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Cardiac changes in epilepsy

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>AEDs</td>
<td>Anti-epileptic drugs</td>
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<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<td>bpm</td>
<td>Beats per minute</td>
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<td>DMN</td>
<td>Dorsal motor nucleus</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>GTCS</td>
<td>Generalized tonic-clonic seizure</td>
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<tr>
<td>HF</td>
<td>High frequency component of HRV</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>HRV</td>
<td>Heart rate variability</td>
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<tr>
<td>IB</td>
<td>Ictal bradycardia</td>
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<tr>
<td>IC</td>
<td>Insular cortex</td>
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<tr>
<td>IT</td>
<td>Ictal tachycardia</td>
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<tr>
<td>LC</td>
<td>Locus coeruleus</td>
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<tr>
<td>LF</td>
<td>Low frequency component of HRV</td>
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<tr>
<td>MIBG</td>
<td>meta-iodobenzylguanidine</td>
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<tr>
<td>NE</td>
<td>Norepinephrine</td>
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<tr>
<td>NN</td>
<td>The intervals between normal successive sinus beats</td>
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<tr>
<td>NTS</td>
<td>Nucleus tractus solitarius</td>
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<tr>
<td>OS</td>
<td>Sympathetic division of the ANS</td>
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<tr>
<td>PS</td>
<td>Parasympathetic division of the ANS</td>
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<tr>
<td>PTZ</td>
<td>Pentylentetrazol</td>
</tr>
<tr>
<td>SCD</td>
<td>Sudden cardiac death</td>
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<tr>
<td>SDNN</td>
<td>The standard deviation of all normal RR intervals</td>
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<tr>
<td>SUDEP</td>
<td>Sudden unexpected death in epilepsy</td>
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<td>TKS</td>
<td>Takotsubo syndrome</td>
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<td>TLE</td>
<td>Temporal lobe epilepsy</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>TWA</td>
<td>T-wave alternans</td>
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<tr>
<td>vEEG</td>
<td>Video encephalogram</td>
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<tr>
<td>VN</td>
<td>Nervus vagus</td>
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<td>VNS</td>
<td>Vagus nerve stimulation</td>
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<tr>
<td>XTEL</td>
<td>Extratemporal lobe epilepsy</td>
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Abstract

Introduction: Epilepsy is a common neurological disorder with a big impact on the lives of over 65 million people worldwide and is characterized by spontaneous recurring seizures. A seizure can induce autonomic dysfunction with a resulting effect on the heart. Cardiovascular changes due to the epileptic autonomic dysfunction in turn may be linked to sudden unexpected death (SUDEP), which is the leading cause of death in epilepsy patients with 4 deaths per 1000 patient-years. Therefore it is crucial to identify the cardiovascular changes linked to the autonomic dysfunction. This thesis reviews the different aspects of epilepsy related autonomic cardiac changes of the already conducted studies. Methodology: A Pubmed search using different keywords resulted in 133 articles published between 1986 and octobre 2015. Results: The autonomic nervous system (ANS) plays a very complex role in epilepsy. Many studies revealed autonomic changes in the pre-ictal, ictal, interictal and post-ictal state. These autonomic changes result in changes in heart rate variability, heart rate (HR) and electrocardiogram (ECG) morphology. Some studies show that SUDEP is linked to autonomic cardiovascular changes in epilepsy. Research shows these changes can be quantified into risk factors for SUDEP, which can identify high-risk patients in whom prediction measuring can be undertaken. High-risk patients can be identified with genomic biomarkers. Another implication of epilepsy-related autonomic effects is seizure detection based on the pre-ictal and ictal autonomic changes. Methods based on the autonomic changes that can be used for seizure detection are HR monitoring, ECG monitoring and the cervical vagus electroneurogram. Last, the presence of epilepsy-related autonomic effects may aid in response prediction for treatment with nervus vagus stimulation (VNS). Studies show a relation between the ANS, VNS and the heart. Discussion: Results concerning the pathophysiology of autonomic alterations in epilepsy are still controversial. None of the theories regarding this pathophysiology are conclusive and none of them can explain all the alterations in epilepsy, it is therefore possible all these theories are partly true and are linked to each other. Future studies regarding the cardiac changes in epilepsy should wield the same exclusion criteria and consider using the same definitions. It isn’t always possible to see whether cardiac changes seen in epilepsy are due to use of certain medication or intrinsic to epilepsy. Confounding drugs should therefore be taken into account when conducting a study regarding autonomic changes in epilepsy. More research should be conducted on the identification of a high risk population for SUDEP in epilepsy and furthermore on the
prevention of SUDEP. Biomarkers might aid in the identification of the high-risk population. Extensive closed loop systems involving a detection device able to detect seizures in the pre-ictal stages and a response system able to preemptively stop a seizure from developing, should also be developed in the future. Further investigation as to how this is possible is necessary. Because a relation exists between the ANS, VNS and the heart; it is possible that the VNS response is dependent on the ictal autonomic changes existing in the patients with epilepsy. With the discovery of this link, ictal autonomic changes could be used as a predictor of VNS response. This link should be investigated in future studies. **Conclusion:** further research is necessary.

**Samenvatting in het Nederlands**

Epilepsie is een veel voorkomende neurologische aandoening met een grote impact op het leven van meer dan 65 miljoen mensen over de hele wereld en wordt gekenmerkt door spontane terugkerende epileptische aanvallen. Een aanval kan autonome dysfunctie veroorzaken met gevolgen voor de cardiale functies. Cardiovasculaire veranderingen als gevolg van de epileptische autonome dysfunctie kunnen op hun beurt worden gekoppeld aan plotselinge onverwachte dood (SUDEP), welke de belangrijkste doodsoorzaak is bij patiënten met epilepsie met in totaal 4 sterfgevallen per 1000 patiëntjaren. Daarom is het essentieel om de cardiovasculaire veranderingen verbonden met de autonome dysfunctie te identificeren. In deze thesis wordt een overzicht gegeven van de verschillende aspecten van aan epilepsie gerelateerde autonome cardiale veranderingen adhv informatie afkomstig van de reeds uitgevoerde studies. De informatie over deze uitgevoerde studies is afkomstig van Pubmed. In totaal zijn 133 artikels gebruikt. Het autonome zenuwstelsel speelt een zeer complexe rol bij epilepsie. Veel studies toonden autonome veranderingen aan in de pre-ictale, ictale, interictale en postictale fase. Deze autonome veranderingen leiden tot veranderingen in de hartslagvariabiliteit, de hartslag en de morfologie van het elektrocardiogram. De resultaten met betrekking tot de pathofysiologie van autonome veranderingen in epilepsie zijn nog steeds omstreden. Geen van de theorieën over deze pathofysiologie zijn overtuigend en geen van hen kan de veranderingen in epilepsie verklaren, daarom is het aannemelijk dat al deze theorieën deels correct zijn en met elkaar gelinkt zijn. Het is niet altijd mogelijk om te zien of cardiale veranderingen waargenomen bij epilepsie, veroorzaakt worden door gebruik van bepaalde medicijnen of inherent zijn aan epilepsie. Er moet dus rekening worden gehouden met beïnvloedende medicatie bij het uitvoeren van een studie met betrekking tot autonome veranderingen bij epilepsie.
Sommige studies tonen aan dat SUDEP samenhangt met de autonome cardiovasculaire veranderingen bij epilepsie. Deze veranderingen zouden kunnen worden gekwantificeerd in risicofactoren voor SUDEP en adhv deze risicofactoren zouden hoog-risico patiënten kunnen worden gekwantificeerd. Hoog-risico patiënten zouden eventueel kunnen worden geïdentificeerd met genomische biomarkers. Meer onderzoek moet worden gedaan naar de identificatie van een hoog risico populatie voor SUDEP in epilepsie en naar de preventie van SUDEP. Een andere implicatie van epilepsie-gerelateerde autonome effecten is de detectie van een epilepsieaanval op basis van de pre-ictale en ictale autonome veranderingen. Methoden die autonome veranderingen kunnen detecteren en zo een aanval kunnen detecteren, zijn hartslagmonitoring, ECG monitoring en de cervicale nervus electroneurogram. Uitgebreide closed loop systemen waarbij een detectiesysteem in staat is om aanvallen te detecteren in de pre-ictale fase en een response systeem in staat is om een aanval te stoppen alvorens deze verder ontwikkeld, moeten ook worden ontwikkeld in de toekomst. Verder onderzoek naar hoe dit mogelijk is, is noodzakelijk. Ten slotte kan de aanwezigheid van epilepsie gerelateerde autonome effecten helpen bij responspredictie voor behandeling met nervus vagus stimulatie (NVS). Studies tonen een zeker verband aan tussen het autonome zenuwstelsel (ANS), VNS en het hart. Aangezien er een verband bestaat tussen het ANS, VNS en het hart, is het mogelijk dat de VNS response afhankelijk is van de ictale autonome veranderingen bestaande in patiënten met epilepsie. Als dit verband duidelijker wordt in de toekomst, kunnen de ictale autonome veranderingen worden gebruikt ter voorspelling van VNS respons. Uit dit alles kunnen we concluderen dat uitgebreid verder onderzoek noodzakelijk is.
1. Introduction

1.1. Introduction to epilepsy and it’s autonomic effects
Epilepsy is a condition characterized by recurrent epileptic seizures, unprovoked by any immediate identified cause [1, 2]. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy affects 0.5-1% of the population worldwide of which many patients are limited in their daily activities because of their disease, despite taking medication. The two major categories of seizure type used worldwide are epilepsy characterized by partial seizures and epilepsy characterized by generalized seizures [3]. Partial seizures can be complex or simple. In contrary to complex partial seizures, simple partial seizures give no alteration in consciousness. Partial seizures can generalize secondarily. Prevalence and incidence of epilepsy differ by demographic factors including age, gender, race and socioeconomic status. Epilepsy remains a clinical diagnosis [4]. This explains why misdiagnosis is common: epilepsy is often confused with non-epileptic paroxysmal events.

Anti-epileptic drugs (AEDs) are the fundamentals in the treatment of epilepsy [5]. Thirty-forty percent of patients still suffer seizures after multiple trials of AEDs. These patients have medically refractory epilepsy. Patients with medically refractory epilepsy may benefit from non-medical treatment such as surgery, a diet or nervus vagus stimulation therapy (VNS).

Epilepsy and seizures can induce changes in autonomic function [6]. The autonomic nervous system (ANS) consists of two major divisions: the sympathetic system (OS) and the parasympathetic system (PS). Normally, the activity of these divisions is in dynamic balance. In epilepsy and during seizures, one division of the ANS can dominate over the other. This creates an autonomic imbalance. This imbalance can have serious clinical consequences on cardiac function [7]. The sympathetic nervous system mediates adaptive and protective effects in the heart, increases or decreases HR (depending on the catecholamine receptor), can increase myocardial contractility, can facilitate conduction through the atrioventricular node, and pacemaker activity of the sinoatrial node. Parasympathetic stimulation decreases HR by decreasing sinoatrial node discharge rate and atrioventricular node conduction velocity with minimal or no effect on cardiac contractility. This explains why an autonomic shift as a result of an acute seizure can have dangerous consequences, for instance causing an asystole.
1.2. Implications of the autonomic effects in epilepsy.
One of the implications of epilepsy-related autonomic alterations of heart function is sudden unexpected death in epilepsy (SUDEP) [8]. SUDEP is a sudden, unexpected, non-traumatic and non-drowning death, occurring in benign circumstances in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus. SUDEP occurs with an incidence of 4 deaths per 1000 patient-years. SUDEP is an important factor to be considered in epilepsy, because it is the leading cause of death in people with chronic refractory epilepsy.

Another implication is seizure prediction. The occurrence of seizure-induced cardiac changes would allow to identify ictal activity in a non-invasive way [9]. This would be of major interest for seizure prediction, allowing alarm systems and even closed-loop treatment systems. A closed loop system is the combination of the detection system and response system. The response system could alert the patient, his/her caretakers or the physician. Ideally, seizure detection occurs early or even before clinical onset.

The last implication is the prediction of response to VNS. The vagus nerve (VN) is the tenth cranial nerve. It consists of efferent and afferent fibers. The afferent fibers modulate the brain via the brain stem. The VN is the main parasympathetic output structure in several organ systems, the heart being one of them. A link between ANS, VNS and the heart has been confirmed [10]. The use of the ictal autonomic changes as a predictor of VNS response is still a hypothetical idea based on our current understanding of the autonomic changes in epilepsy, implicating the involvement of the ANS in the epileptogenic regions [10-12]. These types of epilepsy might have better responses to VNS treatment.

1.3. Goal of this review
This manuscript reviews the autonomic cardiac effects of epilepsy and its potential implications on different levels of the management of epilepsy and related events. The available literature will be discussed and compared. Potential weaknesses and future directions will be pointed out.
2. Search strategy and selection criteria

The PubMed database was first searched for articles published between 2009 and April 2015. The terms “epilepsy”, “nervus vagus” and “cardiac changes” were first applied. 17 articles were found. After application of the exclusion criteria 7 references were kept for detailed evaluation. The next search terms used were “cardiac changes in epilepsy”. This gave 214 potentially relevant references. After application of the exclusion criteria 14 references were kept for detailed evaluation. The terms “sudep” and “cardiac” gave 161 potentially relevant references, 17 references were kept for detailed evaluation. Then the terms “sudep” and “prevention” were used. This gave 82 potentially relevant references, 2 references were kept for detailed evaluation. The terms: “predict effectiveness vagus stimulation” gave 2 articles, 1 was kept after application of the exclusion criteria. The terms ‘ictal cardiac changes” gave 53 potentially relevant references, 1 reference was kept for detailed evaluation. The terms ‘pre-ictal changes” gave 30 potentially relevant references, 1 reference was kept for detailed evaluation.

For more information and results, it was found that older articles were necessary. Therefore the database PubMed was searched again in October 2015 with no publication date limit.

For the introduction, PubMed was searched with the terms “Epilepsy definition”. Out of 352 articles, 2 articles were kept. The terms “autonomic nervous system cardiac function” gave 37141 results. 2 results were kept.

For more general information on the connection between epilepsy and the cardiac effects, PubMed was searched with the search words ‘epilepsy” and “heart rate changes”. 272 articles were found. After application of the exclusion criteria, 15 articles were kept. The terms “bradycardia” and “epilepsy” showed 424 results, 3 articles were kept. PubMed was also searched for similar articles of the article ‘Ictal tachycardia: the head-heart connection.’. 112 articles were found, 10 articles were kept. PubMed was also searched for similar articles of the article ‘Cardiac changes in epilepsy’. 110 articles were found. After application of the exclusion criteria, 2 articles were kept. The terms “HRV” showed 7680 results, 2 articles were kept. The terms ‘cardiac ischemia” and “epilepsy” showed 500 results, 4 articles were kept. The terms “repolarization” and “epilepsy” showed 74 articles, 7 articles were kept. The terms “HRV” and “Epilepsy” showed 82 articles, 1 article was kept.
For more information on SUDEP, PubMed was searched for similar articles of the article ‘Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study.’ 156 articles were found. After application of the exclusion criteria, 4 articles were kept. The terms “epidemiology of SUDEP” showed 241 articles, 1 article was kept. “SUDEP risk” showed 322 articles, 6 articles were kept. “SUDEP prevention” showed 120 results, 4 articles were kept.

For more information on VNS, PubMed was searched for with the terms “VNS outcome”. This showed 383 results, 6 articles were kept. “epilepsy” and “treatment outcome” showed 74 results, 7 results were kept. “epilepsy” and “heart” and “VNS” showed 50 results, 7 articles were kept. “epilepsy”, “vagus nerve” and “norepinephrine” showed 15 results, 4 articles were kept. “Safety” and “VNS” showed 112 articles, the original safety study that got the FDA approval was kept and the original efficacy study was also kept.

The terms “seizure prediction” showed 851 results, 3 articles were kept.

Exclusion criteria were: case reports, articles not relevant to the thesis, duplicates and research conducted on animals, articles that were outdated by more recent superior research, articles where full text wasn’t available via UGent. Exceptions to this: case reports were included in the case of ictal asystole, because no large research studies exist on this subject. Animal studies were also included if research in humans was inconclusive on the matter.

In the end 134 studies were included.
3. Results

3.1. Autonomic effects of epilepsy

3.1.1. Anatomy

The ANS has central and peripheral components [13]. The central ANS includes the insula, the anterior cingulate gyrus, the ventro-medial pre-frontal regions, the amygdala, the bed nucleus of stria terminalis, the hypothalamus, periaqueductal grey matter, peribrachial nucleus and finally the driver nuclei in the brain stem. All autonomic structures are part of a central autonomic network. This network receives and integrates information from the viscera, endocrine, internal and external environments and the brain to influence the effector mechanisms. The effector nuclei are located in the medulla. Within the dorsal medial medulla the nucleus tractus solitarius (NTS) is the primary transfer point for all viscerosensory information entering the central autonomic network. One of the main motor output centers is the nucleus ambiguous. Within the ventro-lateral division are concentrated the cardiac pre-ganglionic parasympathetic neurons, these neurons will be important to remember for the later explanation of the cardiac changes during epileptic seizures and it’s relation to SUDEP. Vasomotor preganglionic sympathetic neurons are localized in the rostral ventrolateral medulla.

The nervus vagus (VN) originates in the medulla oblongata from the dorsal motor nucleus (DMN) and NA in the medulla oblongata [14]. The DMN has a tonic output on HR; the NA is responsible for phasic vagal output to the heart. Increase in vagal efferent activity results in decrease of HR, atrio-ventricular conduction and ventricular excitability. A close coupling between the respiratory centers and the cardiovascular system exists.

The ANS is a very complex system with extensive pathways that all work together to exert tonic, reflex and adaptive autonomic control [13, 14]. Seizure onset within the neocortical and/or limbic cortices that are part of this network may affect the autonomic output which can become apparent in multiple autonomic functions of the body [13, 14]. These ictal autonomic manifestations may allow to identify ictal activity outside the brain. Focal simple partial seizures may produce flushing, sweating, and piloerection, while complex partial seizures produce a broader spectrum of autonomic signs, including changes in HR and rhythm, blood pressure (BP), gastrointestinal motility, and secretion [15]. Generalized tonic-clonic seizures may be associated with severe increases in BP, changes in HR, changes in heart conduction, marked bradycardia and even asystole. The autonomic manifestations are influenced by posture, satiety, thirst and sleep. Most studies
have used the cardiac and cardiorespiratory manifestations, as a result of their ease of monitoring. These changes in autonomic function can have serious consequences.

In relation to seizures, 4 distinct brain states exist: interictal state, a pre-ictal state, an ictal state and in the end a post-ictal state, as illustrated in figure 1 [16]. Many studies have revealed that there are autonomic changes in the pre-ictal phase as well as in the ictal, interictal and post-ictal phases [4, 13, 17].

![Figure 1](image)

**Figure 1:** Transition phases in epilepsy. Source: ‘Haut, S.R., et al., Clinical features of the pre-ictal state: mood changes and premonitory symptoms. Epilepsy Behav, 2012. 23(4): p. 415-21.’

### 3.1.2. Cardiac parameters to measure autonomic changes

HR is an important cardiac parameter derived from the RR interval that is easy to monitor and measure [1]. Algorithms of the HR can be adapted to individual patients. Another
parameter that is being used to investigate autonomic changes is heart rate variability (HRV).

HRV is measured by the variation in the beat-to-beat interval and it can be an indicator of the effect of sympathetic and parasympathetic input to the heart [10, 18, 19]. Lower HRV is said to make patients more vulnerable to tachycardia and fibrillation and sudden cardiac death (SDC) [14, 20]. The heart rate (HR) varies from beat to beat. This variability is a result of the multiple physiologic mechanisms that regulate the instantaneous HR [21]. Short-term HR regulation is mainly overseen by sympathetic and parasympathetic neural activity. Thus, HR fluctuations give information about the ANS. Different analysis methods exist which use the HRV as a parameter. HRV measurement is usually based on the sequence of RR intervals. Fluctuations in PR interval due to modulation of atrioventricular nodal conduction, premature ventricular contractions and premature atrial contractions can confound the measurements. One common way to analyze HRV is by time domain measures. The simplest and most often used measures are the instantaneous HR, intervals between normal successive sinus beats (NN), the standard deviation of all normal RR intervals (SDNN), average HR, mean NN interval, and the difference between the longest and shortest NN interval. Another way to analyze HRV is by frequency domain measures, these provide spectral analysis of the R-R time series that expresses HRV as a function of frequency. This gives us more information about the different periodically working sources of the variability of heartbeat generation. Although debated, some authors suggest that while the low frequency component (LF; 0,04-0,15Hz) is the result of both parasympathetic and sympathetic regulation, the high frequency component (HF; 0,15-0,40Hz) is the result of vagal regulation of the heart and the LF/HF ratio gives us more information about the sympathetic regulation on the heart [19]. More extensive information on HRV measurement methods can be found in the appendix.

Other examples of cardiac parameters are electrocardiogram (ECG) changes, including T-wave inversion, ST-depression and QTc interval [14].

3.1.3. **Pathophysiology of autonomic alterations in epilepsy**

In patients with seizures, epileptic discharges are thought to propagate to the central autonomic network and change or disturb normal autonomic control [14]. The pathophysiology of the autonomic alterations in epilepsy differs in the 4 brain states related to seizures.
3.1.3.1. Pathophysiology of the ictal autonomic alterations

Seizure onset within the neocortical and/or limbic cortices that are part of the complex network of the ANS may affect the autonomic output which can become apparent in multiple autonomic functions of the body (figure 2) [13, 14]. The relation between the cortical and subcortical structures involved in the regulation of cardiovascular functions is shown in figure 3. An important study performed by Oppenheimer et al. in 1992 showed that stimulation of the left insular cortex (IC) provokes a HR decrease and depressor response and stimulation of the right IC provokes a HR increase and pressor responses [22].

This is evidence of a hemispheric specific organization with the pressor response lateralized to the right and depressor response to the left hemisphere [23]. This evidence has only been reproduced in electrically induced seizure, not in studies “in real life”, allowing discussion. The lateralization theory can be used to explain pressor responses seen in seizures originating from the temporal lobe (TLE) contrary to the depressor responses seen in extratemporal seizures (XTLE) [1, 14, 17, 24]. Pressor responses in TLE could be the result of discharges in the right IC and depressor responses in XTLE could be the result of discharges in the left IC and amygdala. This theory would explain why Britton et al. found bradyarrhythmia (a depressor response) to be stronger in association with bilateral hemispheric seizure discharges [25]. However, cases of right hemispheric seizures associated with asystole (also a depressor response) exist, and this questions the lateralization theory [26]. Another theory can be formed, namely that the involvement of both hemispheres by propagation of discharges from the dominant hemisphere to the nondominant hemisphere may lead to the generation of asystole [24, 27]. It isn’t always easy to show the lateralization of epileptogenic focus with scalp electroencephalogram (EEG) [27]. Ictal scalp EEG can show false lateralization in 3-7.5% of patients with mesial TLE.

In 1990 Goodman et al. proved stimulation of the basolateral amygdala provokes BP increase and HR decrease and stimulation of the rostral amygdala provokes depressor effects and variable HR changes [28]. According to Leung et al. stimulation of the cingulate gyrus results in HR and BP decrease [29].

Another important subcortical structure that could be associated with the ictal cardiovascular changes is the thalamus. Guye et al. proved corticothalamic coupling in
human temporal lobe epilepsy [30]. Britton et al. found that the thalamus plays a role in seizure generalization and that this in turn increases the ictal autonomic alterations [25].

Contrary to the lateralization theory, selective activation of either sympathetic or parasympathetic centers during seizures could be responsible for the difference in seizures to exert either a depressor or a pressor response [31]. This is an interesting theory which needs more extensive research. It needs further investigation to elucidate how non-selective seizure discharges can selectively activate sympathetic or parasympathetic centers. This theory alone cannot explain why seizures are sometimes associated with combined pressor and depressor reactions. This could be explained with additional peripheral mechanisms [17]. Such an additional mechanism could be for example that the cardiovascular response to a seizure in turn gives additional sympathetic or parasympathetic discharges which changes the response again.

Another possible pathophysiological mechanism: interictal discharges can alter the parasympathetic-sympathetic balance [17]. The sympathetic as well as the parasympathetic center can become the dominant center. If the sympathetic center becomes dominant, and there is non-selective sympa-tho-parasympathetic activation prior to or during seizures, this could lead to pressor responses. The same is valid for parasympathetic dominance and depressor responses. More research is necessary, because this theory hasn’t been proven yet.

Figure 3: Cortical and subcortical structures involved in the regulation of cardiovascular functions. AN, amygdalian nucleus; CG, cingulate gyrus; IC, insular cortex; PFC, prefrontal cortex; Sy and Psy, sympathetic and parasympathetic efferents. Source: ‘Sevcencu, C. and J.J. Struijk, Autonomic alterations and cardiac changes in epilepsy. Epilepsia, 2010. 51(5): p. 725-37.’
3.1.3.2. Pathophysiology of the interictal autonomic alterations

Some studies show that HRV changes in epilepsy result from interictal autonomic alterations [14, 17]. This includes combined inhibition of sympathetic and parasympathetic tones, inhibition of either the sympathetic or parasympathetic tone or low parasympathetic tone associated with high sympathetic tone [32].

Interictal autonomic alterations could also be the consequence of the use of AEDs. Lotufo et al. performed a meta-analysis of 6 studies that compared patients with AEDs versus patients without treatment [33]. For the LF index as well as the HF index, no significant differences were observed between groups, there was a non-significant trend for lower LF ratios in treated patients. This means that epilepsy treatment did not only not positively influence vagal dysfunction (by increasing HF values), but also has a possible negative influence on sympathetic activity. Hallioglu et al. found that treatment of seizures with AED prevents worsening effects on autonomic cardiac control [34]. On the other hand Persson et al. found carbamazepine treatment can also have a negative effect on HRV [35]. Carbamazepine can suppress the parasympathetic and sympathetic function in patients with epilepsy [36]. The negative effects of AEDs on HRV are confirmed in the article by Sevcencu et al [17]. In short: AEDs may alter autonomic functions or induce proarrhythmic effect [14, 17, 33].

3.2. Cardiac changes related to epilepsy

3.2.1. Ictal changes

3.2.1.1. Ictal HR changes

As mentioned, based on OS or PS dominance, the HR during an ictal event may increase or decrease. Ictal tachycardia (IT) is the occurrence of sinus tachycardia (HR > 100 beats per minute (bpm)) either prior to, during, or shortly after the onset of ictal discharges [1]. Ictal Bradycardia (IB) is the occurrence of sinus bradycardia (HR <50 bpm) either prior to, during, or shortly after the onset of ictal discharges [17]. It has been reported in up to 100% of the seizures [1]. Eggleston et al. reviewed 34 articles that reported the prevalence of IT in patients with epilepsy. The weighted average of the percentage of patients in which IT was present was 82%, the weighted average of the absolute change in HR was an increase of 34,23 bpm per seizure. The HR can go up to 200 bpm [17, 37, 38]. IT has two patterns: continuous and steady increase in HR or abrupt discontinuous increase in HR followed by a continuous steady increase [1, 17, 31]. Leutmezer et al. found that the HR increases steadily in TLE and abruptly in XTLE [31]. Typically, the HR goes back to
normal post-ictal [38]. In some cases, the IT lasts till after the seizure offset [39]. IT can be associated with extrasystoles or atrial fibrillation [17, 37]. As the example of Leutmezer et al. given above already showed, variability exists between several different seizure types [31]. Eggleston et al. calculated that an average of 71% of partial seizures is associated with IT and/or significant HR changes [1]. Within these partial seizures there also is variability, Oliveira et al. said that the complex seizures are more associated with tachycardia than the simple seizures [40]. Opherk et al. showed that secondarily generalized seizures are more likely to be associated with tachycardia and increase the magnitude and acceleration of tachycardia [1, 17, 41]. For the generalized seizures Eggleston et al. calculated a weighted average of 64% of the seizures associated with IT and/or significant HR changes [1]. In partial seizures, several studies showed a bigger increase in HR during TLE than in XTLE [1, 14, 17, 31, 39, 40]. Leutmezer et al. suggest that TLE with a mesial lobe onset causes IT more often [1, 17, 31]. Results of a study conducted by Schernthaner et al. however showed no difference between seizures with a mesial lobe onset and seizures with a lateral temporal lobe onset [42]. Di Gennaro et al. and Mayer et al. showed earlier onset of the IT in the mesial temporal seizures [39, 43].

IB is less prevalent [14, 17, 44]. Devinsky et al. found IB in less than 5% of epilepsy patients. Isik et al. performed a study in children, this study recorded no bradycardia or decreased HR during the seizures [45]. When IB occurs, it can degenerate to asystoles [44]. Schuele et al. found that 0.3-0.4% of the seizures associated with IB result in asystoles [46]. This all points to a low prevalence of IB and associated asystoles. However, not all bradyarrhythmia patients are admitted to the epilepsy unit and the seizure with bradyarrhythmia isn’t always monitored. Rugg-Gunn et al. used implantable loop recordings and found a prevalence of 16% for ictal asystoles [17, 24, 38]. According to Reeves et al. the HR in IB typically drops to 20-40 bpm and accelerates back to normal when the seizure has ended [47]. This IB follows one of two patterns just like IT: continuous and steady decrease in HR, or abrupt discontinuous decrease in HR followed by a continuous steady decrease [38]. According to Serafini et al. IB is most prevalent in seizures with temporal lobe origin and seems stronger in association with bilateral hemispheric seizure discharges [17, 24]. As said before, the study by Isik et al. performed in 18 children, showed no significant difference in HR when seizures of temporal and extratemporal origin were compared [45]. IT or IB can be preceded by the opposite HR change or by oscillatory HR patterns [17, 38, 39].
No clear correlation has been identified between the ictal HR changes and MRI or CT findings. This could be because IT and IB occur without brain abnormality or because the imaging techniques applied are limited [17, 47].

In some cases, IB can lead to asystole [24, 48]. The information about asystole during an epileptic seizure is mostly retrieved from case studies. The pathophysiology remains largely unknown. It could be due to brain hypoperfusion as a consequence of the BP drop [38]. The subsequent hypoperfusion suppresses the cortical electrical activity and therefore terminates the ictal discharge and the associated asystolic episode. It is a dangerous consequence, which should be quickly recognized and treated.
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<td>42 years</td>
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<td>Generalized tonic-clonic seizures</td>
<td>Generalized tonic-clonic seizures</td>
<td>Complex partial seizure originating in right frontotemporal region</td>
<td>Medically intractable partial seizures</td>
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<td>16 seconds</td>
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<td>18.5 seconds</td>
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Table 1: summary of the 5 cases reports discussed below

Serafini et al. describe a case report about a 33-year-old right-handed woman with a right temporo-parietal lobe epilepsy showing a 19 s asystole during a cluster of seizures while being monitored with EEG [24]. The asystole followed IB. The woman was referred because of drug resistant focal epilepsy with numerous falls. In a previous seizure a slight bradycardia was already noted. Physical and neurological examinations were normal. In the first night that she was monitored she experienced 5 seizures, which were all
accompanied by bradycardia and 1 of the 5 seizures was accompanied with a period of asystole. All cardiac assessments were normal.

Mehvari et al. report asystole (respectively 16 and 60 seconds) in 2 right-handed male subjects (13 and 42 years old) with secondary generalized tonic-clonic seizures [48]. In the 13-year-old male, physical and neurological examinations were normal. His MRI showed near symmetrical signal abnormality at parietooccipital regions bilaterally accompanied by mild gliosis and volume loss. The seizure that ended in asystole shared bilateral rhythmic EEG activity with a maximum to the left associated with right-sided clonic jerk and head and eye deviation to the right. The 42-year-old male had a mild paresis in the right upper extremity and in the distal part of the right lower extremity. He had Babinski sign in his right side. Brain CT showed left parasagittal encephalomalacia. The article doesn’t mention whether the patients had IB during the seizure.

Wittekind et al. describe a 32-year-old man recently diagnosed with epilepsy because of a syncopal event after a witnessed fall without tonic/clonic movements [49]. On hospital day 2, EEG/ECG registered a complex partial seizure originating in the right frontotemporal region; the seizure lasted 48 seconds on EEG registration. Thirty-one seconds after ictal onset, there was an episode of profound asystole that lasted 18,5 seconds. The preceding rhythm was normal sinus rhythm without any conduction disturbance with a ventricular rate of 60 bpm slowing to approximately 50 bpm before complete sinus arrest without any escape rhythm. After 18,5 seconds of asystole, sinus rhythm resumed with a brief period of sinus bradycardia followed by relative tachycardia (100 bpm) compared to baseline. Monitoring did not show apnea during the seizure.

Irsel Tezer et al. report a 39-year-old right-handed male with a 4-year history of medically intractable partial seizures [27]. His habitual seizures mostly involved oral automatisms, rarely secondary generalized seizures occurred. His physical and neurological examinations were normal except for atrophy and mild paresis of the right leg as a sequela of polio virus infection. His cranial MRI showed bilateral hippocampal sclerosis. His cardiological examination showed no abnormality. During hospitalization, 3 clinical attacks were recorded. All three showed a decrease in HR and in the first and third of them asystole appeared for 14 seconds. In the first seizure there was ictal EEG onset on the right temporal lobe, the second seizure EEG showed left temporal rhythmic activity and during the last seizure, was no epileptiform abnormality was visible on EEG.
3.2.1.2. Ictal ECG changes

The first study to demonstrate ictal ECG changes dates back to 1939 [50]. This study reported T-wave flattening secondary to a right temporal-lobe seizure.

IT can be associated with ST-segment changes, often with ST-depression [37, 41, 51, 52]. ST-depression can indicate myocardial ischemia, however, with myocardial ischemia, elevated cardiac troponin levels would be expected which was not found by Woodruff et al. [53]. This could indicate that although ST-depression is present, uncomplicated seizures are not associated with significant ischemia.

A large retrospective study done by Zijlmans et al. showed ictal sinus arrhythmia, atrial premature depolarizations, and sinus pauses [52].

Isik et al. found no evidence of long QTsyndrome in the evaluated children [45]. Ictal QTc however was significantly longer than postictal. There were no significant changes in the QTc variance. Several studies do report either abnormal lengthening or shortening of the QTc on ECG with partial seizures [54-56]. QTc abnormalities are associated with increased risk of SCD [54-57].

3.2.2. Inter-ictal changes

The most studied ECG parameter is the QTc interval. Dogan et al. and Neufeld et al. showed that epilepsy is associated with a prolonged QTc interval, while Teh et al. showed that it is associated with a shortened QTc interval [58-60]. Since this interval is affected by drugs, such as anti-depressants, this should be taken into account when evaluating the QTc interval in epilepsy patients (because epilepsy patients tend to take more antidepressants than a healthy control group), which hasn’t been done in the previous studies mentioned [61]. One way to avoid the confounding of these drugs is to compare the epilepsy patients to patients with recurrent nonepileptic seizures instead of with healthy subjects, because these patients also take more antidepressants than the healthy control subjects [62]. Krishnan et al. used this method to examine the QTc interval, the PR interval and the mean QRS axis in a comprehensive study of 195 patients. In this study 35% of control subjects with recurrent nonepileptic seizures took antidepressants, 41% of patients with definite epilepsy took antidepressants. Krishnan et al. also excluded subjects who used fluoroquinolone, macrolide antibiotics, lithium, methadone, amiodarone, sotalol, dronedarone, digitalis glycosides, procainamide, ibutilide, dofetilide, or methylphenidate at the time of admission or who had a urine toxicology screen positive
for cocaine or amphetamines to avoid affected ECG measurements. This study showed that the PR interval was significantly longer in female patients with generalized epilepsy and in patients with localization-related epilepsy, the QTc interval was not significantly different. The QRS axis was more leftward in female patients with generalized epilepsy and in patients with localization-related epilepsy without a change in QRS interval. Average ventricular rates were not significantly different in epilepsy, as were the average P or T wave axes. The study also showed us that patients with localization-related epilepsy had significantly longer PR intervals and a more leftward axis than patients with primary generalized epilepsy. Overall these data demonstrate that patients with localization-epilepsy and female patients with generalized epilepsy have a significantly longer PR interval and more leftward QRS axis than patients with recurrent nonepileptic seizures.

The PR interval is a measure of atrioventricular conduction speed. A prolonged PR interval is most often caused by a delay in the atrioventricular node. Patients with localization-related epilepsy had an approximately 12- to 15-ms increase in PR intervals compared to the control subjects [62]. This number is within normal limits, but nevertheless striking. Cheng et al. and Noseworthy et al. both conducted an epidemiological study that confirmed that longer PR intervals increase the risk of atrial fibrillation, heart failure, pacemaker implantation and all-cause mortality [63, 64]. In these studies patients who used antiarrhythmic agents or cardiac glycosides were excluded. A longer PR interval in epilepsy could be the result of extrinsic or intrinsic cardiac changes [62, 63].

In the study conducted by Krishnan et al. there was only one subgroup with epilepsy that had a significant increase in QTc-interval: the female patients [62]. In this study the patients on the highest number of AEDs had the shortest QTc interval, the meaning of this is not yet known. The QRS axis change was not associated with a change in the actual QRS interval; it is consequently possible that this shift only reflects a surrogate marker of abdominal obesity in patients with epilepsy.

With regard to HRV Lotufo et al. performed 2 meta-analyses on 39 studies comparing LF and HF HRV values of epilepsy patients with control subjects, but also within epilepsy patients [33]. Namely between patients with and without treatment and between controlled and refractory patients. Linear time- and frequency-domain parameters were analyzed. These analyses showed that epilepsy patients presented with lower HF power (-0,69),
suggesting lower vagal activity in these patients. There were no significant differences in LF power. The sensitivity analysis for HF and LF power did not show that the influence of one particular study could be driving the results.

The meta-analyses also analyzed 4 studies that compared well-controlled versus refractory epilepsy patients [33]. No significant differences between groups were observed for the HF and the LF indexes, this however could be a false-negative result. A study conducted by Mukherjee et al. showed namely that patients with refractory epilepsy have higher vasomotor tone, higher sympathetic tone, lower parasympathetic tone and reactivity [65]. Sathya-prabha et al. found autonomic dysfunction in 56.3% of patients with chronic refractory epilepsy. Sathya-prabha et al. also found that the dysfunction of the autonomic system was more severe if the epilepsy was longer lasting [66]. Ansakorpi et al. showed altered complexity of HR in refractory epilepsy patients [32]. Ronkainen et al. conducted a study that showed loss of HRV and suppressed circadian dynamics in TLE, as well in controlled as in refractory patients [67]. Harnod et al. conducted a study in children and adolescents with complex partial seizures [14, 68]. In this study HR abnormalities were much more frequent compared to adults and occurred in 98% of the complex partial seizures. The study also showed a lower HRV in children with chronic refractory epilepsy. For this reason children with epilepsy can be more susceptible to tachycardia and fibrillation.

Meta-analyses showed no particular influence of age and gender for all analyses [69]. Lotufo et al. also analyzed the HRV time-domain parameters. The patients with epilepsy generally had a lower HRV and vagal activity. In addition, refractory patients showed lower SDNN values. As explained before, HRV changes during the interictal period can be the result of the repetitive seizures which cause changes in autonomic centers. More studies are necessary to observe the long-term effects on HRV in epilepsy. A long-term follow-up study from 2011 performed by Suorsa et al. showed harmful HRV changes in patients with refractory epilepsy after a 6-year follow-up. This wasn’t the case when the epilepsy was well controlled, which can be seen as proof to the theory that the repetitive seizures play an important role in the HRV changes. The lateralization theory for the ictal changes was already mentioned above; this theory also exists for interictal cardiac changes [33]. It says that right-sided epilepsy focus results in increased sympathetic activity (tachycardia and high LF) and left-sided in increased vagal activity (bradycardia and high
The study by Lotufo et al. however does not support this hypothesis since there was evidence for lower HF values and similar LF values in both kinds of epilepsy focus.

One of the studies used in the meta-analyses by Lotufo et al. was the study conducted by Mativo et al. in 2010 [70]. This study also measured the pNN50 above all the other variables already processed in the meta-analyses. Twenty drug-naïve, newly diagnosed epilepsy patients were investigated, this showed a decreased pNN50 in epilepsy patients compared to the control group, i.e. there was a decreased percentage of successive normal R-R intervals of more than 50 ms.

Similarly to the ictal autonomic changes, interictal cardiac changes could be the consequence of the use of AEDs. Valproaic acid, an AED, inhibits CYP3A4 [71]. CYP3A4 is an important enzyme, responsible for the metabolism of –among other things–drugs that prolong QTc. Another AED that could prolong QT is phenytoin [72]. Withdrawal of carbamazepine can give a HRV decrease [73].

3.2.3. Pre-ictal changes
Ictal cardiac changes can precede the seizure onset [1, 14, 17, 31, 39, 42, 43, 45, 50, 52].

3.2.3.1. Pre-ictal HR changes
45.7% of seizures monitored by Schernthaner et al. indicated pre-ictal HR changes [42]. Leutmezer et al. reported 75.9% of all seizures had HR changes that preceded ictal onset, with HR changes preceding EEG seizure onset by 14 s in the temporal lobe and by 8 s preceding EEG seizure onset in extratemporal origins of seizures [31]. Di Gennaro et al. stated that in 98% of the total mesial seizures, the HR increase occurred 5 s before the ictal EEG discharge while in 95% of the total lateral seizures, ictal HR increases coincided with the onset of the ictal EEG discharge [43]. Zijlmans et al. reported 23% and Mayer et al. reported 28% of all seizures had an associated pre-ictal tachycardia [39, 52]. Behbahani et al. analyzed 133 epileptic seizures in 12 patients with epilepsy [19]. 82.7% of seizures showed an increase in HR 5 minutes prior to seizure onset and 70.15% showed an increase 10-30 minutes prior to seizure onset. A HR decrease was seen in 8.27% of seizures 5 minutes prior to onset and in 16.31% 10-30 minutes prior to onset.

3.2.3.2. Pre-ictal HRV changes
Furthermore, Behbahani et al. analyzed the HRV parameters of the 133 seizures [19]. Triangular index was noted to be decreased in 33.83% of seizures 5-10 minutes prior to seizure onset and increased in 45.11% of seizures 5-10 minutes prior to seizure onset. The
results present a significant increase in LF/HF ratio relative to baseline in 78.19% of seizures 5 minutes before onset, which indicates a shift in autonomic balance from parasympathetic to sympathetic output. An increase in SD2/SD1 ratio’s was seen in 81.2% of seizures, 5 minutes prior to onset. This was most likely due to reduced parasympathetic and enhanced sympathetic cardiac tone. These findings support the concept that closer segments to the seizure represent a continuum of increasing sympathetic dominance to those segments away from the seizure. The results indicate that during pre-ictal period of seizures, increase of the sympathetic and inhibition of parasympathetic function occurs in most epileptic seizures regardless of epileptic type, especially in closer segments to the seizure (5 minutes).

The finding of kolsal et al. support these findings [74]. They observed significant increases in nLF and LF/HF values before the seizure relative to the daytime values.

3.2.4. Post-ictal changes
Isik et al.’s study performed in 18 children showed that the mean HR remained significantly higher than the mean basal HR during the postictal period [45]. Surges et al. found a persistent imbalance in autonomic function with prevailing sympathetic influence following a secondarily generalized tonic-clonic seizure (GTCS) [55]. Postictal HRV was reduced and HR recovery was significantly slower following secondarily GTCS.

3.3. Implications of epilepsy-related autonomic effects
3.3.1. SUDEP
People with epilepsy may die unexpectedly for unknown reasons at a rate up to 24 times greater than the general population [8, 50, 75, 76]. SUDEP is defined as a sudden, unexpected, nontraumatic, witnessed or unwitnessed death while in a reasonable state of health and without any obvious cause, excluding status epilepticus in whom postmortem examination does not reveal a structural or toxicological cause for death. SUDEP is the leading cause of death in people with refractory epilepsy. The underlying pathophysiology remains unclear. The incidence is estimated to be 2 per 1000 person years in population based studies [50, 77]. In high-risk patients this can go up to 10 per 1000 person years. There are three different pathways thought to cause SUDEP, but none of these on their own explain SUDEP completely. The first pathway is the neurogenic pathway; this mechanism explains how epilepsy can cause severe sympathetic discharge in the posterior part of the hypothalamus and in the ventral and dorsal medulla, which in turn causes lethal secondary neurogenic pulmonary edema. Another mechanism that can explain SUDEP is
the respiratory pathway: central respiratory depression can be the result of the epileptic discharges. This depression can cause central or obstructive apnea and laryngeal spasms. The third pathway is the cardiovascular pathway, which will be explored in view of this manuscript. Besides these three important triggers in the pathophysiology of SUDEP, the evidence for individual predisposing risk factors is growing [4, 14, 76, 78, 79]. The most consistent identified risk factors for SUDEP are the following: poor compliance with AEDs, young age (20-45 years old), early age of onset of seizures, increased refractoriness of epilepsy, presence of generalized tonic-clonic seizures, male gender, nocturnal seizures and being in bed at the time of death [50, 76, 78-80]. Genetic predisposition is probable [80]. SUDEP is twice as prevalent in males, most in African Americans [81]. The risk among patients with presumably chronic, often refractory epilepsy is higher [82]. The highest risk has been reported among epileptic surgery candidates or patients who continue to have seizure-recurrence after brain surgery [50, 83]. Despite the fact that there are known risk factors, they do not allow to predict the occurrence of SUDEP. In heart disease, HRV is a predictor of SCD [50, 80]. Some research suggests that we can draw the same conclusion for SUDEP.
3.3.1.1. SUDEP as a result of acute cardiac effects of seizures

Figure 4: Cardiac factors contributing to SUDEP. Source: Velagapudi, P., et al., *Cardiac arrhythmias and sudden unexpected death in epilepsy (SUDEP)*. Pacing Clin Electrophysiol, 2012. **35**(3): p. 363-70. [50]

Figure 4 gives an overview of all the theorized cardiac factors contributing to SUDEP. This manuscript will discuss some of these factors in depth one by one in the next paragraphs.

**Lock-step phenomenon**

The cardiovascular pathway explains how epileptic seizures can cause cardiac arrhythmias including ictal asystole and the lock-step phenomenon [50, 84]. The lock-step phenomenon occurs when seizure induced activation of the central ANS results in a synchronization of cardiac autonomic discharges with epileptogenic activity, suggesting a possible mechanism of spreading of electrical abnormal propagation, either interictal or ictal, from the cortex to ANS regulatory centers, able to generate arrhythmogenic potentials. The phenomenon can cause lethal bradyarrhythmia or asystole [50]. Some
studies found that SUDEP was more likely to occur during sleep [85, 86]. Nobili et al. searched for a possible link between SUDEP and sleep. Their study found that the lock-step phenomenon can be amplified during non-rapid eye movement. This causes periods of cortical and autonomic arousal during the sleep. Seizures during sleep could also be responsible for a sudden switch from a predominant vagal tone to an extreme sympathetic tone which might trigger lethal arrhythmias [50, 72].

**HR changes**

To date, only one large study has investigated the incidence and mechanisms of SUDEP and near SUDEP in epilepsy monitoring units on an international level [8]. This study is called the MORTEMUS study. The MORTEMUS study used video electroencephalogram (vEEG) and cardiorespiratory monitoring to evaluate epilepsy patients. Nine near-SUDEP cases and 18 SUDEP cases were assessed. In all the SUDEP cases a GTCS preceded the cardiorespiratory arrest. The sequence of respiratory and cardiac events that led to terminal cardiorespiratory arrests could be ascertained in 10 patients with monitored SUDEP. These patients all experienced bradycardia starting between 15 and 140 s after seizure onset; culminating in asystole in 9 patients. In 3 patients this asystole was terminal, the other 6 patients experienced a spontaneous reverse of the cardiorespiratory arrest after a median duration of 13 s of asystole. In these 6 patients restored HR showed persistent bradycardia until terminal asystole in 2 patients, while in the other 4, bradycardia resumed only after the onset of terminal apnoea. This in turn leads to terminal asystole. In conclusion: a GTCS triggers central apnoea, severe bradycardia, transient asystole and postictal generalized EEG suppression, which in turn can lead to SUDEP.

Tachycardia and development of tachyarrhythmia during seizures is another possible cause of SUDEP. Nei et al. indicated that ictal HR were higher in SUDEP patients than in controls [37]. Ventricular tachyarrhythmia could be the result of pathological cardiac repolarization occurring in epilepsy without an underlying cardiac disease [50]. This can be a possible cause of SUDEP.

**ECG changes**

Ventricular tachyarrhythmia can be a causal factor in SCD [50, 87]. The onset of ventricular tachyarrhythmia could be facilitated by known seizure-related alterations of cardiac repolarization, including both prolongation and shortening of QT intervals as well as increased QT dispersion on an ECG [87]. According to Natelson et al. seizures can
cause QT abnormalities [50, 88]. QT dispersion has been seen in up to one third of people with epilepsy [87]. The exact effect of epilepsy on the interictal QTc interval is not yet known completely. The QTc prolongation associated with epilepsy seen in some studies could be because of cerebral dysregulation, cardiorespiratory interactions, and release of stress hormones with seizures [56, 89]. Seyal et al. observed that the same patient can sometimes have a seizure accompanied by oxygen desaturation below 90% during the post-ictal period and sometimes have a seizure without oxygen desaturation [57]. They analyzed the ECG during the 1 min prior to seizure onset and during the ictal-postictal period. Consecutive QT intervals were measured. An abnormally prolonged QTc was found during the post-ictal period in several patients, which was 4 times more present in the seizures accompanied with desaturation compared to those without desaturation. An abnormally shortened QTc also seen in some patients 2 times more in post-ictal periods accompanied with desaturation. Another parameter to measure QT is the QTd, this is the difference between the longest and the shortest QT intervals within an ECG [90]. Although Akalin et al. and Neufeld et al. found an increased QTd in people with epilepsy compared with controls, Extramiana et al. found this increased QTd not to significantly associated with SUDEP [59, 90, 91]. In contrary to the mixed results about the link between epilepsy, QT dispersion and SUDEP, the link between SUDEP and short QT syndrome is more clear [50, 91]. Short QT syndrome is a syndrome that shortens the refractory period. This can cause ventricular fibrillation and SCD. When a patient has short QT syndrome in seizures, SUDEP can occur as a consequence of the ventricular fibrillation.

Another electrocardiography indicator of this pathologic cardiac repolarization are ventricular late potentials [87]. According to a study by Surges et al. 22 of 45 people with epilepsy displayed ventricular late potentials compared with one of 19 controls.

The last measure of cardiac repolarization is T-wave alternans (TWA) [87]. This reflects the beat-to-beat variability of morphology and amplitude of the T-wave and is an independent predictor for sudden death and cardiovascular mortality. In people with pharmacoresistant epilepsy, TWA has been found to be significantly enhanced for at least 15min after cessation of a convulsive seizure.
Cardiac ischemia
This is most common in epilepsy patients that already have an underlying coronary artery disease. Repetitive seizures may cause ischemia and myocardial infarction [92].

Takotsubo syndrome
Takotsubo syndrome (TKS) or high stress induced cardiomyopathie occurs after a stressful event, potentially after repetitive seizures [50, 93]. The mechanism isn’t yet fully understood. The criteria for TKS are: reversible akinesis or dyskinesis of the left ventricular segment, associated with new ECG ST-segment or T-wave abnormalities mimicking acute myocardial infarction [94]. TKS predisposes patients to embolism, cardiogenic shock, heart failure, arrhythmia and sudden death. Dupuis et al. found 59 documented cases of possible TKS secondary to seizures, including 4 cases of relapsing TKS after new seizures. One case was lethal. Patients who have had TKS have a high risk of relapse. The link between TKS syndrome and SUDEP is suspected, but not yet proven.

3.3.1.2. SUDEP as a result of an inappropriate ANS response

Changes in autonomic system
As said before, a seizure can lead to an imbalance between the sympathetic and the parasympathetic output. One way to demonstrate this, is what is called ‘Cardiac sympathetic imaging’ [95]. This is an imaging technique that uses meta-iodobenzylguanidine (MIBG). A reduction in cardiac uptake of MIBG could point to an increased sympathetic nervous discharge. Such reductions were shown by Drushki et al. interictally in patients with chronic TLE. Kerling et al. specifically showed a pronounced reduction in cardiac MIBG uptake in patients who had experienced ictal asystole [50, 96]. This could mean that an impaired postganglionic sympathetic innervation in patients with epilepsy is a factor that can cause SUDEP.

HRV
In analogy to the strongly predictive nature of low HRV for increased mortality in heart disease and its association with increased risk of lethal arrhythmias and SCD, Tomson et al. and Mukherjee et al. found evidence that low HRV can also be a risk factor for SUDEP [65, 97]. Surges et al. however reported that there were no significant differences in HRV between SUDEP patients and their controls [50, 87]. DeGiorgia et al. conducted a study to test whether HRV is associated with SUDEP risk in patients with severe epilepsy [80]. The study used SUDEP risk as a surrogate marker for SUDEP and it based this surrogate
marker on 7 validated risk factors for SUDEP. In this study, the 18 subjects with poorly controlled partial-onset seizures had a RMSSD that was inversely correlated with the SUDEP-7 inventory score. RMSSD is associated with short-term, rapid changes in HR and is correlated with vagus-mediated components of HRV.

As said when discussing the interictal cardiac changes, there is growing evidence that vagus-mediated autonomic control of the heart is defective in people with severe epilepsy. This can be derived from, among other things, the low HRV in these patients [80]. Diminished vagus influence could lead to inadequate protection from exaggerated sympathetic stress, which occurs during seizures. Furthermore, hypoxia could occur during seizures and be sustained in some cases. The combination of the sustained hypoxia and the diminished vagus influence could lead to myocardial injury and lethal arrhythmias.

3.3.1.3. Predisposing factors to SUDEP

Antiepileptic medications
Some studies show that drug therapy, especially polytherapy, could be an independent risk factor for SUDEP [33, 50]. Valproaic acid and phenytoin can cause a prolonging of QTc which in consequence can cause ventricular tachyarrhythmias [71]. Nobili et al. showed that phenytoin can cause an atrioventricular block or a QT prolongation [72]. Langan et al. conducted a large case-control study of 154 autopsy-confirmed cases of SUDEP. The research showed that the absence of treatment with antiepileptics was a strong risk factor for SUDEP [83]. The MORTEMUS study said antiepileptic drugs were reduced by more than 50% in all of the 9 patients who never had GTCS in the past or were free of such seizures for at least 3 months before vEEG; and completely withdrawn in five, suggesting a role of such withdrawal in promoting the terminal seizure and associated cardiorespiratory arrest [8].

Genetic factors and channelopathies
Ion channels in brain and heart are widely examined in the context of SUDEP. Pathologies of these channels could be related to epilepsy as well as cardiac arrhythmias, thus forming a potential base for SUDEP [50]. Gene mutations associated with cardiological conditions have been found postmortem in up to 13% of people with epilepsy dying suddenly [87]. KCNQ1 is a heart-brain potassium channel gene [98]. Mutations of this gene are known to cause problems in the heart. Goldman et al. studied KCNQ1-mutant mice and found that
this channel is in high abundance in brain regions that are susceptible to epilepsy. Electrical discharges in these regions display abnormalities characteristic of epilepsy often occurring at the same time as abnormal heartbeats. This hints that SUDEP may result from common excitability defects in the brain and in the heart. The SCNIA gene encodes an alpha-unit of brain-type tetrodotoxin-sensitive voltage gated Nav1.1 sodium channel with potential functional effects on cardiac function either directly or through activation of the ANS [99]. Pathological expression of the SCNIA gene can cause SUDEP. Other genes in which genetic variation causes brain-heart dysfunction that could lead to SUDEP are: the KCNA1 gene, SCN8A, HCN2, PRRT2, long GT syndrome genes, KCNQ1, KCNH2, SCN5A and RYR2 [50, 87, 100]. Brugada syndrome could possibly also play a role in SUDEP.

3.3.2. Seizure detection
3.3.2.1. Seizure detection methods
Different methods can be used for seizure detection. Current golden standard is EEG [9]. A downside is that this is a rather uncomfortable method for the patient and that it is not achievable in a long-term setting. At this moment EEG monitoring can only be used in hospital settings, home monitoring via EEG is currently being investigated. Therefore, ictal signatures outside the brain are of relevance. One of the methods that relies on such an ictal signature is accelometry. This device measures changes in velocity and direction. Accelometry is able to detect ongoing motoric seizures. Another method is the analyzeation of motion, velocity, angular speed, etc [101]. These systems are placed on the joints of patients. Accelometry and motion detection systems can only detect a seizure following onset.

3.3.2.2. Seizure detection methods based on epilepsy-related cardiac changes
Changes in HR are easy to monitor and could therefore be the ideal seizure monitoring parameter. A study conducted by Jansen et al. in children however showed that the sensitivity of the ECG changes is low and that there is only a very limited time between the onset of the IB and IT and the onset of the seizure [102]. In contrast to HR, ictal changes in HRV might be more valuable. Kolsal et al. found that mostly the frequency domain measures were important in the pre-ictal period [74]. They compared the frequency domain measures 1h before seizure with the exact time period on another day when there was no seizure during that time of the day. They saw significant increases in LF and LF/HF ratios 1h before seizure. This leads to the possible conclusion that a
predomination of the sympathetic nervous system can be seen 1 hour before the seizure. This could be used to predict a seizure even 1 hour beforehand. Of course, much more research on this domain is necessary [74]. The final ECG parameter that can be used to predict seizures is the ECG morphology, but no research has been conducted on this yet [103].

Another method that uses the pre-ictal autonomic changes isn’t based on ECG, but assesses cervical vagus electroneurogram (VENG) [104]. VENG is a method used to visualize directly recorded electrical activity of neurons in the VN. The electrical activity generated by neurons is recorded by the electrode and transmitted to an acquisition system, which usually allows to visualize the activity of the neuron. Each vertical line in an electroneurogram represents one neuronal action potential. Harreby et al. conducted a study in anesthetized rats in which they found that VENG was able to detect seizures in a timely manner. The period after pentylenetetrazol (PTZ) infusion was divided into categories based on the EEG activity. The second and third categories were called S2 and S3 respectively. The VENG activity in the different categories was then compared to each other. S2 consisted of clusters of spikes with silent periods in between. S3 consisted of the muscle twitches. Seizures were early detected using the VENG, 84 ± 55 s prior to the onset of S2 and 103 ± 51 s prior to the onset of S3 in all PTZ-treated rats, whereas no false positives were seen in the control rats.

3.3.2.3. Seizure prevention
Seizure detection systems can be coupled to warning systems, to alert the patient or more importantly caretakers when a seizure occurs, the response system could also initiate an activity, such as medication administration or activation of a neurostimulator, which could potentially preemptively stop a seizure from developing [103]. This needs further investigation.

3.3.3. VNS response prediction based on ictal autonomic changes
3.3.3.1. What is VNS
About 40% of patients with epilepsy do not respond adequately to medical therapy seizures [5, 105, 106]. This is called medically refractory epilepsy. These patients should take further evaluations to see if they are potential surgical candidates. Only in a minority of patients resective epilepsy surgery is indicated, for the remainder of patients VNS is a third line treatment option that allows to reduce seizure frequency and improve quality of life.
The efficacy of VNS was proven in a study performed by Ben-Menachem in 1994 [107]. Ramsay et al. (part of the same international study group on VNS as Ben-Menachem) proved the safety, side effects and tolerability of VNS, also in 1994 [108]. Long-term efficacy of VNS was proven in a long-term study (mean duration of VNS therapy 10.4 years) by Elliot et al. showing a mean decrease in seizure frequency at last follow-up of 76.3% [109]. Another interesting effect from VNS, apart from the reduction in seizures, is a mood improvement in the patients [5, 110]. Even in patients who didn’t have an effect of VNS on their seizure frequency. Further research to see if this result can be repeated and as to how this is caused is necessary.

The mechanism of action of VNS in relation to the anatomy of the VN and is afferent projections has been studied extensively (for review see [111]). The VN plays an important role in the functions of the heart, in particular in the innervation of the cardiac pacemaker cells [112]. The right efferent VN innervates the sinoatrial node and the left efferent VN innervates the atrioventricular node. VNS is implanted on the left side. The afferent fibers from the nerve follow following route: viscera ➔ NTS ➔ locus coeruleus (LC) ➔ hypothalamus, dorsal raphe, nucleus ambiguus, DMN of the VN, amygdala, and thalamus ➔ IC. Hassert et al. and Manta et al. conducted studies in rats that showed that with VNS there is a local increase in extracellular norepinephrine (NE) levels of the hippocampus, amygdala or prefrontal cortex [113, 114]. An increased c-Fos expression was also seen in the LC [115]. The increase in NE levels and c-FOS expression suggests the LC forms a link between the action of VNS and it’s antiepileptic effect. Krahl et al. also found that LC lesions suppress the seizure attenuating effects of VN stimulation [116]. Vonck et al. found ipsilateral thalamic inhibition in VNS stimulation [117]. This ipsilateral thalamic inhibition may play a role in the antiseizure effect of VNS.

3.3.3.2. Technical aspect of VNS

The left VN may have a lesser impact on the heart than the right VN, therefore a generator is surgically implanted under the left clavicula with 2 subcutaneous electrodes stimulating the left VN in the neck [118]. Stimulation typically occurs in a cycle of 30s every 5 minutes.

3.3.3.3. Relation between ANS, VNS and the heart

Since the efferent fibers of the left VN innervate the atrioventricular node, VNS may have an effect on the heart [105].
BP
First, VNS was found to have an effect on the BP [10]. Cadeddu et al. conducted a study in 10 patients to evaluate cardiovascular modulation during VNS. Doppler imaging, 24-h BP monitoring and HRV evaluation were performed. A significant increase in BP was seen, both during night and day. This can be seen as a result of the connection of the VN with visceral reflexes, modulating BP [119, 120].

HR
Second, VNS affects the instantaneous HR. In the study of Frei et al. consistent bradycardia was seen in 3 patients and a biphasic response with first tachycardia followed by bradycardia was seen in the two other patients when the VNS started stimulating the nerve [121]. A study conducted in rats by Agarwal et al. observed two types of acute VNS effects [122]. First, there was a lowering of the immediate HR which lasted for approximately 10 s, and next, there was a transient increase in HR. VNS also effects the average HR [122]. Agarwal et al. noticed a decrease in the average HR during the first 1.2 days following the start of VNS followed by an increase over 3.9 days. This increase remained for the whole duration of the VNS period and returned to normal afterwards.

Autonomic modulation: HRV
Third, VNS may have an effect on HRV [11, 12]. Cadeddu et al. found a significant increase in SDSD, RMSSD and pNN50 at night, these parameters are correlated with vagus-mediated components of HRV [10]. A lower LF/HF ratio was also seen in all patients, however this result was non-significant. The lowest ratio was seen at the moment the BP was the highest. Another study on the effect of VNS on HRV was a study conducted in 5 subjects by Frei et al. [121]. This study showed mixed results: 2 patients showed significant decreases in HRV, 2 patients showed significant increases and the last remaining patient a decrease at 2,0 mA and a significant increase at 3,25 mA. A case study by Koenig et al. in an 8 year-old girl with Lennox-Gastaut-Syndrome showed that her originally extreme impaired HRV increased drastically with VNS [123]. This indicates an improvement of autonomic modulation after VNS. Modulation capacity is the ability to change between sympathetic and vagal influences.

ECG
A reduction in TWA is seen in patients after VNS implantation [18, 105]. TWA is a measure of cardiac repolarization. This reflects the beat-to-beat variability of morphology
and amplitude of the T-wave and is an independent predictor of risk of sudden death and cardiovascular mortality [87]. The reduction in TWA proves that there is a reduction in cardiac electrical instability [18, 105]. Krishnan et al. saw that the presence of an active VNS device did not significantly alter baseline ECG variables compared with other patients with epilepsy [62].
4. Discussion

4.1. Cardiac changes related to epilepsy

4.1.1. Pathophysiology of autonomic alterations in epilepsy

Epileptic seizures are associated with several changes in autonomic functions, which may lead to cardiovascular changes before, during or after the ictal event [45]. Many studies have investigated the effects of epilepsy on the autonomic control of the heart. The results are controversial. It’s still unclear whether imbalance of sympathetic, vagal, or both systems is present in epilepsy [33]. Several theories exist regarding the pathophysiology of the ictal autonomic alterations, including the lateralization theory, the selective activation of either sympathetic or parasympathetic centers during seizures and the theory saying interictal discharges can alter the parasympathetic-sympathetic balance [26]. None of these theories are conclusive. Evidence for the lateralization theory has only been reproduced in electrically induced seizure, the mechanism of how non-selective seizure discharges can selectively activate sympathetic or parasympathetic centers is still under debate and interictal discharges haven’t been proven to cause alteration of the parasympathetic-sympathetic balance. None of these theories alone can fully explain all the autonomic effects seen in epilepsy. In reality, all of these theories may be partly true, and the real pathophysiology of the autonomic alterations may consist of a combination of several theories. Future studies should observe ictal as well as interictal parameters.

The exact brain structures involved in the pathophysiology haven’t been identified yet. Important structures that are thought to play a role are: thalamus, amygdala, insula and gyrus cingulatum [13, 14]. More research is necessary to get more certainty about the exact involvement of these structures.

AEDs may alter autonomic functions or induce proarrhythmic effect, which makes the use of AEDs a confounding factor in studies of the pathophysiology of the interictal autonomic alterations.

4.1.2. Ictal cardiac changes related to epilepsy

IT is the most often reported ictal change. A great inter- and intra-individual variability exists, thus, although a patient may have a history of IT, not every seizure may be associated with increased HR [1]. IB is a less prevalent, but important ictal cardiac change. IB can lead to ictal asystole, which can be fatal. Because most of the knowledge we have on ictal asystole is from case studies, it is possibly an underestimated consequence of seizures. It’s not possible for this manuscript to draw definite conclusions.
on asystole during an epileptic seizure, because the information about asystole during an epileptic seizure is mostly retrieved from case studies. A large prospective study is necessary to be able to understand the prevalence and the consequences of ictal asystole in epilepsy patients. Due to the fatality of ictal asystole, the diagnosis of ictal asystole requires high clinical suspicion. Any case of syncope should alert the physician to the possibility of ictal asystole and promote a cardiac work-up.

A great range of definitions of IT and IB exists between different studies, thus making the comparison of results across articles difficult. Each study wielded other exclusion criteria.

IT can be associated with ST-segment changes, often with ST-depression [37, 41, 51, 52]. ST-depression could indicate myocardial ischemia, elevated cardiac troponin levels are a consequence of this ischemia. Woodruff et al. didn’t find elevated cardiac troponin levels, according to Woodruff et al. this could indicate that uncomplicated seizures are not associated with significant ischemia [53]. However, the article didn’t state whether ST-depression was present in these patients, which could mean that the studied patients didn’t have ST-depression. As a consequence, the ST-depression seen in other studies can’t be linked to the troponin levels in the study by Woodruff et al. Another study should be conducted measuring both ST-segment changes and cardiac troponin levels.

Several studies report either abnormal lengthening or shortening of the QTc on ECG with partial seizures [54-56]. Isik et al. however didn’t find any QTc abnormalities [45]. Most of the studies presented were performed on adults, but the study of Isik et al. was performed in children. It can’t be known for sure that the results in children can be extrapolated to adults and vice versa. The QTc interval is affected by a large group of different drugs, making it difficult to draw definite conclusions from QTc interval changes. Future studies should try to take these confounding drugs into account when analyzing the QTc interval.

4.1.3. Inter-ictal changes
Common interictal changes reported are: QTc interval changes [58-60], prolonged PR interval [62] and lower HRV [33]. A prolonged PR interval may increase the risk of atrial fibrillation, heart failure, pacemaker implantation, and all-cause mortality. These findings support the need for more definitive premortem cardiac structural imaging studies such as echocardiography and/or cardiac magnetic resonance imaging to identify individuals that
may be at risk. Since patients taking antiarrhythmic agents or cardiac glycosides were excluded in these studies, this prolonged PR interval may be intrinsic to epilepsy itself.

The precise pathway to the inter-ictal HRV changes remains unclear. A hypothesis suggests that while LF is the result of both parasympathetic and sympathetic regulation, HF is the result of vagal regulation of the heart and the LF/HF ratio gives us more information about the sympathetic regulation on the heart [19]. This hypothesis remains heavily debated. Extensive research has to be conducted in the future to find the definite link between the LF and HF component and the parasympathetic and sympathetic regulation. With this link the HRV could be used as a standard parameter to measure the ANS output on the heart in all studies concerning cardiac changes in epilepsy.

4.1.4. Pre-ictal changes
Common pre-ictal changes reported are: HR changes and a significant increase in LF/HF ratio [19]. All studies of timing of HR increase in relation to seizure onset however are subject to potential sampling error involving capture of true seizure onset. This means pre-ictal changes can either be underreported or over reported.

4.1.5. Post-ictal changes
Few research has been conducted concerning the post-ictal changes in epilepsy. One study showed postictal HRV reduction and a slow HR recovery following secondarily GTCS [55]. Impaired HR recovery after exercise and reduced HRV both predict cardiac mortality and SCD. Thus, more research should be conducted regarding the post-ictal changes to investigate this impaired post-ictal HR recovery and the link with SUDEP.

4.2. Implications of epilepsy-related autonomic effects

4.2.1. SUDEP
SUDEP is a serious consequence of epilepsy. The cardiovascular pathway is thought to play a role in the cause of SUDEP [50, 77]. Only one large study has investigated the incidence and mechanisms of SUDEP and near SUDEP in epilepsy monitoring units on an international level [8]. Ideally, more international studies should give more clarity on the pathways leading to SUDEP.

4.2.1.1. SUDEP as a result of acute cardiac effects of seizures
Acute cardiac effects theorized to play a role in the pathophysiology of SUDEP are: lock-step phenomenon, HR changes, ECG changes, cardiac ischemia and Takotsubo syndrome. The lock-step phenomenon has been deducted from experimental evidence in animal
models, more extensive research ideally in humans is necessary to prove the existing of this phenomenon and the link with SUDEP. Not much data exists on seizure-related fatal ventricular tachyarrhythmias, meaning more research is necessary before conclusions can be made on the link between the tachyarrhythmias and SUDEP. ECG changes are confirmed in epilepsy patients. The mechanism to how these changes come to exist are less clear. As said before, drugs are a big confounding factor. A possibility is that the QTc interval changes are a result of the effects of AEDs and are independent of epilepsy itself. Cardiac ischemia in epilepsy patients isn’t common and therefore can’t be the explanation of SUDEP. In conclusion: a definite link between these acute cardiac effects in epilepsy and SUDEP has not been proven. More research should be conducted to find the definite link between epilepsy and these cardiac changes and to find the link between these changes and SUDEP.

4.2.1.2. SUDEP as a result of an inappropriate ANS response

An association was seen between the SUDEP-7 score and the HRV. This is an important finding, however this study contained some limitations making it necessary to perform the study again in a larger population. The SUDEP-7 score requires refinement in the future, since not all risk factors for SUDEP have been discovered yet.

4.2.1.3. Predisposing factors to SUDEP

Some studies show that drug therapy, especially polytherapy, could be an independent risk factor for SUDEP. This points to a need for screening for cardiac conditions in epilepsy patients before treatment [14, 17, 33, 50].

Genetic abnormalities are known to play an important role in SUDEP. It is obvious that identification of these genetic factors can help us to calculate the risk of SUDEP in an individual patient and can even help us in the search for therapies to prevent SUDEP. Molecular autopsy studies of SUDEP victims should be considered in future clinical trials.

4.2.1.4. The prevention of SUDEP

As evident from the above, there are still a lot of questions as to understanding the pathophysiology of SUDEP, risk factors and identification of high-risk population. A growing knowledge of these things will allow to develop preventive measures, to prevent SUDEP. There are two types of preventive measures [124, 125]. Primary measures prevent the happening of an arrest. Examples of such preventive measures could be: good control of seizures, avoidance of trigger factors, adherence with medication, improvement
in quality of life, reduction of stress, participation in physical activity and sports, … A second type of measurements are the measures that prevent SUDEP after the cardiac arrest. For example: supervision at night for patients at high risk, supervision after a tonic-clonic seizure, family members’ knowledge of CPR

Identification of high-risk population is crucial to be able to prevent SUDEP in the future. According to all the information above, it should be possible to quantify SUDEP risk among patients with epilepsy. Up to now this has not been a complete success [100, 126]. The possibility of a connection between an interictal sympathetic and parasympathetic dominance and the ictal cardiac effects has been described previously in this manuscript. This leads to the conclusion that HRV monitoring in patients with epilepsy could be used to assess cardiovascular risk during seizures [17].

Biomarkers might be helpful to identify the high-risk population for SUDEP. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [127]. Such a biomarker is currently lacking. If we would be able to identify a genomic biomarker for SUDEP, we could give patients personalized therapeutic options based on their genome [100]. Recent studies have been searching for neurocardiac genes that play a role in SUDEP. More research is still necessary to evaluate just how much these genes contribute to SUDEP and how these genes can be used for risk assessment. The identification of reliable genomic biomarkers for SUDEP is challenging since epilepsy is a genetic complex and heterogeneous disease. Some gene variants may even be beneficial, serving as genomic biomarkers indicative of protection against SUDEP. Thus, genomic biomarkers will probably need to be considered as part of a comprehensive molecular profile, rather than in isolation.

A reliable system of risk stratification would allow to identify epilepsy patients with high SUDEP risk. Until such a system is developed, it is unclear who should undergo extensive cardiovascular monitoring and who shouldn’t. The role of pacemakers in preventing death in high-risk epilepsy patients hasn’t been established [50]. Rugg-Gunn et al. conducted a prospective study in refractory epilepsy patients with implantable loop recorders [38]. This study showed that the frequency of appearance of IB with asystole could be reduced with a prophylactic permanent pacemaker. However as it is unclear whether this asystole is responsible for SUDEP, this doesn’t guarantee a complete risk reduction of SUDEP.
Moreover, the low incidence of ictal asystole, makes the usefulness of prophylactic pacemaker implantation questionable [128, 129]. Since tachyarrhythmia such as ventricular tachycardia and ventricular fibrillation may be an important cause of SUDEP in long-standing epilepsy, the implantable cardioverter-defibrillator (ICD) is hypothesized to be useful in the prevention of SUDEP [50, 130]. An ICD continually monitors heart rhythm and can send low- or high-energy electrical pulses to correct an abnormal heart rhythm. ICDs will initially send low-energy pulses to restore heart rhythm, but switch to high-energy pulses when the low-energy shocks are ineffective. Pacemakers, however, only give low-energy electrical pulses to restore regular heartbeat. Therefore, ICDs are thought to be more effective in patients at high-risk for SUDEP caused by arrhythmias. There’s no proof of its usefulness yet. Badheka et al. however suggested a potential role of ICD placement for primary and secondary prevention of SCD in epilepsy.

4.2.2. Seizure detection

4.2.2.1. Seizure detection methods based on epilepsy-related cardiac changes

The LF and LF/HF ratios of the HRV seem to be good parameters to use as a seizure detection method. However, in ECG monitoring it can be difficult to make the difference between normal physiological arousals and the arousal because of a seizure. This may be ameliorated by combining it with a chest accelerometer [103]. VENG can also be used as a parameter for seizure detection, although not much research has been conducted on VENG detection in epilepsy.

4.2.2.2. Detection systems in the context of SUDEP

Seizure detection systems can be coupled to warning systems, to alert the patient or more importantly caretakers when a seizure occurs [103]. Such a closed loop system consists of a measuring or detection device, data transmission, data processing, and a corrective response within an output loop. In this case the response is alarming the caretaker. This caretaker can then enable a proper position, stimulate the patient, seek help when necessary. When necessary a trained caretaker can give CPR, administrate medication, clear the airway, reducing the risk for SUDEP [83]. The timescale involved with the early neurovegetative breakdown that leads to SUDEP after GTCS suggests a potential window for life-saving intervention, in as much as all patients in whom CPR was started within 3 min after cardiorespiratory arrest were successfully resuscitated. This means it would be useful to teach CPR to the caretakers and family of patients with epilepsy.
4.2.2.3. Seizure prediction and prevention

Since significant increases were seen in LF and LF/HF ratios in the pre-ictal state up to 1h before seizure, it may be possible to predict an upcoming seizure up till 1h beforehand. This is an interesting domain to conduct research on in the future. Further research is also necessary to investigate the pre-ictal ECG morphology and pre-ictal VENG changes in the interest of seizure detection. Ideally, a detection system should be developed that may detect a seizure in the pre-ictal state. Such a detection system can become incorporated in a closed-loop system in which the response system could initiate an activity, such as medication administration or activation of a neurostimulator, which could potentially preemptively stop a seizure from developing. Such a cardiac-based seizure detection algorithm that automatically triggers VNS has been investigated in an epilepsy monitoring unit setting by Boon et al [131]. Thirty-one patients with drug resistant epilepsy were evaluated. The closed-loop system used in the study detected the patients HR and triggered the VNS when ictal HR increases of at least 20% were registered. The detection algorithm had a sensitivity of at least 80% for detecting ictal HR increases. In this study the median observed latency ranged from 6 to 35 seconds after seizure onset, meaning the detection and stimulation occurred prior to clinical seizure onset in only a minority of patients. After 3–5 days of treatment with closed-loop VNS only, a statistically significant reduction in seizure severity was observed. An overall improvement in the quality of life was found at the 12-month follow-up visit. This demonstrates that ECG-based seizure detection can provide a valuable addition to the currently available treatment modalities. Larger population studies as well as longer follow-up data are necessary to draw definite conclusions.

4.2.3. VNS response prediction based on ictal autonomic changes

Studies show that VNS is useful in preventing seizures [5, 105, 106]. The exact mechanism of action of VNS in reducing epileptic seizures remains unclear.

4.2.3.1. Relation between ANS, VNS and the heart

VNS has shown to have effect on the heart in epilepsy. Effects that were seen were: raised BP [10], changes in HRV parameters [10, 121, 123], changes in HR [122], reduction in TWA [18, 105]. This shows a relation exists between ANS, VNS and the heart. Shromer et al. hypotheses that VNS is cardioprotective in patients with epilepsy, but this theory hasn’t been proven yet. Currently, VNS is even being investigated as a therapeutic option in heart failure [132]. A case study by Koenig et al. in an 8 year-old girl with Lennox-Gastaut-Syndrome showed that her originally extreme impaired HRV increased drastically
with VNS. These studies also show us there is a large inter-individual difference in the effect of VNS on HRV and more research should be conducted [10, 121, 123].

4.2.3.2. Ictal autonomic changes as a predictor of VNS response
Unfortunately not all patients respond to VNS and predictors of response are largely unknown [110, 133, 134]. Because a relation exists between ANS, VNS and the heart; it is possible that the VNS response is dependent on the ictal autonomic changes existing in the patients with epilepsy. With the discovery of this link, ictal autonomic changes could be used as a predictor of VNS response. The thalamus and the LC are thought to play a role in the antiepileptic effect of VNS. The LC is part of the sympathetic ANS and thalamus is located on the efferent pathways of the VN to several cortical areas, meaning the thalamus and the LC may be the common link between the autonomic changes in epilepsy due to discharges in the cortical areas and the antiepileptic effect of VNS.

4.3. Conclusion
Cardiac changes in epilepsy have been proven to exist, however a lot of uncertainty still exists concerning these changes and their pathophysiology. Researchers believe these changes have implications in three important domains: the prevention of SUDEP, seizure prevention and VNS response prediction. More research should be conducted regarding these implications.

Epileptic seizures are associated with several changes in autonomic functions, which may lead to cardiovascular changes before, during or after the ictal event [45]. Many studies have investigated the effects of epilepsy on the autonomic control of the heart. The results are controversial. Several theories exist regarding the pathophysiology of the ictal autonomic alterations, however none of these theories are conclusive and none of the theories alone can fully explain all the autonomic effects seen in epilepsy. More research is necessary to get more certainty about these theories and about the exact contribution of the brain structures involved in the pathophysiology. Future research should try to eliminate AEDs as a confounding factor.

IT and IB have been seen often in epilepsy, hypothesis is that IB can lead to ictal asystole. A large prospective study is necessary to be able to understand the prevalence and the consequences of ictal asystole in epilepsy patients. The link between the ST-depression during IT and potential myocardial ischemia in epilepsy should be further examined. The precise pathway to the inter-ictal HRV changes should be investigated in the future, as
well as the definite link between the LF and HF component and the parasympathetic and sympathetic regulation. More research should also be conducted regarding the post-ictal changes to investigate this impaired post-ictal HR recovery and the link with SUDEP.

The exact pathway and all the involved causal factors leading to SUDEP should be further researched. Furthermore it is necessary to identify all the risk factors for SUDEP to be able to take preventive measures in the high-risk population. The identification of reliable genomic biomarkers for SUDEP can aid to identify this high-risk population.

In the context of seizure prevention, a detection system should be developed that may detect a seizure in the pre-ictal state. Such a detection system can become incorporated in a closed-loop system in which the response system could initiate an activity, such as medication administration or activation of a neurostimulator, which could potentially preemptively stop a seizure from developing.

The relation between ANS, VNS and the heart needs to be further examined, as well as the ictal autonomic changes in the context of the prediction of VNS response.
5. References


Appendix

One common way to analyze HRV is by time domain measures. The simplest and most often used measures are the instantaneous heart rate, intervals between normal successive sinus beats (NN), the standard deviation of all normal RR intervals (SDNN), average HR, mean NN interval, and the difference between the longest and shortest NN interval. SDNN is typically measured over 24 hours and reported in units of ms. Two variants of the SDNN are the SDNN index and the SDANN index. The SDNN index is the mean of all the 5-minute standard deviations of NN intervals during the 24-hour period, while the SDANN index is the standard deviation of all the 5-minute NN interval means. Another time domain measure is the root-mean-square successive difference (r-MSSD, in ms, measured over 24 hours). The pNN50 calculates the percentage of differences between successive NN intervals over 24 hours that are greater than 50 ms, i.e. they compare successive beats [19, 21]. The triangular index uses a histogram is created of the RR intervals. The index is calculated by dividing the integral area of the distribution by its maximum height, i.e. RR distributions with greater variability will have a greater triangular index [19].

Time domain measures only give an overall HRV measure. Frequency domain measures provide spectral analysis of the R-R time series that expresses HRV as a function of frequency. This gives us more information about the different periodically working sources of the variability of heartbeat generation. There are four frequency bands: ultralow frequency (ULF), very low frequency (VLF), low frequency (LF; 0,04-0,15Hz) and high frequency (HF; 0,15-0,40Hz). Here, we will discuss only HF and LF, as suggested in literature measures of sympathetic and parasympathetic output to the heart. Although debated, some authors suggest that while the LF component is the result of both parasympathetic and sympathetic regulation, the HF component is the result of vagal regulation of the heart and the LF/HF ratio gives us more information about the sympathetic regulation on the heart [19]. Both LF and HF components can be identified by power spectral analysis [19, 20]. Frequency domain analysis is performed by taking a series of numbers along the time axis and computing the Fourier transformation [21].

Traditionally, linear features were used to analyze the HRV in the time and frequency domains. These features however do not represent the dynamics of the heartbeat generation and do not capture the complexity of the total system of sinus node activity.
modulation. Nonlinear features however led to new parameters that can give additional information about the autonomic tonus. An example of something that can be measured with these new nonlinear features is the power density of HR fluctuations. This power density falls with frequency as 1/f. One hypothesis is that if the power density doesn’t fall with the frequency as 1/f, this is pathologic. The nonlinear techniques should be seen as a completion of the linear [19-21].