy cohorts. In addition, we collected data regarding demographics, epilepsy and seizure type, epilepsy etiology as well as epilepsy treatment in patients who died of SUDEP.

Results of this systematic review have been reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Two authors (G.E., F.D.) independently searched from the first date available up to January 2022 using the following syntax: ("SUDEP" OR "Sudden unexpected death in epilepsy") AND ("HRV"

TABLE 1 Articles included in the systematic review.

Authors (year)	SUDEP patients	Control patients	HRV analysis (time interval)	HRV analysis parameters	HRV during wake and sleep	Included in the pooled data analysis
Surges et al. (2009)	7	7	Long-lasting (1 h)	Mean RR, SDNN, RMSSD, LF/HF	Yes	Yes
Rauscher et al. (2011)	1	0	Long-lasting (1 h)	SDNN, RMSSD, LF, HF, LF/HF	Yes	Yes
Jeppesen et al. (2014)	1	9	Short-lasting (30 min)	SDNN, RMSSD, pNN50, LF, HF, LF/HF	Yes	Yes
Lacuey et al. (2016)	2	0	Short-lasting (5 min)	Mean RR, LF/HF	No	Yes
Myers et al. (2018)	10	40	Short-lasting (5 min)	Mean RR, SDNN, RMSSD, pNN50	Yes	No
Szurhaj et al. (2021)	20	20	Ultra short-lasting (2 min)	SDNN, RMSSD, LF/HF	No	No
Sivathamboo et al. (2021)	31	56	Short-lasting (5 min)	SDNN, RMSSD, LF, HF	Yes	No

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, low frequency/high frequency ratio; Mean RR, mean of successive RR intervals; pNN50, the proportion of successive RR intervals (NN) that differ by more than 50 ms divided by the total number of NN intervals; RMSSD, root mean square differences of successive RR intervals; SDNN, standard deviation of the RR intervals; SUDEP, sudden unexpected death in epilepsy.

OR "heart rate variability variability"). The following electronic databases and data sources were systematically searched: MEDLINE (accessed through PubMed), EMBASE, and Google Scholar.

As per the inclusion criteria, we selected articles written in English and studies that reported at least one HRV parameter measurement. Hence, for each included study we evaluated the consistency of HRV parameter changes, comparing SUDEP cases and respective controls. For the pooled data analysis we considered articles that reported HRV measurements expressed in mean ± standard deviation (SD).

We performed individual and comprehensive quality assessments for each study, looking for selection bias (i.e., whether the diagnostic methods for epilepsy patients were described and the matching of controls was adequate) and measurement bias (i.e., whether HRV analysis was performed according to the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force guideline). The quality of studies included in the meta-analysis was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS), which ranges from 0 to 9. Studies scoring ≥5 were regarded as having good quality [29]. Seven reviewers (G.E., F.D., S.C., J.L., F.A., C.C., C.V., S.L.S.) independently screened the retrieved articles for inclusion. Disagreements were collegially discussed and resolved. Data were extracted on a digital spreadsheet. The entire list of variables used for statistical analysis and missing data is reported in Table S2.

We extracted and collected the following patients' data: age, sex, comorbidity (Yes or No), SUDEP classification (definite, possible, probable, none) [30], SUDEP risk score [26], seizure semiology, seizure frequency, seizure etiology, epilepsy syndrome diagnosis, anti-seizure medication (ASM) therapy (number and type), surgery of epilepsy (Yes or No), vagal nerve stimulation (Yes or No), HRV recording methods (long-lasting or short-lasting recording, acquisition during wake or sleep state), HRV parameters analyzed. If available, data on HRV during sleep were also collected.

The final study protocol was registered in the PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/PROSPERO/, registration number CRD42021291586).

Statistics

For statistical analysis we considered only the studies that evaluated HRV in a resting state condition according to the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force's guideline [14] and reporting results as absolute values and/or mean ± SD. We performed a pooled analysis using descriptive statistics (mean ± SD, frequency) to depict the pooled dataset. We compared HRV parameters between the SUDEP-group and the Control-group using pooled mean difference (MD) comparison [31]. The level of significance was $p < 0.05$. Cases with insufficient information were not included in the statistical analysis. Data were analyzed using IBM SPSS™.

TABLE 2 Demographics and clinical data.

Parameter	SUDEP ($n = 72$)
Age (years)	33.1 ± 11.6
Sex (M)	37
Seizure types	
Focal	25 (35%)
Focal-to-bilateral	19 (26%)
Tonic–clonic	9 (13%)
Not available	19 (26%)
Epilepsy types	
TLE	21 (29.2%)
FLE	3 (4.2%)
IGE	3 (4.2%)
Not available	36 (50%)
Epilepsy syndrome	
Dravet syndrome	9 (13%)
Etiology	
Unknown etiology	28 (39.9%)
Known etiology	44 (61.1%)
Genetic	13
Structural	31
Drug-resistant	
Yes	64 (88.9%)
No	8 (11.1%)
Vagal nerve stimulation	
Yes	2 (2.8%)
No	70 (97.2%)
Surgical treatment	
No	64 (88.9%)
Yes	8 (11.1%)

Abbreviations: FLE, frontal lobe epilepsy; IGE, idiopathic generalized epilepsy; M, male; SUDEP, sudden unexpected death in epilepsy; TLE, temporal lobe epilepsy.

RESULTS

Literature search

The literature search yielded 1180 articles (MEDLINE: 128 results; Google Scholar: 853; EMBASE: 126; other sources: 73). Of the 1180 records screened, the full texts of 31 articles were reviewed for eligibility. Of these, 24 articles were excluded (see Table S3 for exclusion reasons). Only seven retrospective studies (five case–control studies and two case reports) fulfilled the selection criteria and accessed the following steps (Figure 1) [29,33-38].

The quality assessment revealed that the risk of selection bias was low as almost all studies used age- and gender-matched controls. All of them had confirmed epilepsy diagnosis according to International League Against Epilepsy (ILAE) criteria. Measurement

TABLE 3 Heart rate variability analysis and electrocardiogram recording methods.

Parameter	SUDEP (*n* = 72)
ECG recording	
Ultra-short-term	20 (27.8%)
Short-term	44 (61.1%)
Long-term	8 (11.1%)
HRV during awake and sleep	
Yes	50 (69%)
No	22 (31%)
HRV analysis parameters	
Both time and frequency domain	62 (86.1%)
Only time domain	10 (13.9%)

Abbreviations: ECG, electrocardiogram; HRV, heart rate variability; SUDEP, sudden unexpected death in epilepsy.

bias evaluation showed that all the studies performed HRV analysis according to the international criteria [14]. According to the NOS, five articles reviewed were scored 5, one article was scored 4, and one article was scored 3 (detailed score results are shown in Table S4).

Details of the included articles are reported in Table 1.

Demographics and clinical features

Data of 72 patients who died of SUDEP (37 males, mean age: 33.1 ± 11.6 years) were extrapolated from the included studies. SUDEP diagnosis was made according to ILAE diagnostic criteria in all cases [31]. Diagnosis of possible or definite SUDEP was made in 64 cases (64/72, 88.9%). The SUDEP-7 inventory was evaluated before SUDEP occurrence in just one study [37] showing a high score, which was related to increase risk of mortality.

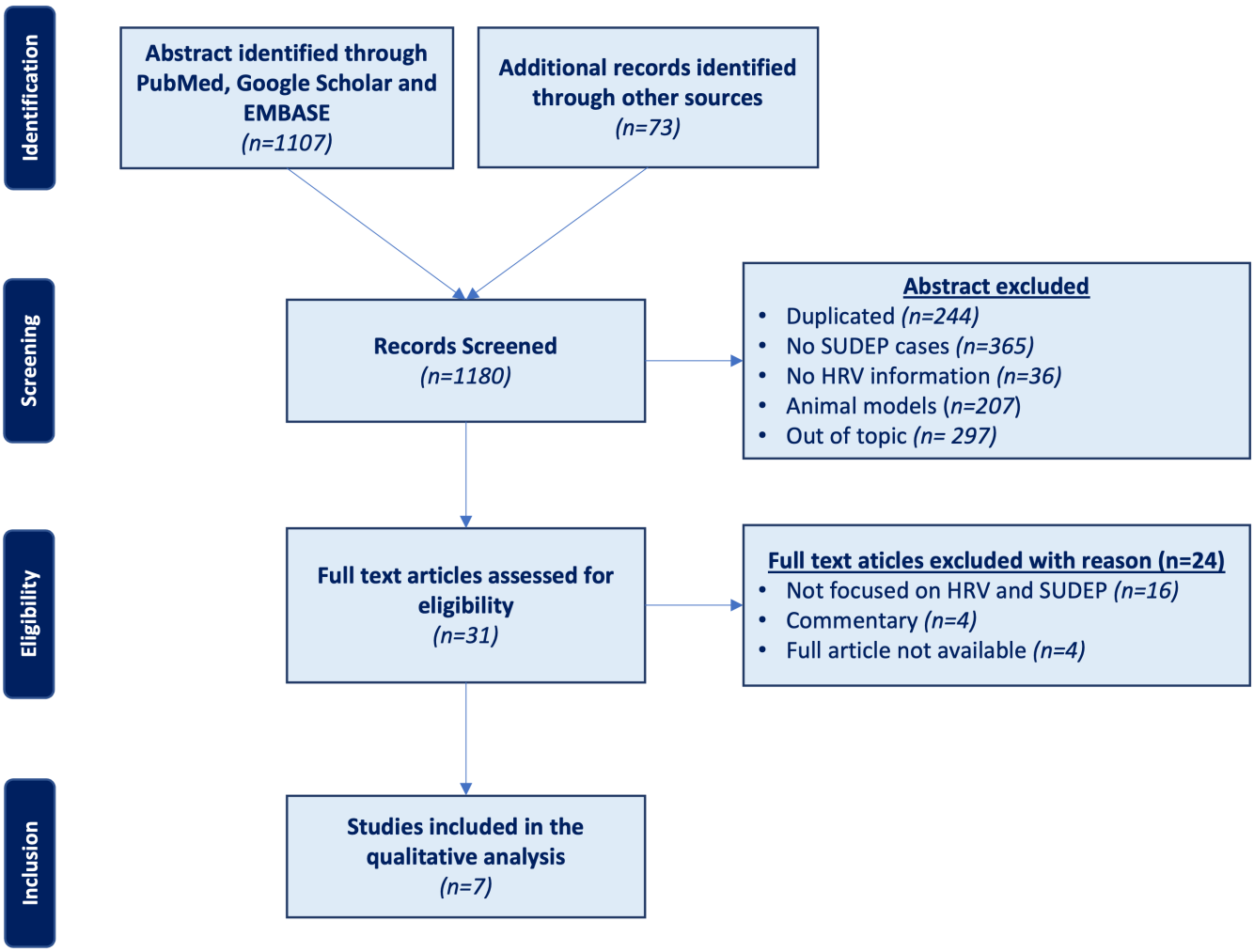

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram describing the literature search; 1180 records were screened from which seven articles (two case reports and five retrospective studies) were selected. HRV, heart rate variability; SUDEP, sudden unexpected death in epilepsy.

TABLE 4 Summary of heart rate variability modification between sudden unexpected death in epilepsy and controls according to the included case–control studies.

Authors (year)	SUDEP patients	Control patients	Mean RR	SDNN	RMSSD	LF/HF	Mean RR	SDNN	RMSSD	LF/HF
			Wake	Wake	Wake	Wake	Sleep	Sleep	Sleep	Sleep
Surges et al. (2009)	7	7	↑	↑	↓	↑	↓	↑	↑	↑
Jeppesen et al. (2014)	1	10	NA	NA	↑	↓	NA	↓	↓	↓
Myers et al. (2018)	10	40	↓	↓	↓	NA	↓	↑	↑	NA
Szurhaj et al. (2021)	20	20	NA	↑	↑	↓	NA	NA	NA	NA
Sivathamboo et al. (2021)	31	56	NA	↓	↓	NA	NA	↓	↓	NA

Note: The upward arrow (↑) indicates a higher value found in the SUDEP cases when compared to controls. By contrast, the downward arrow (↓) indicates a lower value in SUDEP cases when compared to controls. No statistical differences were detected between cases and controls according to the mentioned parameters in the respective studies.

Abbreviations: LF/HF, low frequency/high frequency ratio; meanRR, mean of successive RR intervals; NA, not available; RMSSD, root mean square differences of successive RR intervals; SDNN, standard deviation of the RR intervals; SUDEP, sudden unexpected death in epilepsy.

According to seizure type, 25 patients (25/72, 35%) had only focal seizure, 19 patients (19/72, 26%) presented focal and focal-to-bilateral seizures, whereas nine patients (9/72, 13%) had tonic–clonic generalized seizures. Temporal lobe epilepsy (TLE) (21/72, 29.2%) was the most common epilepsy type reported, followed by frontal lobe epilepsy (FLE) (3/72, 4.2%) and idiopathic generalized epilepsy (IGE) (3/72, 4.2%). Dravet syndrome (9/72, 13%) with *SCN1A* mutation was the only epilepsy syndrome described associated with SUDEP. Epilepsy etiology was described in 44 patients, with 13 patients with a genetic etiology (13/72, 18.1%) and 31 patients with a structural etiology (31/72, 43.1%).

Sixty-four patients (64/72, 88.9%) showed a pharmacoresistant epilepsy. Specific information about patients' treatment were available in three studies [33,37,38]. A total of 24 patients (24/72, 33.3%) were treated with sodium channel blockers (i.e., lacosamide, carbamazepine, or phenytoin). Eight patients (8/72, 11.1%) underwent surgical treatment of epilepsy. Two patients (2/72, 2.8%) were treated with vagal nerve stimulation (VNS).

No information was reported about the past medical history of endocrine disorders, metabolic deficits, uremia, or any other known disease that could have affected autonomic functions, including sleep-related apnea.

Demographics and data on past medical history are summarized in Table 2.

HRV analysis methods

ECG recording and data length

In all the reviewed studies, ECG recordings were obtained through an EEG + ECG integrated system which consisted of a 21-lead EEG recording and an associated 1-lead ECG system. Only in one patient was HRV analysis performed over an ECG with a simultaneous stereo-EEG + ECG recording. Generally, if multiple EEG + ECG recordings were available, the one with the best ECG data quality was chosen. In all but one study [34], HRV analysis was performed in a resting-state condition (i.e., patients lying on the bed with a normal breathing rate).

The time interval between the EEG + ECG recording and SUDEP occurrence was reported in 34 patients (47.2%). Only in one patient was HRV analysis performed on an EEG + ECG recorded concomitantly SUDEP occurrence [28]. In most cases, HRV analysis was performed on the last EEG + ECG recording available (median: 730 days before SUDEP occurrence, IQR: 365–2007). HRV analysis was performed on less than 5 min of ECG recording (i.e., ultra short-term recordings) in 20 patients (27.8%), on 5 min of ECG recording (i.e., short-term recordings) in 44 patients (88.9%), whereas only in eight patients (11.1%) HRV data were calculated over longer ECG recordings. In 50 patients (69.4%), HRV parameters were evaluated during wake and sleep periods.

Details of ECG recordings are reported in Table 3.

TABLE 5 Heart rate variability analysis during wake and sleep according to groups.

Parameter	SUDEP (mean ± SD)	*n*	Controls (mean ± SD)	*n*	$\beta \pm SE\beta$	Pooled comparison *p*-value
Mean RR wake (ms)	830.41 ± 150.41	9	799 ± 143.81	7	−31.41 ± 74.39	0.679
SDNN wake (ms)	71.8 ± 21.24	9	76.64 ± 24.89	11	4.84 ± 10.49	0.917
RMSSD wake (ms)	42.88 ± 23.53	9	48.92 ± 22.99	11	6.04 ± 10.44	0.570
LF/HF wake	4.27 ± 2.45	11	2.93 ± 1.73	11	−1.34 ± 0.90	0.154
Mean RR sleep (ms)	936 ± 172.08	7	994 ± 193	7	58 ± 97.73	0.564
SDNN sleep (ms)	77.27 ± 51.29	8	84.31 ± 44.49	16	7.04 ± 19.57	0.722
RMSSD sleep (ms)	52.99 ± 53.17	8	52.82 ± 55.96	16	−0.17 ± 22.92	0.994
LF/HF sleep	3.03 ± 0.81	3	1.97 ± 1.46	16	−1.06 ± 0.88	0.245

Note: Mean ± SD, $\beta \pm SE\beta$ for the mean differences.

Abbreviations: LF/HF, low frequency/high frequency ratio; Mean RR, mean of successive RR intervals; RMSSD, root mean square differences of successive RR intervals; SDNN, standard deviation of the RR intervals; SD, standard deviation; SE, standard error; SUDEP, sudden unexpected death in epilepsy.

HRV analysis parameters

HRV analysis during wake was made according to both time and frequency domain parameters in 62 patients (86.1%). In contrast, only a time-domain analysis was performed in the remaining 10 patients (13.9%). In particular, the most reported time-domain parameters were the standard deviation of the RR intervals (SDNN, 97.2%), the root mean square differences of successive RR intervals (RMSSD, 97.2%), and the mean of successive RR intervals in milliseconds (ms) (Mean RR, 26.4%). Moreover, the main frequency domain parameter was the low frequency/high frequency ratio (LF/HF, 43.1%). Nonlinear analysis was performed in only one patient (1.4%).

HRV analysis during sleep was made according to time and frequency domain parameters in 40 patients (55.6%). In contrast, only a time-domain analysis was performed in 10 patients (13.9%). As in the waking state, the most reported parameters were the SDNN (50/72, 69.4%), RMSSD (50/72, 69.4%), and Mean RR (18/72, 25%) for the time domain, and LF/HF (40/72, 55.6%) for the frequency domain. Nonlinear analysis was performed in only one patient (1.4%).

Summary of HRV modification in case–control studies

To assess how consistent changes in HRV were associated with SUDEP, we summarized the mean modification of the most frequently reported HRV parameters (see Section 'HRV analysis parameters'), comparing SUDEP cases with respective controls (Table 4). According to the single included studies, even if no statistical differences were reported in all the explored HRV parameters, a trend toward a reduction of SDNN, RMSSD, and LF/HF during the wake phase as well as a reduction of Mean RR, SDNN, RMSSD, and increased LF/HF during the sleep state were reported in most of the SUDEP population.

It has to be acknowledged that the control groups in the included studies showed some inconstancies (i.e., epilepsy and seizure type as well as diagnosis of pharmacoresistant epilepsy), which may impair the significance of this comparison.

HRV pooled analysis

According to the inclusion criteria (see Methods Section), only four articles [29,35,37,38] (two case reports and two case–control studies) were included in the pooled analysis, which enrolled 11 patients who died of SUDEP (four patients with defined and seven patients with probable diagnosis) and 16 controls. Controls patients in the included studies showed a remarkable consistency according to demographics, seizure type, and pharmacoresistant epilepsy.

Due to the heterogeneity of the HRV parameters analyzed in the included studies, we considered only those parameters explored in a consistent number of patients, as reported in the Section 'HRV analysis parameters'.

According to HRV analysis performed during the awake status, no differences between SUDEP subjects and controls were observed in terms of Mean RR (p-value = 0.679), SDNN (p-value = 0.9179), and RMSSD (p-value = 0.570). A non-significant trend toward an increased LF/HF (p-value = 0.154) was observed in the SUDEP group. No significant differences between groups were detected during the sleep either for Mean RR (p-value = 0.564), SDNN (p-value = 0.722), or RMSSD (p-value = 0.994). Also in this case, a trend of increased LF/HF (p-value = 0.24) was reported in the SUDEP group.

HRV pooled analyses are summarized in Table 5.

DISCUSSION

In the present review, we collected clinical and HRV data of 72 patients who died of SUDEP. In line with the current literature [2], most of the patients who developed SUDEP were male and presented

with pharmacoresistant epilepsy. Surprisingly, our data highlight that a great number of patients in the SUDEP group showed only focal seizures in the context of TLE. These data are intriguing if we consider the pivotal role of the temporal lobe in the central autonomic network [39] – a system encompassing cortical, midbrain, and brainstem areas involved in the central control of autonomic functions – and may support autonomic dysfunction as a major cause leading to SUDEP occurrence.

According to our results, patients in SUDEP cohorts hardly ever underwent surgical treatment or VNS therapy. Surgical and neurostimulation approaches are fundamental in pharmacoresistant focal epilepsy and may help patients in achieving a reduction of seizure frequency as well as seizure freedom. Generally, non-eligibility to these procedures may be related to several factors including the epilepsy type and etiology, the localization of the seizure onset zone, the concomitant comorbidities, or the low access to specialized neurosurgical epilepsy centers. However, it was not possible to ascertain the reason a low rate of such procedures was detected.

It has to be pointed out that the demographics and clinical characteristics described in the SUDEP population present a strong selection bias given the fact that these data only refer to patients who underwent HRV evaluation.

With regard to HRV parameters evaluation, our data show that patients who died of SUDEP did not present any differences compared to surviving patients with pharmacoresistant epilepsy. However, our meta-analysis shows a trend towards an increased LF/HF in both the wake and sleep state in the SUDEP group. The physiological origin underpinning the LF/HF ratio has been the subject of debate in recent years. Indeed, the LF/HF ratio has been considered for a long time a reliable substitute measure of the cardiac autonomic balance [39-41] even though more recent evidence rejected its validity as a sympathovagal balance index [42]. However, several studies have reported that this index has prognostic value regarding the mortality risk due to cardiovascular [19,20] or non-cardiovascular causes [21-25]. Even though the LF/HF ratio may represent a possible index to identify patients with a higher risk of SUDEP, no major conclusion can be drawn on the basis of the available evidence.

Furthermore, the summary of HRV modification between SUDEP and controls, according to the current literature, highlighted a trend towards a reduction of Mean RR, SDNN, and RMSSD during wake and sleep phases in the SUDEP population. According to the literature, SDNN and RMSSD are reliable indexes of cardiovagal components [43]. A reduced cardiovagal output increases the risk of death for cardiovascular and non-cardiovascular causes. In addition, a reduction of RMSSD, pNN50 (the proportion of successive RR intervals [NN] that differ by more than 50 ms divided by the total number of NN intervals), and SDNN have been associated with higher values in the SUDEP-7 score [10,27,44]. Thus, this evidence supports the possible cardioautonomic imbalance in patients who died of SUDEP.

A major result of our systematic review is the significant inhomogeneity among the measures and reports on HRV analyses in SUDEP cohorts. This finding is noteworthy since the heterogeneity can profoundly affect our understanding of the cardio-autonomic alterations, which may have a substantial role in SUDEP prediction. For this reason, the present article is not only aimed at highlighting methodological biases but also prompts suggestions to achieve better standardization of procedures and improve the reliability of future studies on this topic.

Time interval between ECG recordings and SUDEP

The time interval between SUDEP occurrence and the referral EEG + ECG recording used for the HRV analysis varied consistently in the included studies. The EEG + ECG assessment, considered as "pre-mortem evaluation" was seldom performed during an adequate period (e.g., at most 1 month before the patient's death). Even 2-year pre-mortem recordings were considered reliable data to be evaluated for research purposes. Furthermore, no studies performed a follow-up analysis, carrying out, even retrospectively, multiple and extended evaluations of HRV measurements over time in the examined patients. Indeed, the presence of an HRV worsening trajectory over the years in patients who died of SUDEP could enforce this method's prognostic and predicting value.

HRV parameters choice

Several parameters regarding time and frequency domains were analyzed in the included studies. As a first issue, units of measurement of frequency domain parameters (i.e., absolute value expressed in ms^2, or relative value expressed as a percentage or normalized unit) were not always specified. The correct interpretation of HRV frequency domain parameters depends on the actual type of units of measurement. For example, HF only represents a reliable index of a cardiovagal component when expressed in absolute values (ms^2). In contrast, its interpretation is questionable when expressed in relative values (percentage or normalized unit).

As a second issue, the choice of HRV parameters was rarely oriented to test a specific hypothesis (e.g., the modification of cardiovagal balance in patients who died of SUDEP) rather than a random presentation of variables without any underlying physiological meaning [43]. Indeed, it must be pointed out that the HRV modifications observed in the SUDEP group do not allow the possibility of drawing any conclusion about the possible cardiac sympathovagal imbalance or cardiovagal dysfunction in this population. Supporting this statement, HRV parameters more closely associated with the cardiovagal function (RMSSD, SDNN, pNN50, and HF) [39] did not differ between the two groups.

HRV circadian variation

It is well known that HRV exhibits circadian variations [45,46]. Autonomic activity shows a circadian rhythm with a predominance

of sympathetic tone during the day and a significant relative increase in vagal tone during the night and the first hours after awakening [45-47]. According to the literature, adverse cardiovascular events show a clear circadian pattern, with maximal occurrence during the morning hours [48,49]. Indeed, there is a ~40% higher incidence of acute myocardial infarction, sudden cardiac death, atrioventricular block, ventricular fibrillation, ventricular tachycardia, and ischemic events between 06:00 h and 12:00 h compared with the rest of the day [50]. In almost all the reviewed studies, there is no mention of the time of EEG-ECG recording in patients and controls. Recordings must be performed taking into consideration the circadian variation of HRV to avoid the misinterpretation of results between patients and controls due to physiological HRV variation.

Epilepsy-related factors and ASM impact on HRV

All the included studies generally did not focus on the possible influence of ASMs [52] or certain epilepsy-related factors (i.e., lateralization of the epileptic focus) [53] on HRV analysis.

The influence of ASM on HRV has been frequently stressed in the current literature [52]. Some ASMs can modify HRV and be associated with developing cardiac conduction abnormalities and arrhythmias. Supporting this evidence, some studies showed that sodium channel blockers such as carbamazepine and phenytoin could lead to autonomic impairment and HRV modifications [54]. However, of all the included studies, only four [29,33,37,38] reported details about specific ASM regimens and performed a subgroup analysis to shed light on the possible correlation between the administration of certain ASMs and HRV worsening.

The possible influence of the specific localization of the epileptic focus in patients with TLE on HRV modifications represents a second pitfall. In fact, according to the literature [53], the right localization of the epileptic focus may reduce the HRV and the vagal output. Hence, more details are needed to correctly interpret the HRV modifications in the SUDEP cohort.

CONCLUSIONS

HRV analysis is a valuable method for assessing cardiovascular risk and cardioautonomic impairment. The autonomic imbalance may play a pivotal role in SUDEP occurrence. Although a possible association between HRV changes and SUDEP risk has been reported, the exact mechanism remains unclear. In our study, we show a trend towards an increased LF/HF ratio both in wake and sleep states in the SUDEP group; these findings could be interpreted as a potential new biomarker useful in clinical practice for SUDEP risk stratification. However, there is still no common strategy in the analysis and recording of EEG-ECG for HRV calculation. Hence, although a possible association between HRV changes and SUDEP occurrence has been reported, caution should be paid in interpreting these data considering some methodological issues. The possible correlation between HRV changes and SUDEP could guide the choice of ASM, as some drugs significantly affect HRV [52,55]. Future studies should be performed with more rigorous methods to better understand the predictive value of HRV modifications over SUDEP occurrence.

AUTHOR CONTRIBUTIONS

G.E. and F.D. contributed to the conception and design of the study. G.E., F.D., and S.C. organized the database. C.V. performed the statistical analysis. G.E., F.D., and S.L.S. wrote the manuscript. All authors contributed to manuscript revisions and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this article is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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