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**AUTONOMIC CARDIAC
CONTROL IN PATIENTS WITH
EPILEPSY**

**SPECTRAL ANALYSIS OF HEART RATE
VARIABILITY**

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To Carin, Samuel, Joel and Jacob

ABSTRACT

The heart is affected by the central nervous system via sympathetic and parasympathetic efferents from autonomic centers in the brain stem. By assessing the beat to beat variation of the RR-intervals of the heart, i.e. the heart rate variability (HRV) it is possible to separately analyse sympathetic and parasympathetic effects on the heart. With spectral analysis of HRV the variability is separated into different bands, a high frequency band (HF) reflecting mainly parasympathetic control and a low frequency band (LF) reflecting sympathetic control. The total frequency power (TP) reflects all cyclic variations in the recorded period

A reduced HRV is a well documented prognostic factor for sudden death in many conditions and might also be of relevance for sudden death in epilepsy (SUDEP). The risk of sudden death is 24 times higher in people with epilepsy compared to the general population, with highest incidence among candidates for epilepsy surgery and particularly those with a poor surgical outcome (continuing seizures after surgery). Frequent tonic-clonic seizures, polytherapy with antiepileptic drugs and high serum concentrations of the antiepileptic drug carbamazepine (CBZ) have been identified as a risk factor for SUDEP.

Our underlying hypothesis for the present project is that persons with epilepsy may have a disturbed autonomic heart control, and that such alterations might be a factor making them susceptible to SUDEP. The general aim was to study heart control with spectral analysis of HRV, based on digital ECG recordings, on patients with epilepsy of different stages and to analyze effects on HRV of different therapeutic interventions.

We investigated HRV in patients with newly diagnosed epilepsy (NDE). We found no effect of epilepsy per se but treatment with CBZ significantly reduced LF, HF and TP.

We also assessed HRV before epilepsy surgery in patients with refractory temporal lobe epilepsy (TLE) and found that the patients with poor surgical outcome, one year after surgery had reduced HRV already before surgery in contrast to the patients who became seizure free after surgery. This difference might be linked to the higher risk of SUDEP reported in patients with poor surgical outcome. HRV was also assessed after epilepsy surgery in the same patients but we found no effect on HRV by TLE surgery.

We also investigated circadian variation of HRV in patients with NDE and refractory TLE and assessed the effect of drug treatment and surgery. In the NDE patients, treatment with CBZ decreased the night/day ratio of TP. Temporal lobe resection in the patients with refractory TLE did not change the night/day ratio.

Taken together our results indicate that there is an impaired autonomic cardiac control, reflected in decreased HRV, preferentially among the type of epilepsy patients that have been considered to have a higher risk of SUDEP.

Key words: SUDEP, autonomic nervous system, heart rate variability, epilepsy, carbamazepine, epilepsy surgery

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LIST OF ABBREVIATIONS

AED	antiepileptic drug
ANOVA	analysis of variance
ANS	autonomic nervous system
CAN	cerebral autonomic network
CBZ	carbamazepine
CNS	central nervous system
CT	computerized tomography
ECG	electrocardiography
EEG	electroencephalogram
HF	high frequency power
HRV	heart rate variability
ILAE	International League Against Epilepsy
JME	juvenile myoclonus epilepsy
LF	low frequency power
MPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
NTS	nucleus tractus solitarius
PAG	periaqueductal gray matter
PET	positron emission tomography
PSD	power spectral density
SD	standard deviation
SDRR	standard deviation of RR-intervals
SSR	sympathetic skin response
SUDEP	sudden unexpected death in epilepsy
TLE	temporal lobe epilepsy
TP	total frequency power
VLF	very low frequency power

1 BACKGROUND

1.1 EPILEPSY

Epilepsy is one of the most common serious chronic neurological disorders, globally affecting some 50 million people (Tomson, 2006). The prevalence has been estimated to between three and eight per 1,000 (Forsgren et al., 2005) and the incidence in developed countries is around 50/100,000/year (Sander, 2003). Epilepsy is not one single condition, but a diverse family of disorders, having in common an abnormally increased predisposition to seizures. According to the most recent definition of the International League Against Epilepsy (ILAE) (Fisher et al., 2005), at least one seizure is required to establish the presence of epilepsy; a predisposition as determined for example by a family history, or by the presence of epileptiform EEG changes, is not sufficient. The definition does not include the requirement of a seizure being "unprovoked," a key concept of prior definitions (ILAE, 1981). Instead, the definition requires in addition to at least one seizure, the presence of an enduring alteration in the brain that increases the likelihood of future seizures. Under this concept, the diagnosis of epilepsy would not require two seizures; it would require only one epileptic seizure in association with an enduring disturbance of the brain capable of giving rise to further seizures. A single epileptic seizure due to an enduring epileptogenic abnormality would indicate epilepsy, and a single epileptic seizure in a normal brain would not (Fisher et al., 2005).

Epilepsy may occur at any age, and has many possible presentations and causes. Although the incidence in childhood has fallen over the past three decades in developed countries, this reduction is matched by an increase in elderly people (Duncan et al 2006). Risk factors vary with age and geographical location. Epilepsy caused by head trauma, central nervous system infections, and tumours can occur at any age. Cerebrovascular disease is the most common cause of epilepsy in people over 60 years (Granger et al., 2002). Monogenic inherited epilepsies are rare but genetic variation can determine the susceptibility to epilepsy (Gutierrez-Delicado and Serratos, 2004).

1.1.1 Classification of seizures and epilepsy

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epileptic seizures result from specific abnormal patterns of excitability and synchrony among neurons in select brain areas, usually, – but not necessarily – involving the cortex (Engel, 2006). The seizure presentation depends on the location of onset in the brain and the patterns of propagation (Fisher et al., 2005). Seizures can affect sensory-, motor-, and autonomic function, consciousness, emotional state, memory, cognition, or behaviour. Sensory manifestations can include somatosensory, auditory, visual, olfactory, gustatory, and vestibular senses, as well as more complex internal sensations (Fisher et al., 2005).

Seizures are classified as either partial (focal) or generalized. Partial seizures only involve a localized part of the brain, whereas generalized seizures involve, from onset, the whole of both hemispheres. The term *secondary generalization* is used to describe a

partial seizure that spreads and becomes generalized. Partial seizures may be subdivided into simple and complex seizures. Simple seizures do not affect consciousness, whereas complex seizures do. Primarily generalized seizures can be sub-classified into absence seizures, myoclonic seizures, clonic seizures, tonic-clonic seizures and atonic seizures, depending on their semiology and EEG-activity (ILAE, 1981). This classification does not, however, describe etiology, prognosis or pathophysiology. Because of that, the ILAE proposed a classification of epilepsies and epilepsy syndromes (ILAE, 1989). This was an attempt to classify epilepsy in terms of anatomy, etiology, EEG findings, seizure type, precipitation and syndromic features. It had as its basis the same hypothesis that underlays the seizure classification, the differentiation of partial from generalized epilepsies. The epilepsies and the epileptic syndromes are divided into 1.Localization related; 2.Generalized; 3.Undetermined; and 4.Special syndromes. The localization related and the generalized epilepsies are then further subdivided into idiopathic, symptomatic, or cryptogenic (where an underlying lesion is presumed, but not discovered) (Walker and Shorvon, 1997). One example of a cryptogenic/symptomatic localization related syndrome is the Temporal Lobe Epilepsy (TLE), characterized by recurrent, unprovoked partial (simple or complex and sometimes secondary generalized) seizures, originating from the temporal lobe.

1.1.2 Treatment of epilepsy

1.1.2.1 Drug treatment of epilepsy

Antiepileptic drugs (AEDs) are the treatment of choice for the majority of patients with epilepsy. The aim of the treatment is to obtain seizure control, and thus improving the quality of life and reducing morbidity and mortality associated with seizures. With drug treatment, 60-70% of the patients with newly diagnosed epilepsy become seizure free (Sander, 2003). The mechanism of action for the different drugs are not fully understood, mainly because most of the drugs were discovered through screening programs in animal models based on effects on seizures and not on cellular mechanisms (Duncan et al., 2006). Many AEDs have multiple effects on neurons in the central as well as the peripheral nervous system. Some of the mechanisms are sodium-channel modulation or inhibition, calcium-channel modulation or inhibition, GABA augmentation, NMDA receptor inhibition, glutamate reduction and synaptic vesicle protein modulation (Duncan et al., 2006). In Sweden, the first line drug for seizures with partial onset is carbamazepine (CBZ), and for seizures with generalized onset often valproate or lamotrigine. The treatment of patients with refractory seizures is complicated; these patients are often prescribed combinations of AEDs in high doses. In a study on 470 previously untreated patients with epilepsy, 47 % responded with seizure control to their first AED. Thirteen percent were seizure-free on the second AED, and 1% on the third attempted monotherapy. Only 3% were controlled with two AEDs, and none with three (Brodie and Kwan, 2002). Thus, around 35 % of newly diagnosed patients will continue to have seizures despite medication.

1.1.2.2 Surgical treatment of epilepsy

For patients with refractory seizures despite adequate medication referral to an epilepsy surgery center for investigation should be considered. The objective of the investigation is in general to identify a removable seizure focus. This is achieved through convergence of results from several different sources, e.g. seizure history, seizure semiology, neuroimaging (MRI or CT-scan), ictal and interictal EEG, and preferably also functional imaging such as Positron Emission Tomography (PET) (Engel et al., 1982). If an epileptogenic focus is found, the multi-disciplinary team also tries to anticipate the functional deficits after possible surgery. This is done by detailed neuropsychological testing and sometimes an amobarbital test to lateralize language and memory function, with the ultimate goal to avoid unnecessary cognitive deficits after surgery (Wada and Rasmussen, 1960). The presurgical workup takes several months and during this time the patient should receive detailed information to ensure realistic expectations from the irreversible procedure.

The most common surgical procedure is temporal lobe resections for TLE. In the dominant hemisphere, temporal lobe removals usually extend back 4.5–5 cm. In the non-dominant hemisphere, the resection can be extended further but will then often result in a contralateral, superior quadrantanopsia. The antero-medial temporal lobectomy with amygdalo-hippocampectomy is a modification of the classical temporal lobectomy, reducing the amount of cortical removal and extending the hippocampal resection (Spencer et al., 1984). Extra-temporal resections are less frequent. Other techniques are hemispherectomy, e.g. in young patients with chronic encephalitis, and corpus callosotomy in patient with severe drop-attacks, and multiple subpial transections in patients with seizure focus in eloquent cortical areas (Bauman et al., 2005; Gates et al., 1987; Rasmussen, 1983).

After anterior temporal resection, approximately 60% of the patients become seizure-free (Wiebe et al., 2001). Complications occur but are uncommon. In a Swedish study reporting the postoperative outcome of 247 temporal lobe resections for epilepsy, five patients experienced hemiparesis, two hemianopsia and two patients had dysphasia. Four patients had reversible cranial nerve palsies (Rydenhag and Silander, 2001). In a multicenter retrospective follow-up study of patients who had undergone epilepsy surgery from 1980 through 1990 in Sweden, resective surgery was performed in 143 cases (94 temporal, 31 extratemporal, nine multilobar, and nine other major resective procedures) and palliative procedures in 16 cases (13 callosotomies and three stereotactic amygdalotomies) (Malmgren et al., 1997). Two years after surgery, 50% of the patients were seizure free. Of all patients, 76 % reported better global health after surgery than before, 19% that the operation had led to negative effects (Malmgren et al., 1997).

1.2 SUDDEN UNEXPECTED DEATH AS A CONSEQUENCE OF EPILEPSY

1.2.1 Background

Patients with epilepsy may suffer from stigma, exclusion, restrictions, overprotection, and isolation, which also become part of the epileptic condition (Fisher et al., 2005). In addition there may be serious medical consequences of epilepsy. These include accidents and physical injuries following seizures (Persson et al., 2002; Tomson et al., 2004). Mortality in epilepsy is also increased 2–3 fold (Sander, 2003). The cause of this excess mortality may be related to the etiology underlying epilepsy, e.g. brain tumour or cerebrovascular disease, or be more directly caused by the seizures, for example through status epilepticus and accidental injury during seizures. However, when an otherwise healthy person with epilepsy dies unexpectedly in benign circumstances, it may be due to sudden unexpected (“unexplained”) death in epilepsy (SUDEP). The definition of SUDEP remains somewhat controversial. In 1995, Nashef et al defined SUDEP as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post mortem examination does not show a toxicological or anatomic cause for death (Nashef et al., 1995). In 1997, Leestma et al. defined the criteria for SUDEP slightly differently (Leestma et al., 1997):

1. The subject had epilepsy, as defined by Gastaut and the World Health Organization (WHO): “a chronic disorder characterized by recurrent seizures due to excessive discharge of cerebral neurons” (Gastaut, 1973).
2. The subject died unexpectedly while in a reasonable state of health.
3. The fatal attack occurred “suddenly.” The complexity of this definition was discussed. It was recognized that the final ictus must occur precipitously and unexpectedly, but that death might not occur for several hours (Leestma, 1990). Death may have occurred presumably from a seizure-associated cardio-respiratory arrest and its complications, and not from status epilepticus. Sudden collapse and death may also have occurred without an observable seizure.
4. The death occurred during normal activities (e.g., at work, at home, in or around bed) in benign circumstances.
5. An obvious medical cause of death was not found. (An exception would be the presence of sudden cardiac arrhythmia, which may be related to the mechanism of SUDEP. Death in water if the victim does not show evidence of drowning, may also be attributable to SUDEP.)
6. SUDEP was excluded in the presence of status epilepticus or acute trauma in the setting of a seizure.

Definite SUDEP cases meet all of the above criteria and have sufficient descriptions of the circumstances of death. Probable SUDEP meets the criteria but lacks post mortem data. Possible SUDEP include cases where SUDEP cannot be ruled out, but where there are insufficient descriptions of the circumstances of death and no post mortem report available.

1.2.2 Incidence of SUDEP

The risk of sudden death is 24 times higher in people with epilepsy compared to the general population (Ficker et al., 1998). In a recent meta-analysis, the annual incidence of SUDEP was reported to range from 0 to 10:1,000. It was highest in cohorts of candidates for epilepsy surgery and in epilepsy referral centers (2.2:1,000–10:1,000), intermediate in patients with mental retardation (3.4:1,000–3.6:1,000), and lowest in children (0–0.2:1,000). The incidence was similar in autopsy series (0.35:1,000–2.5:1,000) and in studies of epilepsy patients in the general population (0–1.35:1,000). The median proportion of SUDEP in relation to overall mortality in epilepsy was 40% in the high risk group, and 4% in the low-risk groups (Tellez-Zenteno et al., 2005).

1.2.3 Pathophysiology and risk factors of SUDEP

In most cases SUDEP appears to be seizure related. In a series of witnessed SUDEP cases (Langan et al., 2000), convulsions were reported in 12/15 cases. Signs of preceding seizures were reported in 67% in a case-control study of 42 SUDEP cases from Norway (Kloster and Engelskjon, 1999). SUDEP occurring while the patient is under EEG/ECG monitoring is rare. One such case occurred in a video telemetry unit during a secondarily generalized epileptic seizure (Bird et al., 1997). Case-control studies report a higher SUDEP risk in people with more frequent seizures and in those with a history of generalized convulsive seizures (Langan et al., 2005; Nilsson et al., 1999). This supports the assumption that most SUDEP cases are precipitated by a seizure.

This view is also supported by the finding of increased expression of heat shock-protein HSP-70 in the hippocampal neurons of SUDEP patients, suggesting the occurrence of an ictal discharge just before SUDEP (Thom et al., 2003).

The mechanisms of death in SUDEP are however unclear. There are two main theories: seizure-induced respiratory dysfunction and seizure-induced cardiac dysfunction.

Respiratory mechanisms: In a sheep model of sudden epileptic death, the animals who died were those with a greater rise in pulmonary vascular pressure and hypoventilation in response to a seizure. When airway obstruction was excluded in a second study of tracheostomized sheep, central apnoea and hypoventilation were observed in all animals, causing or contributing to death in two (Johnston et al., 1997). In a polysomnography study on patients undergoing EEG-video recordings, apnoea was seen in 10 of 17 patients and in 20 of 47 clinical seizures (three secondary generalized, 16 complex partial, and one tonic). Apnoea was central in 10 patients, but obstructive apnoea was also recorded in three. (Nashef et al., 1996). Taken together, this suggests that disturbed respiratory function in response to a seizure may play a role in the mechanism of SUDEP

Cardiac mechanisms: In studies on rats, electrical stimulation of the posterior insular cortex resulted in increasing degrees of heart block, leading to escape rhythms, ventricular ectopics, and ultimately death in asystole (Oppenheimer et al., 1991). Animal models of epilepsy suggest that even interictal epileptogenic activity may induce changes in the autonomic nervous system, which could result in cardiac arrhythmia (Lathers and Schraeder, 1982; Lathers et al., 1987).

In the polysomnography study, an increased heart rate was common during seizures (91% of seizures) while bradycardia/sinus arrest was documented in four patients (Nashef et al., 1996). In another study of 19 patients with refractory focal epilepsy, ECG was monitored with an implantable loop recorder. ECGs were captured in 377 seizures. In 16 patients, median heart rate during habitual seizures exceeded 100 beats per min. Ictal bradycardia (<40 beats per min) was rare, occurring in eight recorded events in seven patients. Four patients had bradycardia or periods of asystole with subsequent permanent pacemaker insertion. Three of these four had potentially fatal asystole (Rugg-Gunn et al., 2004). Clinical studies indicate that patients with epilepsy may have impaired autonomic cardiovascular regulation also in the interictal state, although it is unclear whether the observed reduction in cardiovascular responses is due to the epilepsy and the interictal discharges, or to the treatment with AEDs (Ansakorpi et al., 2002; Ansakorpi et al., 2000; Frysinger et al., 1993; Isojarvi et al., 1998; Massetani et al., 1997; Tomson et al., 1998). These data support the hypothesis that cardiac dysfunction could be a contributing mechanism to SUDEP and that impairment of autonomic cardiac control may play an important role in this respect.

1.3 HEART FUNCTION AND THE AUTONOMIC NERVOUS SYSTEM

1.3.1 Introduction

The autonomic nervous system (ANS) is an extensive neural network capable of regulating the homeostasis of the body by controlling visceral functions such as the heart, smooth muscle, secretory glands and hormone secretion. Although most of these systems are out of conscious control, we all know from personal experience that thoughts and sensory stimuli such as visual, auditory or tactile inputs can affect these functions (e.g. tachycardia from fear). The ANS is divided into a central component – the central autonomic network (CAN) – and a peripheral component – the sympathetic and the parasympathetic nervous system.

1.3.2 The central autonomic network

The central autonomic network (CAN) is an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioural responses essential for survival. It includes the insular cortex, the medial prefrontal cortex, the amygdala, the hypothalamus, the periaqueductal gray (PAG), the parabrachial complex, the nucleus of the tractus solitarius (NTS), and the ventrolateral medulla (Verberne and Owens, 1998). Inputs to the CAN are multiple, including viscerosensory inputs relayed on the NTS and humoral inputs relayed through the circumventricular organs (the midline structures bordering the 3rd and 4th ventricles outside the blood-brain barrier, e.g. the pineal gland, the median eminence, the subfornical organ, and the area postrema) (Benarroch, 1993). The CAN controls preganglionic sympathetic and parasympathetic, neuroendocrine, respiratory, and sphincter motoneurons (Benarroch, 1993).

1.3.2.1 The Insular cortex

The insular cortex receives visceral and sensory information from baroreceptors and chemoreceptors from the cardiovascular system (Verberne and Owens, 1998). There are afferent connections from the medulla oblongata and pons, the thalamus and the hypothalamus (Verberne and Owens, 1998). There is a viscerotopical organisation of the insular cortex with taste-responsive neurons located anteriorly, general visceral modalities dorsally and posteriorly, gastric mechanoreceptor-responsive dorsally and anteriorly, and cardiopulmonary inputs located ventrally and posteriorly (Cechetto and Saper, 1987). Electrical stimulation of the posterior insular cortex in rats resulted in heart block leading to escape rhythms, ventricular ectopics and ultimately death in asystole (Oppenheimer et al., 1991).

In the rat, monkey and man, sympathetic cardiovascular control is generally represented in the right insula, although pronounced insulo-insular connectivity has been demonstrated. Pro-arrhythmic shifts in cardiac sympathovagal balance occur after human stroke, including left insular lesions (Oppenheimer, 2006). The insula has widespread connections with different parts of the brain including the NTS, the rostral ventrolateral medulla, the pons, the thalamus, the amygdala and the hypothalamus (Verberne and Owens, 1998).

1.3.2.2 The medial prefrontal cortex (MPFC)

Neurons in the MPFC can exert an inhibitory influence on sympathetic vasomotor function. The mechanisms are not completely understood, but involve inhibition of sympatho-excitatory neurons of the rostral ventrolateral medulla (Verberne and Owens, 1998). In contrast to the insular cortex, the MPFC receives little direct general visceral information, and inputs are mainly from limbic structures such as the amygdala and the hippocampus (Verberne and Owens, 1998). The MPFC seems to be involved in the response to a number of stressors, suggesting a role in the emotional modulation of the sympathetic vasomotor function (Verberne and Owens, 1998). After electrical stimulation of the MPFC in anaesthetized rats, depressor response on heart rate predominate (Verberne and Owens, 1998). However, in unanaesthetized rats there are reports of pressor responses (Tavares et al., 2004).

1.3.2.3 The amygdala

Sensory inputs from the cortex, thalamus and hypothalamus converge in the amygdala to inform it of potential dangers in the environment. The amygdala has direct projections to the hypothalamus, PAG, the pontine reticular formation, the parabrachial nuclei, the locus coeruleus, and the dorsal motor nucleus of the vagus nerve (Ansakorpi, 2003). The projections suggest an important role in the integration of somatic and autonomic responses associated with affective defence (Ottersen, 1981). In anaesthetized rats, electrical stimulation in amygdala complex induced tachycardia. In non-anaesthetized rats, electrical stimulation in these nuclei elicited arching of the back, piloerection, sitting up and boxing with the forepaws or running, jumping or squealing, a complex defence reaction (al Maskati and Zbrozyna, 1989).

1.3.2.4 The hypothalamus

The main function of the hypothalamus is homeostasis, or maintaining the body's status quo. Factors such as blood pressure, body temperature, fluid and electrolyte balance, and body weight are regulated (Silbernagl and Lang, 2000). Hypothalamus receives inputs from several sources, e.g. visceral sensory information from the vagus via the NTS, light information from the retina to regulate circadian rhythms and information from the amygdala (Kahle and Frotscher, 2003). Many years ago, Sherrington called the hypothalamus "the head ganglion of the autonomic system" (Ganong, 2005). Stimulation of the hypothalamus produces autonomic responses, but the hypothalamus does not seem to be concerned with the regulation of visceral function per se (Ganong, 2005). Rather, the autonomic responses triggered in the hypothalamus are part of more complex phenomena such as eating, and emotions such as rage (Ganong, 2005). For example, stimulation of various parts of the hypothalamus, especially the lateral areas, produces diffuse sympathetic discharge and increased adrenal medullary secretion, the mass sympathetic discharge seen in animals exposed to stress (the flight or fight reaction) (Ganong, 2005). The lateral hypothalamus has projections to the parasympathetic vagal nuclei in the medulla oblongata and to a cell group descending to the sympathetic system in the spinal cord (Kahle and Frotscher, 2003).

1.3.2.5 Other components of the central autonomic network

At the mesencephalic level, the PAG integrates autonomic responses with antinociceptive and behavioural reactions (Inui and Nosaka, 1993). It also plays a major role in cardiorespiratory regulation; stimulation of it increases the blood pressure and inhibits the baroreflex. The entire pattern of behavioural and visceral components of the defense reaction can be elicited after injection of an excitatory amino acid into the PAG (Inui and Nosaka, 1993).

The rostral ventrolateral medulla is integrated in the sympathetic nervous system and stimulation increases heart rate (Dampney, 1994).

The dorsolateral subnucleus of the NTS contains neurons that discharge in phase with the cardiac cycle and initiate vasodepressor and bradycardiac responses. (Dampney, 1994).

1.3.3 The sympathetic and parasympathetic parts of the ANS

Parasympathetic cells are located in different nuclei throughout the brainstem, as well as a few in the sacral spinal cord (Rohkamm, 2004). Their axons travel to the target organ, synapse in ganglia in or near the organ wall, and finally innervate the organs (Rohkamm, 2004). The efferent axons to the heart, lungs, and pharynx originate in the nucleus ambiguus (and surrounding cells) (Rohkamm, 2004). Functions include decreasing heart rate and bronchial constriction. Most of the afferent axons from the vagus terminate in the NTS, containing information about blood pressure, carbon dioxide levels and gut distension, etc (Rohkamm, 2004).

The cells of the intermediolateral column in the thoracic spinal cord are the source of all the sympathetics (Rohkamm, 2004). They travel to ganglia before reaching the

target organ. The chain ganglia running along the spinal cord distribute sympathetics to the thorax and periphery to increase heart rate, dilate bronchi as well as selectively vasoconstrict and vasodilate in active muscles (Rohkamm, 2004).

The afferents from the sympathetic nerves re-enter the dorsal horn of the spinal cord along-side the sensory afferents from the skin. The sympathetic afferents mainly carry information about visceral pain (Rohkamm, 2004).

1.3.4 Circadian variation in autonomic heart control

Autonomic cardiovascular regulation, as many other human physiological functions, follows a distinct circadian rhythm which is mainly of endogenous origin, controlled by the hypothalamus but also modulated by environmental factors (Korpelainen et al., 1997). For example, arterial blood pressure and heart rate decreases and heart rate variability (HRV) increases during night as a result of increased vagal activity (Korpelainen et al., 1997). Interestingly, the occurrence of sudden cardiovascular death also has a circadian rhythm with increased incidence during the early morning hours (Korpelainen et al., 1997).

Diminished HRV and especially a loss of its circadian oscillation are associated with an increased risk of cardiac arrhythmia and sudden death in coronary artery disease (Korpelainen et al., 1997). In particular, suppressed vagal activity during the night seems to be an unfavorable phenomenon leading to unopposed sympathetic activity and imbalance between the sympathetic and the parasympathetic cardiovascular autonomic regulatory systems (Korpelainen et al., 1997).

1.4 THE AUTONOMIC NERVOUS SYSTEM AND EPILEPSY

Central components of the autonomic nervous system are found in the cerebral cortex, the hypothalamus, the limbic system, the mid-brain (PAG), the medulla (NTS and ventrolateral areas of the medulla), and in the spinal cord (Verberne and Owens, 1998). Ictal and interictal epileptic activity can involve many of these areas and thus induce autonomic symptoms during seizures, potentially affecting autonomic cardiac control ictally and interictally (Lathers and Schraeder, 1982). It has been hypothesized that this can be one mechanism behind SUDEP (Lathers and Schraeder, 1982; Ryvlin et al., 2006; Tomson et al., 1998).

1.5 METHODS FOR MEASURING AUTONOMIC FUNCTION

There is a multitude of methods for measuring autonomic nervous system function in the clinical as well as in the research situation. Some of these methods are briefly discussed below.

1.5.1 Autonomic Challenge Manoeuvres

1.5.1.1 *The Valsalva manoeuvre.*

During this manoeuvre the patient expires against resistance, the intra-thoracic and the abdominal pressure increases causing a decrease in venous return, which results in a baroreflex-mediated tachycardia and peripheral vasoconstriction. After the pressure has been released there is a blood pressure overshoot, due to the persistent increase in peripheral resistance, and a normalization of venous return and stroke volume. In patients with sympathetic dysfunction, the blood pressure increase is absent. The blood pressure increase mediates a baroreflex-induced bradycardia. This bradycardia is a measure of vagal cardiac innervation. The Valsalva ratio is the highest heart rate during expiration divided by the lowest heart rate during the first 20 s after, and is used as an index of the baroreflex-mediated bradycardia (Hilz and Dutsch, 2006). Failure of the heart rate to increase during the positive intrathoracic pressure phase of the Valsalva manoeuvre points to sympathetic dysfunction, and failure of the rate to slow during the period of blood pressure overshoot points to a parasympathetic disturbance (Ropper and Brown, 2005).

1.5.1.2 *Deep breathing test*

Deep metronomic breathing at a rate of six cycles per minute is a test to assess respiratory sinus arrhythmia, with acceleration of heart rate during inspiration and deceleration during expiration under standardized conditions. Heart rate modulation during deep breathing depends on parasympathetic cardiac control. The expiratory/inspiratory ratio (E/I ratio) can be determined from the maximum and minimum heart rate during this respiration.(Hilz and Dutsch, 2006). This is a simple procedure for quantitating vagal function (Ropper and Brown, 2005).

1.5.1.3 *The tilt table test*

Adaptation to prolonged orthostatic challenge can be tested by passive tilting of the patient. During this procedure there is normally a gradual increase in diastolic pressure and heart rate, but no major change in systolic pressure. When tilted, the higher hydrostatic pressure accounts for progressive fluid transudation from circulating blood into the lower-extremity tissues. The reduction of venous return and diastolic cardiac filling induces a decrease of cardiac output. This activates the baroreflex which, in turn, inhibits cardiovagal outflow, enhances sympathetic activity, and thus increases heart rate, peripheral vascular resistance, and blood pressure (Hilz and Dutsch, 2006). The tilt table test is now a routinely used procedure when syncope is suspected, but the diagnosis not being evident from physical examination and routine studies (Ropper and Brown, 2005).

1.5.2 Testing the Sudomotor function

1.5.2.1 Thermoregulatory sweat test

Central and peripheral sudomotor (the sympathetic nerves stimulating the sweat glands) function is tested with an indicator powder. Humidity alters the color of this powder. The patient is put in a sweat chamber with controlled temperature and humidity. Areas of abnormal sweating are calculated as a percentage of the body surface (Hilz and Dutsch, 2006). This method can be used to detect sympathetic failure in small-fiber neuropathies (Ropper and Brown, 2005).

1.5.2.2 Sympathetic Skin Response (SSR)

With electrodes on the palms and soles and reference electrodes on the dorsum of the hands and feet, change in resistance as a result of sweating, is measured. SSR can be evoked by various types of stimulation, such as electrical, acoustic, or inspiratory gasp stimuli. The response is rather variable and there are no definite criteria regarding abnormal responses (Hilz and Dutsch, 2006). SSR can be used to detect sympathetic failure in small-fiber neuropathies (Ropper and Brown, 2005).

1.6 HEART RATE VARIABILITY

1.6.1 Background

HRV is a non-invasive electrocardiographic marker reflecting the activity of the sympathetic and vagal components of the autonomic nervous system (ANS) on the sinus node of the heart. It expresses the total amount of variations of both instantaneous heart rate and RR-intervals (intervals between QRS complexes of normal sinus depolarisations). Thus, HRV analyzes the tonic baseline autonomic function. In a normal heart with a functioning ANS, there will be continuous physiological variations of the sinus cycles, reflecting a balanced sympathovagal state (Sztajzel, 2004). Time domain indices and frequency domain indices constitute the clinically used standard parameters. In 1996, the Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) defined and established standards of measurement, physiological interpretation, and clinical use of HRV for these parameters as found below.

1.6.2 Heart Rate Variability in the time domain

Time domain measures are the most simple to perform. In these methods either the heart rate at any point in time, or the intervals between successive normal complexes, are determined. In a continuous ECG record each QRS complex is detected, and the so called normal-to-normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate, is determined. Simple time domain variables include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval and so forth.

Other time domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, tilt, Valsalva manoeuvre, or phenylephrine infusion. From a series of instantaneous heart rates or cycle intervals, particularly those recorded over longer periods – traditionally 24 h. – more complex statistical time domain measures can be calculated, such as the standard deviation of the NN intervals (SDNN or SDRR), i.e, the square root of variance. Since variance is mathematically equal to Total frequency power of spectral analysis, SDRR reflects all the cyclic components responsible for variability in the period of recording. Other commonly used statistical variables calculated from segments of the total monitoring period include SDANN (the standard deviation of the average NN intervals calculated over short periods, usually 5 minutes, which is an estimate of the changes in heart rate due to cycles longer than 5 minutes) and RMSSD (the square root of the mean squared differences of successive NN intervals), the NN50 (the number of interval differences of successive NN intervals greater than 50 ms), and pNN50 (the proportion derived by dividing NN50 by the total number of NN intervals). All of these measurements of short-term variation estimate high-frequency variations in heart rate and are highly correlated (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996).

1.6.3 Analysis of the frequency domain

The Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) have also defined standards for the frequency domain (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency. Methods for the calculation of PSD may be generally classified as non-parametric and parametric. In most instances, both methods provide comparable results. Three main spectral components are distinguished in a spectrum: Very Low Frequency (VLF), 0.0033–0.04 Hz; Low Frequency (LF), 0.04–0.15 Hz; and High Frequency (HF) 0.15–0.40 Hz components. Total frequency power (TP), 0.0033–0.40 Hz, consists of all the frequency bands. TP, VLF, LF, and HF components are usually measured in absolute values of power (milliseconds squared). The definitions and physiological interpretations are summarized in Table 1.

The RR-interval variations present during resting conditions represent a fine tuning of the beat-to-beat control mechanisms. Vagal afferent stimulation leads to reflex excitation of vagal efferent activity and inhibition of sympathetic efferent activity. The opposite reflex effects are mediated by the stimulation of sympathetic afferent activity. Efferent vagal activity also appears to be under "tonic" restraint by cardiac afferent sympathetic activity. Efferent sympathetic and vagal activities directed to the sinus node are characterized by discharge, largely synchronous with each cardiac cycle, that can be modulated by central (vasomotor and respiratory centers) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators. These oscillators generate rhythmic fluctuations in efferent neural discharge that manifest as short- and long-term oscillation in the heart period. Analysis of these rhythms may permit inferences on the state and function of (a) the central oscillators, (b) the sympathetic and vagal efferent activity, (c) humoral factors, and (d) the sinus node. The

efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental observations of autonomic manoeuvres such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy. More controversial is the interpretation of the LF component, which is considered by some as a marker of sympathetic modulation (especially when expressed in normalized units), and by others as a parameter that includes both sympathetic and vagal influences. Consequently, the LF/HF ratio mirrors the sympathovagal balance or reflects the sympathetic modulations. Total Frequency reflects all the cyclic components responsible for variability in the period of recording (Table 1) (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). The HRV analysis from ambulatory ECG recording is now an important tool in evaluating cardiovascular autonomic regulation (Ansakorpi, 2003). Information about tonic autonomic effects on the heart can be obtained by the traditional time and frequency domain measures (Ansakorpi, 2003). In our studies, we chose to focus on the frequency domain and presented data of VLF, LF, HF and TP and LF/HF ratio, but also SDRR from the time domain.

Table 1. Frequency domain HRV components and their physiological interpretations (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996)

HRV Components	Frequency	Length of cycle	Physiological interpretation
Very Low Freq. (VLF)	0.0033–0.04 Hz	25 sec–5 min	Not completely understood
Low Freq. (LF)	0.04–0.15 Hz	7 sec–25 sec	Associated with baroreflexor control of sympathetic activity. Parasympathetic activity might also influence LF
High Freq. (HF)	0.15–0.40 Hz	2 sec–7 sec	HF reflects respiratory sinus arrhythmia, mainly related to parasympathetic activity.
Total Freq. (TP)	0.0033–0.40 Hz	2 sec–5 min	Reflects all the cyclic components responsible for variability in the period of recording.
LF/HF ratio	N.A.	N.A.	Mirrors sympathovagal balance or reflects the sympathetic modulations.

1.7 HEART RATE VARIABILITY IN EPILEPSY AND OTHER DISEASES

Several studies have assessed HRV in epilepsy. The results are summarized in Table 2. Interictal HRV has been analyzed in patients with chronic TLE and compared to age matched healthy controls in cross sectional studies, with reduced HRV in the epilepsy patient groups as the major finding (Ansakorpi et al., 2000; Massetani et al., 1997; Tomson et al., 1998). Adult patients with TLE were reported to have reduced total power, LF and HF (Massetani et al., 1997), lower LF and LF/HF ratio (Tomson et al., 1998), or a decrease in all frequency domain measures (Ansakorpi et al., 2002).

It has been unclear if the observed impaired autonomic cardiac regulation interictally in patients with medically treated epilepsy is caused by interictal discharges, underlying brain pathology, drugs or other factors. In a cross-sectional study of epilepsy patients on monotherapy with different AEDs (Tomson et al., 1998), patients with TLE had significantly lower LF compared with controls, while those with juvenile myoclonic epilepsy (JME) did not differ from their controls. However, it was not possible to distinguish between the effect of drug therapy and the epilepsy since 18 out of 21 patients with TLE were treated with CBZ, whereas 18 out of 21 patients with JME received valproate. Two previous studies have analyzed HRV in conjunction with abrupt withdrawal of CBZ, both suggesting increased LF/HF ratios after withdrawal, indicating an increased sympathetic tone (Hennessy et al., 2001; Kenneback et al., 1997). These studies assessed effects of abrupt drug withdrawal, rather than direct effects of CBZ on autonomic cardiac control.

In conclusion, epilepsy is associated with altered HRV. Several factors, e.g. seizures and interictal discharges, may contribute. One can only speculate upon the possible clinical relevance of decreased HRV among patients with epilepsy. It is however tempting to discuss these findings in relation to SUDEP, since reduced HRV has been shown to predict mortality – and more specifically sudden death – in other conditions, such as patients awaiting cardiac transplantation (reduced SDRR) (Binder et al., 1992) and after acute myocardial infarction (reduced SDRR, VLF, LF and HF) (Bigger et al., 1992b), (reduced SDRR) (Kleiger et al., 1987). One recent study demonstrated that stroke involving the region of insula (especially the right) leads to decreased LF, HF and SDRR and also to increased incidence of sudden death (Tokgozoglu et al., 1999). Patients with other diseases with an increased risk of sudden death also have decreased HRV, for instance congestive heart failure (reduced SDRR) (Takase et al., 1992), and diabetic neuropathy (reduced LF and HF) (Spallone et al., 1996). Furthermore, drugs such as the anti-arrhythmic agents flecainide and propafenone (using another method as a marker of parasympathetic activity: reduction of the number of two consecutive sinus RR-intervals with a difference of more than 50 ms) (Zuanetti et al., 1991), and the antipsychotic clozapine that reduces HRV (reduced HF and increased LF) (Cohen et al., 2001), are associated with an increased mortality in sudden death (Cohen et al., 2001; Ruskin, 1989).

Table 2. Studies on Heart Rate Variability in patients with epilepsy

Reference	Population	Method	Main findings
Evrengul et al., 2005	Military recruits, longstanding untreated epilepsy, unspecific tonic-clonic seizures (n = 42)	1h supine ECG recording.	Increased SDRR, LF, LF/HF Decreased HF
Massetani et al., 1997	TLE (n = 30)	ECG in supine and tilt position.	Reduced LF and HF in supine and LF/HF in orthostatic position
Tomson et al., 1998	TLE (n = 21) JME (n = 18)	24 h. ambulant ECG.	TLE: Reduced SDRR, LF, LF/HF. JME: Reduced LF/HF
Ansakorpi et al., 2002	Refractory TLE (n = 19) Well controlled TLE (n = 25)	24 h. ambulant ECG.	Decrease in all time and frequency domain
Hennessey et al., 2001	Intractable seizures, abrupt withdrawal of CBZ in Video-EEG monitoring unit (n = 12)	A few h. of supine ECG. One day before and four days after reduction	Increased LF/HF ratio
Kennebak et al., 1997	In-hospital abrupt withdrawal of CBZ and phenytoin due to side effects. Epilepsy (n = 9), Trigeminal neuralgia (n = 1)	24 h. ECG for 5 consecutive days	Reduced TP, VLF, LF
Frysinger et al., 1993	Epilepsy surgery candidates. Seizures postop. (n = 2) and not recommended for surgery (n = 2) compared with good outcome of surgery (n = 13).		Reduced 0.07 Hz–0.15 Hz HRV before surgery in the poor outcome group. (LF = 0.04–0.15 Hz)
Hilz et al., 2003	TLE patients with epilepsy surgery. good outcome (n = 8) poor outcome (n = 8)	10 min ECG recordings in supine position.	Reduced LF, LF/HF ratio after surgery in those seizure free
Ronkainen et al., 2005	TLE patients: Refractory (n = 17), Well-controlled (n = 20)	24 h. ambulant ECG	Decreased night/day ratio of SDRR

2 AIMS

Our underlying hypothesis for the present studies is that persons with epilepsy may have a disturbed autonomic heart control, and that such alterations might be a factor making them susceptible to SUDEP. The general aim has been to study heart control with spectral analysis of HRV, based on digital ECG recordings, on patients with epilepsy of different stages and to analyze effects on HRV of different therapeutic interventions.

Specific aims were:

- To investigate HRV in patients with newly diagnosed epilepsy and to assess the effect of epilepsy *per se* and the effect of carbamazepine treatment on HRV in this patient group. (Papers I and II).
- To assess HRV before epilepsy surgery in patients with refractory TLE and its relation to outcome of surgery (Paper III).
- To investigate the effect of epilepsy surgery on heart control in patients with medically refractory TLE (Paper IV).
- To investigate circadian variation in HRV in patients with newly diagnosed and refractory localization-related epilepsy, and to assess the effects of drug treatment and epilepsy surgery on the night/day time HRV ratio (Paper V).

3 METHODS

3.1 PATIENTS AND SUBJECTS

Most patients and subjects participated in more than one study. The participations are listed in table 3.

3.2 PROCEDURES

3.2.1 Procedures for paper I

Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated newly diagnosed epilepsy. *Manuscript submitted*

We enrolled consecutive adult patients with newly diagnosed epilepsy, without treatment, at the out-patient clinic of the Department of Neurology at the Karolinska University Hospital, Stockholm, Sweden. For each patient one age and sex matched healthy control subject was selected. The newly diagnosed patients with epilepsy and their controls had an ambulatory 24 h. digital ECG recording, during which they were free to practice their normal daily activities. Patients were asked to keep a seizure-diary during the recordings.

Table 3. The 43 patients participating in paper I-V and the 38 healthy subjects participating in paper I and III-V.

Patients				Healthy subjects	
Patient no:	Age/Sex	Epilepsy type ¹	Paper no:	Subject no:	Paper no:
1	33/M	IGE	I	1	I
2	23/M	IGE	I	2	I
3	37/F	UE	I	3	I
4	32/F	IGE	I	4	I
5	19/F	LRCE	I	5	I
6	18/F	IGE	I	6	I
7	72/F	UE	I	7	I
8	69/F	UE	I, II	8	I, V
9	34/M	LRSE	I, II, V	9	I, V
10	32/M	LRSE	I, II, V	10	I, V
11	27/F	LRCE	I, II, V	11	I, V
12	26/M	LRSE	I, II, V	12	I, V
13	72/M	LRCE	I, II, V	13	I, V
14	56/F	LRCE	I, II, V	14	I, V
15	43/M	LRCE	I, II, V	15	I, V
16	76/M	LRSE	I, II, V	16	I, V
17	63/F	LRSE	I, II, V	17	I, V
18	37/F	LRSE	I, II, V	18	I, III, IV, V
19	24/F	LRCE	I, II, V	19	I, III, IV, V
20	33/F	LRSE	I, II, V	20	I, III, IV, V
21	31/F	LRCE	I, II, V	21	I, III, IV, V
22	27/M	LRCE	I, II, V	22	I, III, IV, V
23	33/M	TLE	III, IV, V	23	III, IV, V
24	31/M	TLE	III, IV, V	24	III, IV, V
25	51/M	TLE	III, IV, V	25	III, IV, V
26	47/M	TLE	III, IV, V	26	III, IV, V
27	47/M	TLE	III, IV, V	27	III, IV, V
28	46/K	TLE	III, IV, V	28	III, IV, V
29	47/M	TLE	III, IV, V	29	III, IV, V
30	44/K	TLE	III, IV, V	30	III, IV, V
31	42/M	TLE	III, IV, V	31	III, IV, V
32	42/K	TLE	III, IV, V	32	III, IV, V
33	42/K	TLE	III, IV, V	33	III, IV, V
34	66/M	TLE	III, IV, V	34	III, IV, V
35	43/K	TLE	III, IV, V	35	III, IV, V
36	44/M	TLE	III, IV, V	36	III, IV, V
37	45/K	TLE	III, IV, V	37	III, IV, V
38	30/M	TLE	III, IV, V	38	III, IV, V
39	25/K	TLE	III, IV, V	Paper I: (Persson et al., 2006a)	
40	19/M	TLE	III, IV, V	Paper II: (Persson et al., 2003)	
41	31/M	TLE	III, IV, V	Paper III: (Persson et al., 2005)	
42	23/K	TLE	III, IV, V	Paper IV: (Persson et al., 2006c)	
43	31/K	TLE	III, IV, V	Paper V: (Persson et al., 2006b)	

¹IGE=Idiopathic Generalized Epilepsy, UE=Undetermined Epilepsy, LRSE= Localization-Related Symptomatic Epilepsy, LRCE= Localization-Related Cryptogenic Epilepsy, TLE=Temporal Lobe Epilepsy

3.2.2 Procedures for paper II

Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Res.* 2003;57(1):69-75

We enrolled consecutive adult patients with newly diagnosed epilepsy at the out-patient clinic of the Department of Neurology at the Karolinska University Hospital, Stockholm, Sweden. Every patient underwent a 24 h. ambulatory ECG recording twice, before treatment and after commencement of CBZ treatment. A blood sample for determination of CBZ concentration was obtained immediately before the morning dose at the time of the second investigation. All patients were out-patients and free to practice their normal daily activities. They were asked to keep a seizure-diary during the recordings.

3.2.3 Procedures for paper III

Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. *Neurology* 2005;65:1021-1025

We enrolled consecutive patients accepted for resective epilepsy surgery for refractory TLE from the routine epilepsy surgery programs at the Uppsala University Hospital, Uppsala, Sweden, and the Karolinska University Hospital, Stockholm, Sweden. For each patient one age and sex matched healthy control subject was selected. An ambulatory 24-hour digital ECG recording was performed in all patients at least one day before surgery. They were asked to keep a seizure-diary during the recordings. Surgery outcome was assessed one year after the operation, using the classification suggested by Engel (Engel et al., 1993). Patients with Engel class I were considered to have a “good” outcome, and patients with Engel class II–IV were considered as “poor.” The controls were selected from a bank of previously recorded healthy volunteers.

3.2.4 Procedures for paper IV

Persson H, Kumlien E, Ericson M, Tomson T. No apparent effect of surgery for temporal lobe epilepsy on heart rate variability. *Epilepsy Research* 2006; 70: 127-132. (Persson et al., 2006c)

We enrolled consecutive patients accepted for resective epilepsy surgery for refractory TLE from the routine epilepsy surgery programs at the Uppsala University Hospital, Uppsala, Sweden and the Karolinska University Hospital, Stockholm, Sweden. For each patient one age and sex matched healthy control subject was selected. The controls were selected from a bank of previously recorded healthy volunteers. An ambulatory 24 h. digital ECG recording was performed in healthy controls and in all patients at least six months after surgery. These data were compared with the previously reported HRV data before surgery. Surgery outcome was assessed one year after the operation, using the classification suggested by Engel et al. (1993). All patients had the same outcome classification at the time of the ECG recording as at the one-year follow up. Patients with Engel class I were considered to have a “good” outcome and patients with Engel classes II–IV were considered as “poor”.

3.2.5 Procedures for paper V

Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart rate variability in localization related epilepsy. *Accepted for publication in Epilepsia*. We used previously collected data from two patient groups: **(1) Newly diagnosed epilepsy**; consecutive adult patients with newly diagnosed untreated epilepsy at the out-patient clinic of the Department of Neurology at the Karolinska University Hospital, Stockholm, Sweden. These patients have been reported in a previous study assessing the effect of CBZ in newly diagnosed epilepsy (Paper I and II) (Persson et al., 2003; Persson et al., 2006a). **(2) Epilepsy surgery candidates**; we enrolled consecutive patients from the routine epilepsy surgery programs at the Uppsala University Hospital, Uppsala, Sweden and the Karolinska University Hospital, Stockholm, Sweden. All these patients had refractory TLE and were accepted for resective surgery: These patients are described in detail in a previous report (Papers III and IV) (Persson et al., 2005; Persson et al., 2006c). For each patient one healthy control subject was selected matched for age and sex. The controls were selected from a bank of previously recorded healthy volunteers. All patients and controls had an ambulatory 24 h. digital ECG recording, during which they were free to practice their normal daily activities.

3.3 ASSESSMENT OF HRV

QRS-complexes were classified by an automatic analysis of the digitally recorded ECG signal. The consecutive RR-intervals and the corresponding classification code were exported to an ASCII text file. For the frequency domain analysis 5 min epochs of data were analyzed by custom made software. The time series of RR-intervals were resampled at a frequency of two samples/sec (2 Hz). Gaps in the time series due to non-normal RR-intervals (QRS-labelled by the Aspect System classification as noise or ectopic beats) were filled with values calculated by linear interpolation between the adjacent normal RR-intervals. The computer program checked for misclassified drop beats deviating more than three SDs from the mean normal RR-interval of each epoch. Epochs with more than 4% of non-normal RR-intervals were excluded from further analysis. At least 50% of a 24 h. recording had to be analysable for a tape to be included, in accordance with issued guidance (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). Thus, altogether a maximum of 288 epochs were analyzed per patient and assessment time, representing both active and resting periods. The frequency domain of the time series of RR-intervals was analyzed with an auto-regression method (Burg, 1967). The mean RR-interval of each time series was subtracted and then detrended by applying linear regression. The power spectrum of the frequency domains was divided into four different frequency bands: Total frequency power (TP) 0.0033–0.40 Hz; very low frequency power (VLF), 0.0033–0.04 Hz ; low frequency power (LF), 0.04–0.15 Hz; high frequency power (HF), 0.15–0.40 Hz. In the time domain, the mean of the SD of all normal RR-intervals for all 5 min segments of a 24 h. ECG recording (SD-NN-index) was calculated. All analyzes were first made for the full 24 h. period and additional analyzes were thereafter made for night time (00:00 a.m. to 05:00 a.m.) and day time (07:30 a.m. to 09:30 p.m.), respectively.

3.4 DATA ANALYSIS AND STATISTICS

Significance was assumed for p values < 0.05. Stata 7.0 software was used for data analysis (Stata Corporation, USA).

3.4.1 Paper I

Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated newly diagnosed epilepsy. *Manuscript submitted*

A non-paired t-test was used to compare HRV data between patients and controls. We analyzed the whole 24 h. period but also separately the nighttime (midnight to 05:00 a.m.) and daytime (07:30 a.m. to 9:30 p.m.) periods.

3.4.2 Paper II

Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Res.* 2003;57(1):69-75

A paired t-test was used for statistical analysis of differences before and during treatment with CBZ.

3.4.3 Paper III

Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. *Neurology* 2005;65;1021-1025

A non-paired t-test was used to compare HRV data between patients and controls and between the two patient groups (good and poor surgery outcome). In addition, ANOVA analysis was used to check for side of surgery/seizure onset (left/right) as an explanatory factor for the differences found between the two groups with different outcome of surgery (good outcome/poor outcome).

3.4.4 Paper IV

Persson H, Kumlien E, Ericson M, Tomson T. No apparent effect of surgery for temporal lobe epilepsy on heart rate variability. *Epilepsy Research* 2006; 70: 127-132

A non-paired t-test was used to compare HRV data between patients and controls. A paired t-test was used to assess changes in HRV before and after surgery for all patients, and for the patients with good outcome and the patients with poor outcome separately.

3.4.5 Paper V

Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart rate variability in localization related epilepsy. *Accepted for publication in Epilepsia.*

Mean values of night time (midnight to 05:00 a.m.) and day time (07:30 a.m. to 09:30 p.m.) HRV data were calculated. To describe the circadian rhythm of the HRV we then calculated the night/day time ratio for each HRV measurement. The non-parametric Mann-Whitney two sample test was used to compare the ratios between the patients and controls and between different patient groups. A paired t-test was used for the comparison of the patients before versus during CBZ treatment and the patients before and after epilepsy surgery.

4 RESULTS

4.1 PAPER I

Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated newly diagnosed epilepsy. *Manuscript submitted*

4.1.1 Objective

To study the effect of epilepsy per se on HRV in newly diagnosed, untreated patients.

4.1.2 Results

We compared 22 adult patients with newly diagnosed epilepsy (13 female/9 male) with age and sex matched controls. When analysing the full 24 h. recordings, there were no significant differences between patients and controls in any of the analyzed measures of HRV: standard deviation of RR-intervals ($P = 0.191$), TP ($P = 0.170$), very low frequency power ($P = 0.329$), low frequency power (LF) ($P = 0.161$), high frequency power (HF) ($P = 0.186$) and the LF/HF ratio ($P = 0.472$) (Table 4.). The results were very similar for daytime and nighttime recordings.

4.1.3 Conclusion

We could not demonstrate any significant difference in HRV measures between our patients with untreated newly diagnosed epilepsy and matched healthy controls. This observation needs to be interpreted with some caution because of the limited number of included patients, and the non-significant apparent trend towards lower HRV measures among the patients. Our results, however, suggest that there is no major effect of the epilepsy as such on HRV in patients with newly diagnosed epilepsy. It should be emphasized that this study assessed newly diagnosed patients and that the results may not be applicable to patients with chronic epilepsy. It is possible that repeated epileptic seizures over a long period of time, as well as the pathology underlying chronic epilepsy, could result in impaired autonomic cardiac control, reflected in a reduced HRV.

Table 4. Heart Rate Variability in 22 patients with newly diagnosed untreated epilepsy versus age and sex matched controls, 24 h. recording (t-test).

	Age & Sex matched controls (n = 22)		Patients with epilepsy without treatment vs. controls (n = 22)		
	Mean	95 % C.I.	Mean	95 % C.I.	P-val.
SDRR ¹	76.8	62.1-91.7	65.0	53.8-76.2	0.191
TP ¹	5083	2787-7378	3327	2073-4581	0.170
VLF ¹	1491	1041-1940	1214	841-1586	0.329
LF ¹	2132	1112-3153	1326	740-1911	0.161
HF ¹	1460	490-2429	787	411-1163	0.186
LF/HF ¹	2.77	2.26-3.28	2.52	2.02-3.02	0.472

¹SDRR= Standard deviation of RR-intervals (ms), TP= Total frequency power (ms²), VLF=Very low frequency power (ms²), LF=Low frequency power (ms²), HF=High frequency power (ms²), LF/HF=Low frequency power/high frequency power.

4.2 PAPER II

Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Res.* 2003;57(1):69-75

4.2.1 Objective

To assess the effect of CBZ on HRV in patients with newly diagnosed epilepsy.

4.2.2 Results

Data from 15 adult patients with newly diagnosed epilepsy, planned for CBZ treatment but without other AEDs, attending the Department of Neurology at the Karolinska Hospital in Stockholm, Sweden, were analyzed. All patients had been seizure free at least 24 h. before the ECG-recordings and none reported any seizures during the recordings. When analysing the full 24 h. recordings, patients had significantly lower standard deviation of RR-intervals (P = 0.002), TP (P = 0.001), LF (P < 0.001), VLF (P = 0.002) and HF (P = 0.014) during treatment with CBZ than before (Table 5). The results were very similar for daytime and nighttime recordings.

4.2.3 Conclusion

CBZ can apparently suppress both parasympathetic and sympathetic functions in patients with newly diagnosed epilepsy.

Table 5. Twenty-four hour heart rate variability before and during treatment with carbamazepine (CBZ) in 15 patients with epilepsy (paired t-test).

	Before treatment with CBZ (mean \pm S.D.)	During treatment with CBZ (mean \pm S.D.)	P value
SDRR ¹	63 \pm 24	56 \pm 23	0.002
TP ¹	3079 \pm 2054	2370 \pm 1998	0.001
VLF ¹	1228 \pm 905	1025 \pm 808	0.002
LF ¹	1215 \pm 1030	851 \pm 712	0.0002
HF ¹	636 \pm 688	495 \pm 560	0.014
LF/HF ¹	2.73 \pm 1.07	2.95 \pm 0.92	0.233

¹SDRR= Standard deviation of RR-intervals (ms), TP= Total frequency power (ms²), VLF=Very low frequency power (ms²), LF=Low frequency power (ms²), HF=High frequency power (ms²), LF/HF=Low frequency power/high frequency power.

4.3 PAPER III

Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. *Neurology* 2005;65;1021-1025

4.3.1 Objective

To assess differences in HRV before surgery between good and poor responders to epilepsy surgery and to compare patients with refractory TLE with age and sex matched controls.

4.3.2 Results

We used spectral analysis to prospectively analyze HRV preoperatively in 21 consecutive patients with TLE, who were planned for epilepsy surgery at the routine epilepsy surgery programs at the Uppsala University Hospital, Uppsala, Sweden, and the Karolinska University Hospital, Stockholm, Sweden. The presurgical HRV based on ambulatory 24 h. ECG recordings was analyzed in relation to seizure control at one year after surgery. On clinical assessment after surgery, eleven patients had a good outcome and ten had a poor outcome. The entire group of patients with refractory

epilepsy was first compared with the controls. The patients had significantly lower SD of RR-intervals (SDRR) ($P = 0.025$), TP ($P = 0.036$), VLF ($P = 0.007$) and LF ($P = 0.029$) when compared with controls. HF and the ratio of LF/HF did not differ significantly between patients and controls. As a second step in the analysis, we compared patients with good and poor outcome. Before surgery, the HRV was significantly lower in the patients with ultimately poor outcome in all of the analyzed parameters (SDRR ($P = 0.007$), TP ($P = 0.012$), VLF ($P = 0.026$), LF ($P = 0.034$), HF ($P = 0.046$)) except the ratio between LF/HF ($P = 0.736$). When patients with poor outcome were compared with their controls the SDRR ($P = 0.009$), TP ($P = 0.045$), VLF ($P = 0.007$), LF ($P = 0.031$) were significantly lower in the patients. In contrast, patients with good outcome did not differ significantly from the controls (Table 6). Controlling for side of seizure onset by use of ANOVA did not change the observed differences between the groups with poor and good outcome.

4.3.3 Conclusion

Patients with good outcome of epilepsy surgery have a less impaired autonomic cardiac control before surgery than those with poor outcome. This suggests a pre-existing biological difference between those who become seizure free after surgery and those who do not, a difference that might also be of relevance for the risk of SUDEP.

Table 6. Heart Rate Variability before surgery for the 11 patients with good outcome postoperatively and the 10 patients with “poor” outcome after surgery compared with age and sex matched controls (t-test).

	Good outcome after surgery (Engel class I)					Poor outcome after surgery (Engel class II-IV)				
	Age & Sex matched controls (n = 11).		Patients before surgery vs controls (n = 11)			Age & Sex matched controls (n = 10)		Patients before surgery vs controls. (n = 10)		
	Mean	95% C.I.	Mean	95% C.I.	P-value	Mean	95% C.I.	Mean	95% C.I.	P-value
SDRR ¹	69.3	54.0-84.5	66.1	17.7-54.2	0.72	76.6	54.5-98.7	45.9	37.5-54.3	0.009
TP ¹	3749	1958-5531	3105	1955-4245	0.51	4954	1351-8577	1473	886-2059	0.045
VLF ¹	1408	861-1956	1106	692-1521	0.33	1673	893-2453	584	358-801	0.007
LF ¹	1594	834-2354	1293	668-1918	0.5	2086	656-3517	588	368-807	0.031
HF ¹	746	201-1293	706	333-1078	0.89	1204	-301-2711	300	133-458	0.194
LF/HF ¹	3.48	2.52-4.33	3.11	1.65-4.58	0.54	4	2.78-5.21	2.87	2.39-3.36	0.587

¹SDRR= Standard deviation of RR-intervals (ms), TP= Total frequency power (ms²), VLF=Very low frequency power (ms²), LF=Low frequency power (ms²), HF=High frequency power (ms²), LF/HF=Low frequency power/high frequency power.

4.4 PAPER IV

Persson H, Kumlien E, Ericson M, Tomson T. No apparent effect of surgery for temporal lobe epilepsy on heart rate variability. *Epilepsy Research* 2006; 70: 127-132

4.4.1 Objective

To investigate the effect of temporal lobe surgery for epilepsy on HRV in patients with refractory epilepsy.

4.4.2 Results

We used the same patients and controls as in paper III. A new ambulatory 24 h. digital ECG recording was made in all patients at least six months after surgery. These data were compared with the HRV data before surgery, as reported in paper III. Eleven patients were considered to have a good outcome, and ten to have poor outcome of epilepsy surgery. We first compared the postoperative HRV for the entire group of epilepsy patients versus the controls and thereafter separately the groups with good and poor surgical outcome with their controls. The entire group of 21 patients had significantly lower standard deviation of RR-intervals (SDRR) ($P = 0.002$), TP ($P = 0.011$), VLF ($P = 0.001$) and LF ($P = 0.010$) than the controls. HF ($P = 0.076$) and the LF/HF ($P = 0.132$) ratio did not differ significantly between the patients and controls. When patients with poor surgery outcome were compared with their controls, the SDRR ($P = 0.01$), TP ($P = 0.049$), VLF ($P = 0.008$) and LF ($P = 0.039$) were significantly lower in the patients. In contrast, patients with good outcome did not differ significantly from the controls. Secondly, using each patient as his/her own control, we analyzed HRV after versus before surgery. We found no difference in any HRV measure for the entire group of 21 patients (SDRR, $P = 0.74$; TP, $P = 0.81$; VLF, $P = 0.52$; LF, $P = 0.61$; HF, $P = 0.25$; LF/HF, $P = 0.21$), neither when those with good (SDRR, $P = 0.41$; TP, $P = 0.33$; VLF, $P = 0.99$; LF, $P = 0.82$; HF, $P = 0.19$; LF/HF, $P = 0.07$) and poor surgery outcome (SDRR, $P = 0.41$; TP, $P = 0.33$; VLF, $P = 0.26$; LF, $P = 0.40$; HF, $P = 0.38$; LF/HF, $P = 0.68$) were analyzed separately (Table 7).

4.4.3 Conclusion

We could not demonstrate any effect of TLE surgery on HRV in our patients with refractory TLE. The observed lower HRV in the poor outcome group was present already before epilepsy surgery, as previously reported in paper III. Our observations, however, need to be confirmed in independent studies on larger patient groups.

Table 7. Heart Rate Variability in 24 h. ambulant recordings in 21 patients with temporal lobe epilepsy and in the ten patients with good (Engel I) and eleven patients with poor outcome (Engel II-IV) before versus after temporal lobe surgery (paired t-test).

	All patients 24 h. recording (n = 21)					Good outcome, (Engel I), 24 h. rec. (n = 11)					Poor outcome, (Engel II-IV), 24 h. rec. (n = 10)				
	Before surgery		After surgery			Before surgery		After surgery			Before surgery		After surgery		
	Mean	95 % C.I.	Mean	95 % C.I.	P-val.	Mean	95 % C.I.	Mean	95 % C.I.	Pval.	Mean	95 % C.I.	Mean	95 % C.I.	P-val.
SDRR ¹	52.8	45.7-59.9	51.9	45.9-57.9	0.744	60.5	49.0-71.9	56.5	47.1-66.0	0.406	44.4	38.5-50.3	46.8	39.3-54.3	0.412
TP ¹	2005	1428-2581	1961	1457-2464	0.811	2616	1628- 3604	2334	1474-3193	0.334	1332	1012-1653	1550	1025-2075	0.334
VLF ¹	735	534-937	772	596-948	0.524	924	567-1281	914	635-1194	0.909	528	408-648	616	402-830	0.264
LF ¹	806	548-1065	841	582-1100	0.609	1031	565-1497	1011	558-1464	0.820	559	394-724	655	388-922	0.401
HF ¹	463	252-674	347	253-441	0.252	661	273-1048	408	236.39580	0.188	246	178-314	280	198-361	0.379
LF/HF ¹	2.89	2.25-3.53	3.07	2.49-3.65	0.212	2.72	1.47-3.96	3.13	2.07-4.20	0.067	3.07	2.56-3.58	3.00	2.36-3.63	0.684

¹SDRR= Standard deviation of RR-intervals (ms), TP= Total frequency power (ms²), VLF=Very low frequency power (ms²), LF=Low frequency power (ms²), HF=High frequency power (ms²), LF/HF=Low frequency power/high frequency power.

4.5 PAPER V

Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart rate variability in localization related epilepsy. *Accepted for publication in Epilepsia*.

4.5.1 Objective

To investigate circadian variation in HRV in patients with newly diagnosed and refractory localization-related epilepsy compared with age and sex matched healthy controls, and to assess the effects of drug treatment and epilepsy surgery on the night/day time HRV ratio.

4.5.2 Results

We used previously collected data from two patient groups: (1) *14 patients with newly diagnosed localization related epilepsy*. These patients were among those used for papers I and II. (2) *21 epilepsy surgery candidates* from the routine epilepsy surgery programs at the Uppsala University Hospital, Uppsala, Sweden, and the Karolinska University Hospital, Stockholm. These patients are described in detail in papers III and IV. For each patient one healthy control subject was selected, matched for age and sex. The controls were selected from a bank of previously recorded healthy volunteers.

When patients with newly diagnosed epilepsy were compared with their healthy controls, there were no significant differences in the night/day time ratios of HRV in time or frequency domains, regardless if compared before or after initiation of treatment with CBZ. However, when the patients were used as their own controls, night/day time ratios of SDRR ($P = 0.04$) and TP ($P = 0.04$) were significantly lower during treatment than before, and there was also a trend towards lower LF ($P = 0.06$). With respect to the epilepsy surgery patients, the night/day time ratios of LF ($P = 0.04$) and HF ($P = 0.04$) were significantly lower when compared with controls before surgery, whereas no significant differences between patients and controls were noted after surgery. Furthermore, night/day time ratios did not change significantly after surgery compared to before the operation. We finally compared preoperative night/day time ratios in epilepsy surgery patients with an ultimately poor outcome of surgery (Engel class II-IV; $n = 10$) to those in patients with good surgery outcome (Engel class I; $n = 11$) and found no significant difference between the two groups.

4.5.3 Conclusion

In this *post hoc* analysis of two different cohorts of patients with localization related epilepsy, we have noted that the decrease in HRV that has been observed among people with epilepsy in some aspects may be more pronounced during night time, thus affecting the circadian HRV. Treatment with CBZ significantly reduced night/day time ratios of SDRR and TP in newly diagnosed patients. Patients with refractory TLE had decreased night/day time ratios of LF and HF, hence sympathetic as well as parasympathetic activity, while the surgical procedure did not seem to affect circadian HRV. Although the small number of patients, and low statistical power

call for caution in interpretation of negative results, our findings suggest that the anterior part of the temporal lobe does not play a major role in the circadian regulation of HRV

Table 8. Night (00.00-05.30) /day (07.30-21.30) ratios in 14 newly diagnosed patients with localization-related epilepsy, before versus during treatment with carbamazepine (paired t-test) and in 21 patients with temporal lobe epilepsy before surgery versus age and sex matched controls (Mann-Whitney two sample test)

	Newly diagnosed patients with localization-related epilepsy (n=14)					Medically refractory patients with TLE (n=21)				
	Untreated		Treated with CBZ			Before epilepsy surgery		Age and sex matched controls		
Night/Day ratios	Mean	95 % C.I.	Mean	95 % C.I.	p-value	Mean	95 % C.I.	Mean	95 % C.I.	P-value
SDRR ¹	1.07	0.93-1.22	0.97	0.80-1.14	0.04	0.98	0.82-1.14	1.07	0.94-1.19	0.12
TP ¹	1.58	1.10-2.05	1.33	0.94-1.71	0.04	1.17	0.78-1.56	1.39	1.10-1.69	0.13
LF ¹	1.40	0.83-1.98	1.10	0.73-1.48	0.06	0.96	0.69-1.23	1.29	0.96-1.62	0.04
HF ¹	2.40	1.48-3.32	2.39	1.49-3.29	0.95	1.71	1.08-2.34	2.13	1.68-2.58	0.04

¹SDRR= Standard deviation of RR-intervals (ms), TP= Total frequency power (ms²), LF=Low frequency power (ms²), HF=High frequency power (ms²).

5 DISCUSSION

5.1 USE OF HRV AS A MEASURE OF AUTONOMIC CONTROL

We chose to study cardiac autonomic control with HRV measures because this method is widely used in studies on disturbed autonomic control in relation to sudden death in other diseases (Bigger et al., 1992b; Binder et al., 1992; Cohen et al., 2001; Kleiger et al., 1987; Spallone et al., 1996; Takase et al., 1992; Tokgozoglul et al., 1999; Zuanetti et al., 1991). With use of spectral analysis of HRV it is possible to partly separate the sympathetic components from the vagal components and thus attain more information about the quality of autonomic control (van Ravenswaaij-Arts et al., 1993). HF reflects respiratory sinus arrhythmia and is mainly related to parasympathetic activity (Akselrod et al., 1981; Katona and Jih, 1975; Pomeranz et al., 1985). LF oscillations are associated with baroreflexor control of sympathetic activity (Akselrod et al., 1981; Pagani et al., 1986; Pomeranz et al., 1985), but parasympathetic activity might also influence LF (Saul et al., 1990). The mechanism behind VLF is not completely understood (Kitney, 1973). The LF/HF ratio is commonly considered to reflect the sympatho-vagal balance (Malliani et al., 1994) (Table 2.).

We used 24-hour ambulatory monitoring of HRV and thus received information from night, day, and normal activities. The Task Force on HRV concluded that 24-hour ambulatory monitoring with 24-hour indices appears to be stable and free of placebo effect and may be ideal variables to assess intervention (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996).

5.2 HRV IN EPILEPSY PATIENTS

We have assessed HRV in two patient cohorts representing the extremes of the spectrum of epilepsy – newly diagnosed epilepsy and candidates for epilepsy surgery, respectively – and in addition analyzed the effects of treatment in the two groups. These groups are of special interest since they also represent the extremes regarding risk of SUDEP.

The only previous study of HRV in newly diagnosed epilepsy reported reduced HF, increased LF and consequently an increased LF/HF ratio in 42 young men (military recruits) with newly diagnosed generalized tonic-clonic seizures, compared with healthy controls (Evrengul et al., 2005). In our present study, we could not confirm the findings from the study of Evrengul and collaborators. In contrast, HRV measures in our patients with newly diagnosed epilepsy were not different in any respect from the results obtained in the age and sex matched healthy controls. We cannot exclude that the lack of significance in our study was due to the smaller number of patients and the limited statistical power, but the trends in our study suggests lower LF and LF/HF ratio rather than the opposite, as in the study of Evrengul et al. There are methodological differences that can contribute to the divergent outcomes of the two studies. In order to qualify for inclusion in the study on military recruits with suspected epilepsy, patients had to stay in hospital until they had a seizure recorded on video surveillance in the hospital department. Thus, the patients had been hospitalized for 42 ± 11 (mean \pm SD) days before the ECG recordings. Although it seems unlikely, it is unclear whether the

controls had been subjected to the same procedure. It is conceivable that 42 days of hospitalization in a military hospital awaiting a seizure could contribute to an increased sympathetic tone, which then would explain the findings. In our study, the procedures for assessment of HRV were the same for patients and controls, an ambulatory 24 h. ECG recording. Hence, we were unable to demonstrate any major effects of newly diagnosed epilepsy as such on HRV.

When we examined partially the same patients after commencement of CBZ treatment and compared the results with before treatment, we could for the first time demonstrate that initiation of CBZ treatment in patients with epilepsy results in significantly reduced power in all analyzed frequency bands, indicating suppression of both parasympathetic and sympathetic function. Two previous studies have analyzed HRV in conjunction with abrupt withdrawal of CBZ, both suggesting increased LH/HF ratios after withdrawal, indicating an increased sympathetic tone (Hennessy et al., 2001; Kenneback et al., 1997). These studies assessed effects of abrupt drug withdrawal rather than direct effects of CBZ on autonomic cardiac control, and can therefore not be compared directly with our observations. In a study on patients with TLE, those treated with CBZ had reduced SDRR and Valsalva ratio compared with controls, although this reduction was not statistically significant (Ansakorpi, 2003).

The *post hoc* analysis of circadian variation revealed a particularly marked reduction during night time in SDRR and TP with a reduced night/day time ratio, i.e. a suppressed circadian HRV, in these measures after initiation of CBZ treatment. SDRR and TP are highly correlated measures that combine all sources of HRV, thus indicating unspecific disturbed autonomic cardiac function but providing little insight into the physiologic mechanisms (Bigger et al., 1992b; Sztajzel, 2004). Reduction in these two measures predict mortality in other diseases, for example myocardial infarction (Bigger et al., 1992a; Kleiger et al., 1987). CBZ is a sodium channel blocker with affinity to the type IIA sodium channels both in the CNS and in the cardiac conduction system and myocardium (Hennessy et al., 2001). This affinity is shared with phenytoin and lamotrigine (Catterall, 1999). Further studies are needed to evaluate the effects of phenytoin, lamotrigine and other AEDs on HRV in patients with epilepsy.

In our studies on 21 patients with refractory TLE, eventually operated on with temporal lobectomy, we found lower preoperative HRV in patients awaiting TLE surgery compared with controls. Although this group of refractory epilepsy patients as a whole differed significantly from matched healthy controls, it was the subgroup of patients with a poor outcome of surgery that accounted for the reduction in HRV. Patients with a favourable outcome of the temporal lobe surgery did not differ from healthy controls in their preoperative HRV. This observation suggests that patients with poor outcome of surgery *a priori* differ from those with good outcome, with respect to autonomic cardiac control. Interestingly, another study reported a different 4–9 per minute (0.07 Hz–0.16 Hz) HRV pattern interictally before surgery in four “poor” candidates for anterior temporal lobe resection (two with seizures postoperatively and two patients not recommended for surgery), compared with 13 patients with an excellent outcome of surgery (Frysjinger et al., 1993). This frequency corresponds approximately to the LF we use (0.04–0.15 Hz).

After temporal lobectomy there was still, in accordance with the preoperative data, lower SDRR, TP, VLF, LF but not HF or LF/HF in the poor outcome group, in comparison with the matched healthy controls. We did not find any effect of surgery on

HRV in our study. However, we can not exclude that the apparent lack of effect is related to the small numbers.

In a previous study on sympathetic modulation in 16 patients with TLE who had undergone epilepsy surgery, the postoperative LF/HF ratio was higher in the poor outcome versus the good outcome group (Hilz et al., 2003). We could not confirm this difference. The same study also reported an increase in LF and LF/HF ratio after surgery in the poor outcome group, whereas we could see no effect of surgery on any HRV measure, be it responders or non-responders. There are methodological differences that hamper a direct comparison between our study and theirs. First, they employed a fast Fourier transformation of 10 min HR recordings, whereas we used spectral analysis based on 24 h. recordings under normal daily activities. Secondly, they selected patients after the surgical outcome was known, whereas we included patients prospectively. Finally, there was a slightly higher number of patients in our study, which should increase our statistical power.

The *post hoc* analysis of circadian rhythm of HRV of the same patients demonstrated reduced night/day time ratios in LF and HF before surgery compared with healthy controls, but with very similar ratios after surgery, and thus no significant effect of the operation.

One previous study from Finland has recently reported night/day time ratios of HRV in patients with TLE, 17 with refractory and 20 with well controlled epilepsy (Ronkainen et al., 2005). Although these patients just like ours had localization related epilepsy, they are not directly comparable to our cohorts. All patients in the Finnish study had chronic epilepsy, the mean duration of epilepsy in the well controlled group being 14.2 years. The patients with refractory TLE were not considered suitable for epilepsy surgery. Nevertheless, Ronkainen and co-workers also observed a lower night/day time ratio of SDRR among patients compared with healthy controls (Ronkainen et al., 2005). Even so, they found no significant difference in mean night/day time ratios in LF or HF between patients and controls, whereas we observed reduced night/day time ratios in these spectral components among our refractory epilepsy surgery candidates. Although Ronkainen and collaborators found no differences in night/day time ratios of HRV between those with refractory and well controlled epilepsy, it is likely that the heterogeneity of their cohort could contribute to their failure to detect differences in circadian HRV that were evident in our epilepsy surgery candidates.

5.3 HRV FINDINGS AND RISK FACTORS FOR SUDEP

We could not demonstrate any significant difference in HRV measures between our patients with untreated newly diagnosed epilepsy and matched healthy controls. This observation needs to be interpreted with some caution because of the limited number of included patients and the non-significant apparent trend towards lower HRV measures among the patients. Our results, however, suggest that there is no major effect of the epilepsy as such on HRV in patients with newly diagnosed epilepsy. On the other hand, treatment with AEDs may be a reason for decreased HRV in this type of patients. Treatment with CBZ reduced LF and HF, indicating suppressed parasympathetic and sympathetic function, and also altered the circadian rhythm of cardiac control. In the patients with refractory epilepsy, our findings suggests parasympathetic as well as sympathetic suppression compared with age and sex matched controls. They also had

disturbed circadian rhythm. The alteration in HRV seemed to be more pronounced in the subgroup of patient with eventually poor surgical outcome. Temporal lobe resection *per se* does not seem to alter the HRV. Although the mechanisms behind SUDEP remain unclear, the prevailing hypothesis involves seizure induced cardio-respiratory disturbances mediated by the autonomic nervous system (Nashef et al., 1996). Case-control studies have revealed poor seizure control as the major risk factor for SUDEP (Nilsson et al., 1999; Walczak et al., 2001). However, case-control studies also suggest that treatment with AEDs might contribute. Polytherapy with AEDs has been identified as a risk factor independent of seizure control (Nilsson et al., 1999; Walczak et al., 2001), as have frequent dose changes and high serum concentrations of CBZ (Nilsson et al., 1999).

With respect to the risk of SUDEP, it is intriguing that we failed to find any reduction in HRV in these patients with newly diagnosed epilepsy, a group that probably has the lowest risk of SUDEP among the epilepsy population (Tomson et al., 2005). This is in contrast to the decreased HRV in patients with chronic refractory epilepsy, a high risk group for SUDEP. It is interesting to note that that patients with good outcome of epilepsy surgery, and thus according to other studies (Hennessy et al., 1999; Salanova et al., 2002; Sperling et al., 1999) a lower risk of SUDEP, have a less impaired autonomic cardiac control before surgery than do those with poor outcome. The more pronounced abnormalities in HRV among those with less favourable surgery outcome, may be a reflection of a more widespread epileptogenic zone with involvement of the insula or the frontal operculum (Ryvlin and Kahane, 2003). Stroke involving the region of insula has been shown to result in decreased HRV and also an increased risk of sudden death (Tokgozoglu et al., 1999). In the *post hoc* analysis of the two different cohorts of patients with localization related epilepsy, the HRV was more affected during night time, the time when the risk of SUDEP seems to be highest in such patients. We also found evidence that CBZ reduced TP, LF and HF, in some studies CBZ have been overrepresented in SUDEP cases (Langan et al., 2005; Timmings, 1998), whereas most controlled studies have failed to find an association between a particular AED and SUDEP (Kloster and Engelskjøn, 1999; Nilsson et al., 1999; Walczak et al., 2001). Hence, taken together our results indicate that there is an impaired autonomic cardiac control, reflected in decreased HRV, preferentially among the type of epilepsy patients that have been considered to have a higher risk of SUDEP.

5.4 FUTURE PERSPECTIVES

Our findings thus suggest that epilepsy cohorts with a high risk for SUDEP also have reduced HRV. Further support for this comes from a preliminary retrospective study of seven SUDEP victims. Those with SUDEP had reduced HF on previously recorded ECG compared to other epilepsy patients, healthy controls, and patients with non-epileptic seizures (Eppinger et al., 2004). However, the potential predictive value of reduced HRV for SUDEP needs to be confirmed in large prospective studies. This could focus on high risk cohorts such as epilepsy surgery candidates and be conducted as a multicenter collaboration between epilepsy surgery centers collecting prospective ECG data for spectral analysis from presurgical patient monitoring, and include a long term follow-up to identify future SUDEP cases. Our findings also suggest that HRV might be added to the many methods used for selection of patients likely to benefit

from epilepsy surgery. This hypothesis is also in need of confirmation in larger prospective studies with collection of presurgical ECG data for prospective analysis of HRV in relation to surgical outcome. A study with collection of presurgical ECG with simultaneous intracranial EEG recordings, with focus on the insular lobe, would be useful in order to explore the possible association between seizure activity in the insular lobe and reduced HRV. These data could also be analyzed in relation to surgical outcome to assess if such activity is the common denominator behind poor surgical outcome and reduced HRV. Moreover, such a study might also indicate if reduced HRV could be used for selection of patients for intracranial EEG recordings in the presurgical work-up.

6 CONCLUSION

- We found no effect of epilepsy per se on HRV in patients with newly diagnosed epilepsy (paper I).
- Treatment with CBZ decrease SDRR, VLF, LF, HF and TP, and apparently suppresses both parasympathetic and sympathetic functions in patients with newly diagnosed epilepsy (paper II).
- Before surgery, patients with poor outcome of epilepsy surgery had a more impaired autonomic cardiac control than those with a good outcome. They had diminished SDRR, TP, VLF, LF and HF, indicating suppressed parasympathetic and parasympathetic function (paper III).
- We could not demonstrate any effect of TLE surgery on HRV in our patients with refractory TLE (paper IV).
- In newly diagnosed patients, treatment with CBZ decreases the night/day ratio of SDRR and TP, suggesting that CBZ affects circadian regulation of HRV. Patients with TLE had reduced night/day ratios of LF and HF, hence suppressed parasympathetic and sympathetic function. Temporal lobe resection did not change the night/ratio suggesting that the anterior part of the temporal lobe does not play a major role in the circadian regulation of HRV.

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8 REFERENCES

- Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; 213: 220-2.
- al Maskati HA, Zbrozyna AW. Cardiovascular and motor components of the defence reaction elicited in rats by electrical and chemical stimulation in amygdala. *J Auton Nerv Syst* 1989; 28: 127-31.
- Ansakorpi H. Cardiovascular regulation in epilepsy with emphasis on the interictal state. Faculty of Medicine. Oulu: University of Oulu, 2003: 92.
- Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllyla VV, Isojarvi JI. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2002; 72: 26-30.
- Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllyla VV, Isojarvi JI. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. *Epilepsia* 2000; 41: 42-7.
- Bauman JA, Feoli E, Romanelli P, Doyle WK, Devinsky O, Weiner HL. Multistage epilepsy surgery: safety, efficacy, and utility of a novel approach in pediatric extratemporal epilepsy. *Neurosurgery* 2005; 56: 318-34.
- Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc* 1993; 68: 988-1001.
- Bigger JT, Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. *Am J Cardiol* 1992a; 69: 891-8.
- Bigger JT, Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992b; 85: 164-71.
- Binder T, Frey B, Porenta G, Heinz G, Wutte M, Kreiner G, et al. Prognostic value of heart rate variability in patients awaiting cardiac transplantation. *Pacing Clin Electrophysiol* 1992; 15: 2215-20.
- Bird J, Dembny K, Sandeman D, Butler S. Sudden unexplained death in epilepsy: an intracranially monitored case. *Epilepsia* 1997; 38: 52-56.
- Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurology* 2002; 58: S2-8.
- Burg J. Maximum entropy spectral analysis. 37th Meeting of the Society of Exploration Geophysicists, 1967.
- Catterall WA. Molecular properties of brain sodium channels: an important target for anticonvulsant drugs. *Adv Neurol* 1999; 79: 441-56.
- Cechetto DF, Saper CB. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. *J Comp Neurol* 1987; 262: 27-45.
- Cohen H, Loewenthal U, Matar M, Kotler M. Association of autonomic dysfunction and clozapine. Heart rate variability and risk for sudden death in patients with schizophrenia on long-term psychotropic medication. *Br J Psychiatry* 2001; 179: 167-71.
- Dampney RA. Functional organization of central pathways regulating the cardiovascular system. *Physiol Rev* 1994; 74: 323-64.
- Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet* 2006; 367: 1087-100.
- Engel J, Jr. Report of the ILAE Classification Core Group. *Epilepsia* 2006; 47: 1558-68.
- Engel J, Jr., Kuhl DE, Phelps ME, Crandall PH. Comparative localization of epileptic foci in partial epilepsy by PCT and EEG. *Ann Neurol* 1982; 12: 529-37.
- Engel J, Van Ness P, Rasmussen T. Outcome with respect to epileptic seizures. New York: Raven Press, 1993.

- Eppinger N, Shaumann R, Jokeit H, Buettner U, Kraemer G. Reduced heart rate variability (HRV) in victims of sudden death in epilepsy (SUDEP). *Epilepsia* 2004; 45: 65.
- Evrengul H, Tanriverdi H, Dursunoglu D, Kaftan A, Kuru O, Unlu U, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. *Epilepsy Res* 2005; 63: 131-9.
- Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology* 1998; 51: 1270-4.
- Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46: 470-2.
- Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe - a systematic review. *Eur J Neurol* 2005; 12: 245-53.
- Fryssinger RC, Engel J, Harper RM. Interictal heart rate patterns in partial seizure disorders. *Neurology* 1993; 43: 2136-9.
- Ganong W. 14. Central Regulation of Visceral Function. Review of Medical Physiology - 22nd Ed. New York: Lange Medical Books/McGraw-Hill, 2005.
- Gastaut H. Dictionary of epilepsy. Geneva: World Health Organization. 1973.
- Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE. Response of multiple seizure types to corpus callosum section. *Epilepsia* 1987; 28: 28-34.
- Granger N, Convers P, Beauchet O, Imler D, Viallon A, Laurent B, et al. [First epileptic seizure in the elderly: electroclinical and etiological data in 341 patients]. *Rev Neurol (Paris)* 2002; 158: 1088-95.
- Gutierrez-Delicado E, Serratosa JM. Genetics of the epilepsies. *Curr Opin Neurol* 2004; 17: 147-53.
- Hennessy MJ, Langan Y, Elwes RD, Binnie CD, Polkey CE, Nashef L. A study of mortality after temporal lobe epilepsy surgery. *Neurology* 1999; 53: 1276-83.
- Hennessy MJ, Tighe MG, Binnie CD, Nashef L. Sudden withdrawal of carbamazepine increases cardiac sympathetic activity in sleep. *Neurology* 2001; 57: 1650-4.
- Hilz MJ, Dutsch M. Quantitative studies of autonomic function. *Muscle Nerve* 2006; 33: 6-20.
- Hilz MJ, Platsch G, Druschky K, Pauli E, Kuwert T, Stefan H, et al. Outcome of epilepsy surgery correlates with sympathetic modulation and neuroimaging of the heart. *J Neurol Sci* 2003; 216: 153-62.
- ILAE. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981; 22: 489-501.
- ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989; 30: 389-99.
- Inui K, Nosaka S. Target site of inhibition mediated by midbrain periaqueductal gray matter of baroreflex vagal bradycardia. *J Neurophysiol* 1993; 70: 2205-14.
- Isojarvi JI, Ansakorpi H, Suominen K, Tolonen U, Repo M, Myllyla VV. Interictal cardiovascular autonomic responses in patients with epilepsy. *Epilepsia* 1998; 39: 420-6.
- Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death. *Ann Neurol* 1997; 42: 588-94.
- Kahle W, Frotscher M. Nervous System and Sensory Organs. Color Atlas of Human Anatomy. Vol 3 Nervous System and Sensory Organs. Stuttgart: Georg Thieme Verlag, 2003: 196.
- Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. *J Appl Physiol* 1975; 39: 801-5.
- Kenneback G, Ericson M, Tomson T, Bergfeldt L. Changes in arrhythmia profile and heart rate variability during abrupt withdrawal of antiepileptic drugs. Implications for sudden death. *Seizure* 1997; 6: 369-75.
- Kitney RI. The use of entrainment in the analysis of the human thermoregulatory system. *J Physiol* 1973; 229: 40P-41P.

- Kleiger RE, Miller JP, Bigger JT, Jr., Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59: 256-62.
- Kloster R, Engelskjøn T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. *J Neurol Neurosurg Psychiatry* 1999; 67: 439-44.
- Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. *Stroke* 1997; 28: 2150-4.
- Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry* 2000; 68: 211-3.
- Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology* 2005; 64: 1131-3.
- Lathers CM, Schraeder PL. Autonomic dysfunction in epilepsy: characterization of autonomic cardiac neural discharge associated with pentylentetrazol-induced epileptogenic activity. *Epilepsia* 1982; 23: 633-47.
- Lathers CM, Schraeder PL, Weiner FL. Synchronization of cardiac autonomic neural discharge with epileptogenic activity: the lockstep phenomenon. *Electroencephalogr Clin Neurophysiol* 1987; 67: 247-59.
- Leestma J. Sudden unexpected death associated with seizures: a pathological review. In: Lathers C and Schraeder P, editors. *Epilepsy and sudden death*. New York: Marcel Dekker, 1990: 61-88.
- Leestma JE, Annegers JF, Brodie MJ, Brown S, Schraeder P, Siscovick D, et al. Sudden unexplained death in epilepsy: observations from a large clinical development program. *Epilepsia* 1997; 38: 47-55.
- Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J* 1994; 71: 1-2.
- Malmgren K, Sullivan M, Ekstedt G, Kullberg G, Kumlien E. Health-related quality of life after epilepsy surgery: a Swedish multicenter study. *Epilepsia* 1997; 38: 830-8.
- Massetani R, Strata G, Galli R, Gori S, Gneri C, Limbruno U, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. *Epilepsia* 1997; 38: 363-9.
- Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 1995; 36: 1187-94.
- Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *J Neurol Neurosurg Psychiatry* 1996; 60: 297-300.
- Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet* 1999; 353: 888-93.
- Oppenheimer S. Cerebrogenic cardiac arrhythmias: cortical lateralization and clinical significance. *Clin Auton Res* 2006; 16: 6-11.
- Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF. Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? *Brain Res* 1991; 550: 115-21.
- Ottersen OP. Afferent connections to the amygdaloid complex of the rat with some observations in the cat. III. Afferents from the lower brain stem. *J Comp Neurol* 1981; 202: 335-56.
- Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; 59: 178-93.
- Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Res* 2003; 57: 69-75.
- Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated newly diagnosed epilepsy. Manuscript submitted 2006a.
- Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. *Neurology* 2005; 65: 1021-5.

- Persson H, Kumlien E, Ericson M, Tomson T. Circadian variation in heart rate variability in localization related epilepsy. *Epilepsia*, accepted for publication 30/9 2006 2006b.
- Persson H, Kumlien E, Ericson M, Tomson T. No apparent effect of surgery for temporal lobe epilepsy on heart rate variability. *Epilepsy Research* 2006c; 70: 127-132.
- Persson HB, Alberts KA, Farahmand BY, Tomson T. Risk of extremity fractures in adult outpatients with epilepsy. *Epilepsia* 2002; 43: 768-72.
- Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; 248: H151-3.
- Rasmussen T. Hemispherectomy for seizures revisited. *Can J Neurol Sci* 1983; 10: 71-8.
- Rohkamm R. *Color Atlas of Neurology*. Stuttgart: Georg Thieme Verlag, 2004.
- Ronkainen E, Ansakorpi H, Huikuri HV, Myllylä VV, Isojarvi JI, Korpelainen JT. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2005; 76: 1382-6.
- Ropper A, Brown R. *ADAMS AND VICTOR'S PRINCIPLES OF NEUROLOGY: The McGraw-Hill Companies, Inc*, 2005.
- Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* 2004; 364: 2212-9.
- Ruskin JN. The cardiac arrhythmia suppression trial (CAST). *N Engl J Med* 1989; 321: 386-8.
- Rydenhag B, Silander HC. Complications of epilepsy surgery after 654 procedures in Sweden, September 1990-1995: a multicenter study based on the Swedish National Epilepsy Surgery Register. *Neurosurgery* 2001; 49: 51-6; discussion 56-7.
- Ryvlin P, Kahane P. Does epilepsy surgery lower the mortality of drug-resistant epilepsy? *Epilepsy Res* 2003; 56: 105-20.
- Ryvlin P, Montavont A, Kahane P. Sudden unexpected death in epilepsy: from mechanisms to prevention. *Curr Opin Neurol* 2006; 19: 194-9.
- Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia* 2002; 43: 170-4.
- Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol* 2003; 16: 165-70.
- Saul JP, Rea RF, Eckberg DL, Berger RD, Cohen RJ. Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *Am J Physiol* 1990; 258: H713-21.
- Silbernagl S, Lang F. *Color atlas of Patophysiology*. Color atlas of Patophysiology. Stuttgart: Georg Thieme Verlag, 2000.
- Spallone V, Bernardi L, Maiello MR, Cicconetti E, Ricordi L, Fratino P, et al. Twenty-four-hour pattern of blood pressure and spectral analysis of heart rate variability in diabetic patients with various degrees of autonomic neuropathy. Comparison to standard cardiovascular tests. *Clin Sci (Lond)* 1996; 91 Suppl: 105-7.
- Spencer DD, Spencer SS, Mattson RH, Williamson PD, Novelly RA. Access to the posterior medial temporal lobe structures in the surgical treatment of temporal lobe epilepsy. *Neurosurgery* 1984; 15: 667-71.
- Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. *Ann Neurol* 1999; 46: 45-50.
- Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. *Swiss Med Wkly* 2004; 134: 514-22.
- Takase B, Kurita A, Noritake M, Uehata A, Maruyama T, Nagayoshi H, et al. Heart rate variability in patients with diabetes mellitus, ischemic heart disease, and congestive heart failure. *J Electrocardiol* 1992; 25: 79-88.
- Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93: 1043-65.

- Tavares RF, Antunes-Rodrigues J, de Aguiar Correa FM. Pressor effects of electrical stimulation of medial prefrontal cortex in unanesthetized rats. *J Neurosci Res* 2004; 77: 613-20.
- Tellez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. *Epilepsy Res* 2005; 65: 101-15.
- Thom M, Seetah S, Sisodiya S, Koepp M, Scaravilli F. Sudden and unexpected death in epilepsy (SUDEP): evidence of acute neuronal injury using HSP-70 and c-Jun immunohistochemistry. *Neuropathol Appl Neurobiol* 2003; 29: 132-43.
- Timmings PL. Sudden unexpected death in epilepsy: is carbamazepine implicated? *Seizure* 1998; 7: 289-91.
- Tokgozoglu SL, Batur MK, Top uoglu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. *Stroke* 1999; 30: 1307-11.
- Tomson T. Excess mortality in epilepsy in developing countries. *Lancet Neurol* 2006; 5: 804-5.
- Tomson T, Beghi E, Sundqvist A, Johannessen SI. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention. *Epilepsy Res* 2004; 60: 1-16.
- Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. *Epilepsy Res* 1998; 30: 77-83.
- Tomson T, Walczak T, Sillanpaa M, Sander JW. Sudden unexpected death in epilepsy: a review of incidence and risk factors. *Epilepsia* 2005; 46 Suppl 11: 54-61.
- Wada J, Rasmussen T. Intracarotid injection of sodium amobarbital for the lateralization of speech dominance; experimental and clinical observations. *J Neurosurg* 1960: 226-282.
- Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001; 56: 519-25.
- Walker MC, Shorvon S. Partial Epilepsy Syndromes in Adults. In: Porter R and Chadwick D, editors. *The Epilepsies 2*. Boston: Butterworth-Heinemann, 1997: 141-157.
- van Ravenswaaij-Arts CM, Kollee LA, Hopman JC, Stoeltinga GB, van Geijn HP. Heart rate variability. *Ann Intern Med* 1993; 118: 436-47.
- Verberne AJ, Owens NC. Cortical modulation of the cardiovascular system. *Prog Neurobiol* 1998; 54: 149-68.
- Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; 345: 311-8.
- Zuanetti G, Latini R, Neilson JM, Schwartz PJ, Ewing DJ. Heart rate variability in patients with ventricular arrhythmias: effect of antiarrhythmic drugs. Antiarrhythmic Drug Evaluation Group (ADEG). *J Am Coll Cardiol* 1991; 17: 604-12.