

**CARDIOVASCULAR
REGULATION IN EPILEPSY
WITH EMPHASIS ON THE
INTERICTAL STATE**

**HANNA
ANSAKORPI**

Department of Neurology,
Department of Clinical Neurophysiology,
University of Oulu

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Supervised by
Docent Jouko Isojärvi
Docent Juha Korpelainen

Reviewed by
Professor Torbjörn Tomson
Docent Arne Ylinen

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Department of Neurology, Department of Clinical Neurophysiology, University of Oulu, P.O.Box 5000, FIN-90014 University of Oulu, Finland
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Abstract

Epilepsy is associated with changes in autonomic cardioregulatory function. Ictally, autonomic disturbances may be evident with significant changes in heart rate (HR), blood pressure (BP) and respiration. However, interictal dysfunction of autonomic cardiovascular system may be subtle and it may be recognized only by delicate tools designed for that purpose. The aim of this study was to evaluate the function of the cardiovascular autonomic regulatory system in patients with epilepsy.

Cardiovascular reflex tests were performed on patients with partial or idiopathic generalized epilepsies. Special attention was paid to temporal lobe epilepsy (TLE). An association of refractory and well controlled TLE and hippocampal sclerosis with altered cardioregulation was evaluated by using cardiovascular reflex tests and an analysis of spectral and non-linear analysis of heart rate variation (HRV).

Cardiovascular reflexes were altered both in patients with partial and idiopathic generalized epilepsies who had been treated for epilepsy with antiepileptic drugs (AEDs), whereas patients with newly, untreated epilepsy did not differ from the control subjects. Diminished cardiovascular reflexes also seemed to be associated with carbamazepine (CBZ) treatment. Various parameters of cardiovascular reflex tests and analysis of spectral and dynamic measures of HRV were diminished in patients with TLE compared to the control subjects.

These results indicate that epilepsy, especially TLE, is associated with interictal changes of autonomic cardioregulation. Although these changes seem to be evident in patients with severe form of TLE, patients with well controlled TLE and patients without hippocampal sclerosis also have altered autonomic cardioregulatory function. These results suggest that dysfunction of the cardioregulatory system is rather associated with functional than structural changes of the inner temporal lobe in patients with TLE.

Keywords: autonomic nervous system, cardioregulatory function, heart rate variation, temporal lobe epilepsy

Disce aliquid. Nam cum subito Fortuna recessit,
ars remanet vitamque hominis non deserit unquam.
Marcus Porcius Cato

To my teachers

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Abbreviations

AED	antiepileptic drug
ANOVA	analysis of variance
ANS	autonomic nervous system
ApEn	approximate entropy
AVP	vasopressin
$\alpha 1$	short term correlation of RR interval data
$\alpha 2$	long term correlation of RR interval data
BP	blood pressure
CAN	central autonomic network
CBZ	carbamazepine
CNS	central nervous system
CT	computerized tomography
DM	diabetes mellitus
ECG	electrocardiography
EEG	electroencephalography
GABA	gamma-amino butyric acid
GBP	gabapentin
HF	high frequency
HR	heart rate
HRV	heart rate variation
JME	juvenile myoclonus epilepsy
LF	low frequency
LEV	levetiracetam
LTG	lamotrigine
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTLE	mesial temporal lobe epilepsy
MTS	mesial temporal sclerosis
NTS	nucleus of the solitary tract
OXC	oxcarbazepine
PHT	phenytoin

PNS	parasympathetic nervous system
SD	standard deviation
SD1	instantaneous beat to beat variability
SD2	long-term continuous RR interval variability
SNS	sympathetic nervous system
SPECT	single photon emission tomography
SUDEP	sudden unexpected death in epilepsy
TGB	tiagabine
TLE	temporal lobe epilepsy
TPM	topiramate
VGB	vigabatrin
VLF	very low frequency
VNS	vagal nerve stimulator
VPA	valproate

List of original papers

This thesis is based on the following articles, which are referred to in the text by Roman numerals:

- I Isojärvi JIT, Ansakorpi H, Suominen K, Tolonen U, Repo M, Myllylä VV (1998). Interictal cardiovascular autonomic responses in patients with epilepsy. *Epilepsia* 39(4): 420-426.
- II Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JIT (2000). Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. *Epilepsia* 41(1): 42-47.
- III Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllylä VV, Isojärvi JIT (2002). Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 76: 26-30.
- IV Ansakorpi H, Korpelainen JT, Tanskanen P, Huikuri HV, Koivula A, Pyhtinen J, Tolonen U, Myllylä VV, Isojärvi JIT. Cardiovascular regulation and hippocampal sclerosis. Submitted.

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1 Introduction

Epilepsy is a symptom of a variety of underlying etiological causes, rather than a specific disease (Engel & Pedley 1997). It is a phenomenon that has been recognised over 4000 years ago. For centuries, patients with epilepsy had a stigma of being possessed by supernatural forces during epileptic seizures. And it was not until as recently as during 1969-1970 that laws concerning marriage and compulsory sterilization of patients with epilepsy were repealed in Finland (Lindberg 1995). Today, according to the Finnish Social Insurance Institution, there are more than 45 000 people receiving antiepileptic medication in Finland (Keränen *et al.* 1997).

Increasing research work on human genome, and experimental studies on the pathology of epilepsy have opened a new approach to examine different developmental and post-traumatic pathological brain conditions that eventually lead to the development of epileptic seizures. New imaging techniques, especially the magnetic resonance imaging (MRI), have also widened the scope of epilepsy research work, as well as clinical diagnostic and treatment possibilities. The advanced imaging techniques may help in revealing specific pathologies, and in classifying different types of epilepsy (Cascino *et al.* 1991, Cascino 1997).

Patients have been treated for epilepsy for as long as the seizures have been known. During the last 60 years, major advances have been achieved in the treatment of epilepsy. Advances within antiepileptic drug (AED) treatment and surgical treatment of epilepsy have made it possible to set the goal of epilepsy treatment on seizure-freedom. This goal is achieved in approximately 70%-80% of patients with epilepsy (Cockerell *et al.* 1995). Unfortunately, approximately 20%-30% of all patients with epilepsy continue to have seizures, despite active treatment (Hauser & Hesdorffer 2001). Particular syndromes, i.e. TLE, may be especially difficult to treat (Engel *et al.* 1997).

It has been known for long that epilepsy may be associated with disturbances of autonomic nervous system (ANS) function (Schraeder *et al.* 1989, Frysinger *et al.* 1993, Devinsky *et al.* 1994, Massetani *et al.* 1997, Messenheimer *et al.* 1997, Tomson *et al.* 1998, Druschky *et al.* 2001). During a generalized tonic-clonic seizure, various changes in ANS function can be observed and partial seizures may present themselves as autonomic symptoms (Wannamaker 1985). In addition, epilepsy may be associated with more long-standing forms of ANS dysfunction (Wannamaker 1985).

It is a tribute to the homeostatic safeguards of the organism, that a generalized epileptic seizure is not a fatal event. However, sometimes these safeguards fail, with potentially tragic results. Already at the end of the 19th century, Bacon and his colleagues divided the deaths in an epileptic population into four categories; those due to chronic disease, those due to accidents, those due to status epilepticus and those due to sudden unexpected death in patients with epilepsy (SUDEP) (Bacon *et al.* 1868). The hypotheses of the basic mechanisms behind SUDEP lie on dysfunction of the cardiovascular autonomic regulatory system that exposes a patient to a fatal arrhythmia or central apnea. Although some risk factors of this devastating phenomenon have been identified, there may be a variety of still unknown risk factors contributing to the risk of SUDEP in an individual patient. (Devinsky *et al.* 1994, Johnston *et al.* 1995, Tennis *et al.* 1995, Johnston *et al.* 1997, Nashef 1997, Shorvon 1997, Nashef *et al.* 1998, Nilsson *et al.* 1999, Sperling *et al.* 1999, Walczak *et al.* 2001, Leestma *et al.* 2002)

The basic mechanisms of the cardiovascular regulation have been known for the past two decades and the most important techniques used in the investigation of cardiovascular and other ANS functions have been developed and standardized during that time. With these techniques, e.g. BP and HR changes, can be measured during daily activities or after certain stimuli (O'Brien *et al.* 1986, Goldberger & West 1987, McLeod & Tuck 1987, Saul *et al.* 1987, Suominen 1987, Bannister & Mathias 1988, Denton *et al.* 1990, Huikuri *et al.* 1995, Braune *et al.* 1996, Goldberger 1996, Task Force 1996, Myllylä *et al.* 2002). These investigatory methods have not been widely used in evaluating cardiovascular autonomic functions in patients with epilepsy. However, the previous works suggest that epilepsy itself, as well as AEDs, may alter autonomic functions in patients with epilepsy, but the clinical significance of this phenomenon is still incompletely understood (Wannamaker *et al.* 1985, Schraeder *et al.* 1989, Frysinger *et al.* 1993, Devinsky *et al.* 1994, Massetani *et al.* 1997, Messenheimer *et al.* 1997, Tomson *et al.* 1998, Druschky *et al.* 2001). Moreover, it is not yet known, whether the type or severity of epilepsy is related to the development of changes in autonomic regulatory functions in patients with epilepsy.

Further information on the value of different methods in studying ANS function in epilepsy patients is needed. It is particularly important to identify the prognostic value of altered cardiovascular regulation associated with epilepsy. Furthermore, deeper understanding of the role of epilepsy itself and the different AEDs in inducing cardiovascular autonomic regulatory dysfunction would be important in diminishing the risks related to epilepsy.

This study was designed to elucidate the possible effects of epilepsy on cardiovascular autonomic function. Its aim is also to evaluate the usefulness of two different methods, cardiovascular reflex test and HRV analysis, in studying autonomic cardiovascular regulation in patients with epilepsy. Finally, this study was designed to assess the possible correlations between the severity of TLE and cardiovascular autonomic functions.

2 Review of the literature

2.1 General aspects of epilepsy

2.1.1 Definition

Epilepsy is characterised by recurrent, unprovoked, paroxysmal episodes of brain dysfunction manifesting as a large number of clinical phenomena, like altered levels of consciousness, involuntary movements, abnormal sensory phenomena, autonomic changes and transient disturbances of behaviour. It is a variety of symptoms arising from different kinds of pathologic processes of the brain rather than a specific disease or even a syndrome. During epileptic seizures, there are excessive discharges of electrical activity of the neurones in the brain, and the clinical manifestations depend on the origin and the localization of those pathological discharges. (Browne & Feldman 1983, Waltimo 1983, Engel & Pedley 1997)

2.1.2 Epidemiology

The incidence of epilepsy is 24-53/100 000 person-years in Western countries, whereas in the developing countries it is thought to be higher. The incidence range is higher during the first years of life, falls dramatically thereafter, and increases again in the elderly. Approximately 50% of cases of epilepsy begin in childhood or adolescence (Hauser *et al* 1993). Many studies suggest that males are at a greater risk for unprovoked seizures and epilepsy than female subjects (Hauser 1997). The prevalence of epilepsy is 0,7-0,8% worldwide and the lifetime cumulative incidence is 1-3%. According to the Finnish Social Insurance Institution more than 45 000 patients received antiepileptic medication in Finland in 1996, and 5000 - 6000 of them were children (Keränen *et al* 1997). Seizure-specific incidence or proportions of cases with specific seizure type based

on the International Classification of Epileptic Seizures are provided in several contemporary incidence studies (Hauser 1997). Keränen and his colleagues studied the distribution of seizure types in an epidemiological study of 1220 patients over 15 years of age in Finland (Keränen *et al.* 1988). The epilepsy type was unclassified in 17.5% of the cases. The subclassification of the 82.5% of the cases revealed partial seizures in 56% of the patients and generalized seizures in 26.5% of the patients (Table 1).

Table 1. Distribution of seizure types in an epileptic population in Kuopio, Finland (Keränen et al. 1988).

Epilepsy type	Proportion of cases of epilepsy
Partial seizure	56.0%
Simple partial	7.5%
Complex partial	23.0%
Partial seizure with secondary generalization	25.5%
Generalized seizures	26.5%
Absence seizures	1.0%
Atypical absence seizures	0.5%
Tonic-clonic	23.0%
Atonic	0.7%
Myoclonic	1.3%
Unclassified	17.5%
Total	100%

2.1.3 Etiology

The most common etiologic factors of epilepsy according to the Rochester study are presented in Table 2 (Hauser 1997). All factors that can affect the brain, i.e. head traumas, neoplasms, degenerative diseases, infections, metabolic diseases, ischaemia and hemorrhages, can predispose a person to epilepsy (Vinters *et al* 1993). At present, more and more genetic factors underlying different types of epileptic syndromes are revealed. It is also known that certain brain areas, i.e. temporal and frontal lobes, are more susceptible to produce epileptic seizure activity than the others (Larsen & Iivanainen 1994). However, there are also patients with unresolved etiology of epilepsy (Hauser 1997).

Table 2. Proportion of incidence cases of epilepsy by etiology, Rochester, Minnesota, 1935-1984 (Hauser 1997).

Etiology of epilepsy	Proportion of incidence cases
Idiopathic/cryptogenic	65.5%
Vascular	10.9%
Congenital	8.0%
Trauma	5.5%
Neoplastic	4.1%
Degenerative	3.5%
Infection	2.5%
Total	100%

2.1.4 Classification

A summary of International Classification of Epilepsies and Epileptic Syndromes is presented in Table 3. If there is a known etiology for epilepsy, it is called symptomatic. In cryptogenic epilepsy the presumed pathologic process of the brain can not be detected by the methods in use. Idiopathic epilepsies are more common in children than in adults and comprise a variety of childhood epileptic syndromes with an unknown etiology. (Commission on Classification and Terminology of the International League Against Epilepsy 1989)

Seizures are categorized as partial or generalized and are discussed shortly in the next chapters.

Table 3. International classification of epilepsies and epileptic syndromes (Commission on Classification and Terminology (ILAE, 1989).

Class	Classification
1.	Localization-related (focal, local, partial)
1.1	Idiopathic (with age-related onset) <ul style="list-style-type: none"> Benign childhood epilepsy with centrotemporal spikes Childhood epilepsy with occipital paroxysm Primary reading epilepsy
1.2	Symptomatic <ul style="list-style-type: none"> Chronic progressive epilepsia partialis continua of childhood
1.3	Cryptogenic <p>The symptomatic and cryptogenic categories comprise syndromes of great individual variability that are based on:</p> <ul style="list-style-type: none"> Seizure types (according to the International Classification of Epileptic Seizures) Anatomic localization: Temporal, frontal, parietal, and occipital lobe epilepsies Bi- and multilobar epilepsies Etiology (in symptomatic epilepsies) Specific modes of precipitation
2	Generalized
2.1	Idiopathic (with age-related onset, in order of age) <ul style="list-style-type: none"> Benign neonatal familial convulsions Benign neonatal convulsions Benign myoclonic epilepsy of infancy Childhood absence epilepsy (pyknolepsy) Juvenile absence epilepsy Juvenile myoclonus epilepsy (impulsive petit mal) Epilepsy with grand mal (GTC) seizures on awaking Other idiopathic generalized epilepsies not defined above Epilepsies with seizure precipitated by specific modes of activation
2.2	Symptomatic
2.3.1	Nonspecific etiology <ul style="list-style-type: none"> Early myoclonic encephalopathy Early infantile epileptic encephalopathy with suppression-burst Other symptomatic generalized epilepsies not defined above
2.3.2	Specific syndromes (see the original reference)
3	Epilepsies and syndromes undetermined whether focal or generalized
3.1	With both generalized and focal seizures <ul style="list-style-type: none"> Neonatal seizures Severe myoclonic epilepsy of infancy Epilepsy with continuous spike-waves during sleep Acquired epileptic aphasia (Landau-Kleffner syndrome) Other undetermined epilepsies not defined above
3.2	Without unequivocal generalized or focal features (e.g. many cases of sleep-grand mal)

Table 3 Continued.

Class	Classification
4.	Special syndromes
4.1	Situation-related seizures (Gelegenheitsanfälle)
	Febrile convulsions
	Isolated seizures or isolated status epilepticus
	Seizures due to acute metabolic or toxic factors such as alcohol, drugs, eclampsia

2.1.4.1 *Partial seizures*

Seizures that begin in a focal region of the cerebral cortex, often within one lobe of the brain are termed partial seizures. Partial seizures may remain focal throughout the duration of the seizure or may propagate via neuronal pathways and networks to various regions of the hemisphere (Chabolla 2002). When partial seizure spreads to involve the majority of both cerebral hemispheres, it is said to be secondary generalized (Chabolla 2002). Partial epilepsies comprise slightly over 50% of all epilepsies (Keränen *et al.* 1988, Hauser 1997, Williamson *et al.* 1997).

The signs and symptoms associated with a partial seizure depend on the cortical regions involved. In theory, any function produced by the cortex (e.g. somatosensory, motor, autonomic, psychic phenomena) may be a symptom of a seizure, and the first sign or symptom of a seizure is often, but not always, the best indicator of the site of seizure origin. The most common sites of producing epileptic discharges are temporal and frontal lobes. (Chabolla 2002) TLE is discussed in detail in chapter 2.2.

2.1.4.2 *Generalized seizures*

When epileptic seizure involves both cerebral hemispheres at the onset, it is termed (primary) generalized. At the onset of a generalized seizure patients may experience a vague, indescribable warning, although the vast majority of patients lose consciousness without premonitory symptom. With the loss of consciousness, tonic-clonic convulsions occur. A generalized seizure may also manifest itself as absence, atonic or myoclonic seizures. Idiopathic generalized epilepsies are often childhood idiopathic syndromes, some of which have an excellent prognosis, whereas some of them (e.g. juvenile myoclonus epilepsy (JME)) are thought to require life long medication. (Chabolla 2002)

2.1.5 Diagnosis

Anyone can have an epileptic seizure under stressful conditions (i.e. sleep deprivation, alcohol or drug abuse, infections, hypoglycemia, metabolic changes). However, the diagnosis of epilepsy can be made only after two unprovoked epileptic seizures.

The procedures needed for the diagnosis of epilepsy include medical history with information on the possible predisposing events, a detailed description of the seizures, and clinical evaluation with special respect paid to the cardiovascular and neurological examination. An EEG-recording is usually obtained, and it may reveal focal or generalized spikes and slow waves or other epileptic phenomena. Magnetic resonance imaging (MRI) is recommended as the first line imaging method of the brain when seizures are thought to be of focal origin. MRI may detect pathologic conditions that can not be diagnosed with CT. It is not unusual, however, that the diagnosis of epilepsy is based on medical history and information on the clinical characteristics of the seizures, and EEG and MRI results are normal. (Moshé & Pedley 1997)

2.1.6 Prognosis

The prognosis of epilepsy depends greatly on the underlying cause. At the beginning of the last century, all epilepsies were considered chronic. Later, however, the prognosis has become markedly better with the better epidemiological studies of less selected populations. The studies indicate that when treated, more than two thirds of the patients with newly diagnosed epilepsy soon enter long-term remission. The meta-analyses of recurrence studies found risk rate for seizure recurrence of 0.25 (95% CI, 0.21 - 0.30) at 1 year after discontinuation of the treatment, and of 0.29 (0.21-0.30) at 2 years. Symptomatic epilepsies are more likely to relapse than idiopathic or cryptogenic epilepsies. An abnormal EEG pattern may also increase the risk for the recurrence of seizures. (Sander & Sillanpää 1997)

On the other hand, it is well known that the mortality of the patients with epilepsy exceeds 2-3 times that among the general population. The increased mortality is due to excess morbidity (various brain diseases), accidents during the seizures, status epilepticus, and suicides. The most important epilepsy-related death is SUDEP that accounts for as much as 10-15 % of the deaths among epilepsy patients. SUDEP is discussed in detail in chapter 2.4.1. Many childhood epilepsies have a better prognosis than epilepsies in adults, but there are also severe childhood epilepsies that may eventually lead to increasing neurological deficits and, even, to death. (Sander & Sillanpää 1997)

2.2 Temporal lobe epilepsy

2.2.1 General aspects

TLE is a syndrome presented as quite a unique type of epilepsy. Whereas partial epilepsy comprises slightly more than 50% of all seizure types, the relative incidence and prevalence of different partial seizure types have not been adequately determined (Keränen *et al.* 1988, Hauser 1997, Williamson *et al.* 1997). However, TLE is considered the most common epileptic syndrome and it is estimated that approximately 80% of patients with partial seizures have temporal lobe epilepsy (Dreifuss 1987, Williamson *et al.* 1987). Kun and his co-workers interviewed all male citizens in Singapore at 18 years of age and surprisingly discovered TLE as comprising only 16.9% of all epilepsies being the most common syndrome in this population based study (Kun *et al.* 1999). TLE can be subclassified into mesial temporal lobe epilepsy (MTLE) and lateral temporal neocortical epilepsy. This subclassification is useful, because MTLE comprises the majority of the cases of epilepsy refractory to pharmacotherapy (Babb & Brown 1987). However, it may be remediable to surgery because hippocampal sclerosis can often be seen as an underlying pathology in MTLE (Thadani *et al.* 1995, Benbadis *et al.* 1996). In fact, surgical treatment may abolish seizures in 80-90% of patients with MTLE (Wieser & Williamson 1993).

In MTLE, the first seizures often begin at early childhood to cessate after the childhood years. At that time the seizures are usually well controlled with AEDs. However, the seizures start again after a few years in the adolescence or early adulthood and sometimes they become more severe and progress eventually to refractory epilepsy. Of these patients, many have had febrile seizures in the early childhood (French *et al.* 1993, Wieser & Williamson 1993, Mathern *et al.* 1995). Typical simple partial seizures of the temporal lobe include déjà vu, gustatory, taste or olfactory sensations, panic attacks or sensations of fear or rage. The complex partial seizures consist of a short deterioration of consciousness and oro-alimentary and gestural automatisms. When the seizures become secondary generalized, tonic-clonic convulsions occur. (Engel *et al.* 1997)

Epilepsy arising from the lateral temporal neocortex cannot always be differentiated from MTLE and overlapping may occur (Burgerman *et al.* 1995, Walczak 1995). Although exact statistics are not available, a reasonable estimate would be that less than 10% of patients with TLE have seizure origin in the lateral temporal cortex. Moreover, distinguishing seizure characteristics do not exist (Williamson *et al.* 1997). Sometimes TLE can be difficult to differentiate from psychiatric diseases, since a temporal epileptic seizure may manifest itself even as psychosis. Moreover, TLE, as well as other epilepsies, may be associated with psychiatric co-morbidity (Engel & Taylor 1997).

2.2.2 Focal structural lesions in temporal lobe

In 1880, Sommer described an obvious cell loss seen with a microscope in certain area of the hippocampus in patients with seizures originating from the temporal lobe area (Sommer 1880). It has been established that hippocampal damage is the most common pathology underlying TLE (Babb & Brown 1987).

Neuron loss is usually located in the fields H1 and H3 of the hippocampi, and when the neuron loss is restricted to those areas, it is regarded as the classic hippocampal cell loss (Sutula *et al.* 1989, Babb & Brown 1987, de Lanerolle *et al.* 1992). However, more wide spread neuron loss is often seen in resected temporal lobes of patients with TLE (Margerison & Corsellis 1966, Bruton 1988). The structures suffering from neuron loss in addition to hippocampi include the amygdala, the uncus of the hippocampus and the parahippocampal gyrus. This form of neuron damage is called mesial temporal lobe sclerosis. (Engel 1992, French *et al.* 1993, Wieser *et al.* 1993, Williamson *et al.* 1993, Thadani *et al.* 1995)

In hippocampal and mesial temporal lobe sclerosis (MTS) the damaged neurons are replaced by glial cells to form gliosis that shrinks the volume of the hippocampus and other structures leading to atrophy and sclerosis seen as volume loss and signal changes on MRI. The pathologic changes also include mossy fiber sprouting, dentate gyral dispersion or duplication, and a wide range of neurochemical alterations. Epileptogenic human hippocampus is not a nonfunctioning diseased region of the brain. A number of changes in electrophysiologic, biochemical, neurotransmitter and gene regulation occurring in the surviving cells probably contribute to seizure generation in TLE (Mathern *et al.* 1997).

Whether the hippocampal sclerosis is the “cause” or “consequence” of seizures has been a matter of controversy for over 100 years. Several studies have shown that prolonged febrile and partial seizures, as well as status epilepticus may cause hippocampal damage (Cavanagh & Meyer 1956, Falconer *et al.* 1964, Margerison & Corsellis 1966, Bruton 1988). The evidence exists that the neuronal reorganization continues with recurrent seizures, and clinical observations on the development of medical intractability of MTLE also suggest an ongoing process (French *et al.* 1993, Engel *et al.* 1997). On the other hand, recent studies have shown that, at least in some patients there is an association between an initial precipitating injury (e.g. any significant brain insult) prior to habitual seizure onset and hippocampal sclerosis (Trenerry *et al.* 1993, Mathern *et al.* 2002). However, patients with episodes of generalized tonic-clonic status epilepticus and prolonged partial seizure activity may develop progressive hippocampal neuronal loss in a widespread distribution that is dissimilar to classic Ammon’s horn sclerosis (Pedley & Engel 1997). Today it is concluded that hippocampal sclerosis is presumably both the cause and effect of seizures (Bruton 1988, Gloor 1991, Armstrong 1993, Kälviäinen & Salmenperä 2002, Mathern *et al.* 2002).

Focal cortical dysplasias (e.g. microdysgenesis, heterotopic gray matter and ectopic single neurons), may be encountered in patients with focal epilepsies. These anatomical changes may be detectable in MRI, but for example, microdysgenesis can only be detected histologically. Focal cortical dysplasias may accompany other changes, such as hippocampal sclerosis (dual pathology). (Levesque *et al.* 1991)

2.2.3 MRI-findings in temporal lobe epilepsy

The development of the MRI has without doubt been the most important new diagnostic tool for the evaluation of the individual with epilepsy, and has revolutionized our understanding of the basic mechanisms of epilepsy. MRI-based hippocampal volumetry has been shown to quantitatively indicate the presence of hippocampal volume loss. (Jack *et al.* 1990, Jack *et al.* 1992)

Majority of patients with partial epilepsy have temporal lobe seizures (Dreifuss 1987, Williamson *et al.* 1987), and approximately 90% of patients with nonlesional temporal lobe epilepsy have localization of the ictal onset zone in the amygdala or hippocampus (Spencer *et al.* 1992, Spencer *et al.* 1993). There is now a consensus that MRI is a reliable indicator of MTS in patients with TLE (Jack *et al.* 1990, Jackson *et al.* 1990, Berkovic *et al.* 1991, Cascino *et al.* 1991, Lencz *et al.* 1992, Cascino *et al.* 1993, Spencer *et al.* 1993, Jack *et al.* 1995). The neuroimaging alterations associated with MTS include hippocampal formation atrophy, an increased mesial temporal signal intensity and loss of hippocampal internal structure (Jackson *et al.* 1990, Berkovic *et al.* 1991, Jackson *et al.* 1994).

The optimal MRI technique for visualizing hippocampal anatomy and other mesial temporal structures includes a heavily T1-weighted sequence through an oblique-coronal plane (Jack *et al.* 1992, Jack *et al.* 1995). In most patients, hippocampal atrophy coexists with a medial temporal signal intensity alteration. The signal alteration can best be appreciated on the T2-weighted image and using the FLAIR sequence. The T1-weighted image, in addition to showing hippocampal atrophy, may also reveal a “black hole” in the hippocampus, representing a region of increased signal (Jackson *et al.* 1990, Jackson *et al.* 1994).

2.3 Treatment of epilepsy

2.3.1 General aspects

Although epilepsy is now considered as a condition that for the majority of patients will remit, it may also be a chronic, progressive condition that requires early treatment to prevent complications and to improve the prognosis (Scheuer & Pedley 1990, Pellock & Willmore 1991, Dam 1997). During the last decades, the development of AEDs has been remarkable, but still about 20%-30% of patients with epilepsy suffer from drug-resistant epilepsy (Hauser & Hesdorffer 1991). For some of those patients, cessation or reduction of seizures may be achieved by resective epilepsy surgery (Dam 1997). A new method, vagal nerve stimulator (VNS), has also been introduced in the treatment of epilepsy during the last decade (Dam 1997).

Seizure-freedom with monotherapy (one drug -treatment) is the main goal of the epilepsy treatment today. Fortunately, about two thirds of the patients with epilepsy will

achieve this. However, sometimes two or even three to four AEDs have to be used as polytherapy to control the seizures. For some patients, this works well enough, but the problem lies with the growing number of side effects and interactions of the AEDs that can sometimes be very difficult to cope with (Keränen *et al.* 1997). If polytherapy has to be used to control seizures, it should be done rationally, i.e. mechanisms of the actions of the drugs should be taken into account, as well as metabolic routes for avoiding unwanted interactions.

When a patient has been seizure free 3-5 years, the medication may be considered to taper off. This should be done slowly over several months to prevent a relapse. However, there are some epileptic syndromes, e.g. JME, which require life-time medication. In localization related symptomatic and cryptogenic epilepsies, seizure control may be difficult to achieve, and risk for relapse seizures exists if the medication is stopped. (Keränen 1994, Morton & Pellock 1996)

Based on various publications (Keränen *et al.* 1997, Kälviäinen 2001, Leppik 2001) the recommendations of antiepileptic medications are presented in Table 4. The modernized drug recommendations for various types of epilepsy is expected to be published in Finland in the near future (Isojärvi JIT, personal communication).

Table 4. The recommendations of antiepileptic medications for various types of epilepsy in their alphabetical order in each epilepsy type (modified after Keränen et al 1997, Kälviäinen 2001, Leppik 2001).

Type of epilepsy	Medication
Localization-related epilepsies	Carbamazepine
	Lamotrigine
	Oxcarbazepine
	Phenytoin
	Valproate
(adjunctive therapy)	Gabapentin
	Levetiracetan
	Tiagabine
	Topiramate
Generalized epilepsies	Lamotrigine
	Valproate
	Etosuximide (absence seizures)
(adjunctive therapy)	Topiramate

2.3.2 Antiepileptic medication

In general, no significant differences in the effectiveness of AEDs exists when they are adequately used in relation to the type of seizure. The newer drugs (oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM), gabapentine (GBP), tiagabine (TGB),

levetiracetam (LEV)) appear to be better tolerated but more expensive than standard AEDs (phenytoin (PHT), carbamazepine (CBZ) and valproate (VPA)) (Brodie & Dichter 1996, Perucca 1996). In the following, the general properties of the commonly used AEDs are discussed shortly.

2.3.2.1 Sodium channel blockers

PHT was the first modern antiepileptic drug. It is considered highly effective and cheap and is indicated in partial epilepsies (Browne 1997, Leppik 2001). PHT has a saturable kinetics, problematic interaction profile and various side effects, but it is still widely used in many parts of the world (Browne 1997, Leppik 2001). PHT has previously been used as an antiarrhythmic drug, and it may be considered having protective effects on the heart (Lathers & Schraeder 1982). However, it is known that some antiarrhythmic drugs are associated with increased risk for sudden cardiac death, and there are also reports of triggered arrhythmias during intravenous administration of PHT mainly in the predisposed elderly (Tomson *et al.* 1997).

CBZ is today the most commonly prescribed drug for epilepsy in Europe. It is the first-line AED in partial epilepsies but it is contraindicated in myoclonic and absence epilepsies (Loiseau & Duche 1995, Bird *et al.* 1996). CBZ is usually well tolerated but has a large number of drug interactions (Perucca *et al.* 1984, McLean & MacDonald 1986, Mattson *et al.* 1992). CBZ may sometimes induce atrioventricular conduction delay and brady-arrhythmias in epilepsy patients with or without underlying cardiac disease (Steiner *et al.* 1970, Hamilton 1978, Herzberg 1978, Boesen *et al.* 1983). The suggested role of CBZ for increasing the risk of SUDEP is controversial (Kennebäck *et al.* 1997, Timmings 1998).

OXC is a 10-keto analogue of CBZ developed to avoid autoinduction and potential for drug interactions of CBZ, and it has a number of advantages over CBZ. (Faigle & Menge 1990, Larkin *et al.* 1991). OXC is used as a first-line AED in many countries, including Finland, and it is indicated in partial epilepsies (Dam *et al.* 1989, Grant & Faulds 1992). However, moderate to severe hyponatremia may be seen especially in the elderly and female patients, which may trigger epileptic seizures and cause CNS side effects (Pendelburry *et al.* 1989, Grant & Faulds 1992, Huuskonen *et al.* 1998).

LTG is one of the first AEDs of the new generation, it is well tolerated and indicated as adjunctive or monotherapy in partial and generalized epilepsies, as well as in Lennox-Gastaut syndrome. LTG has a wide spectrum of antiepileptic activity, the mechanism of which is not completely understood. LTG does not induce or inhibit hepatic P450 enzymes. However, the concomitant administration of other AEDs may affect the metabolism of LTG. (Binnie 1997, Leppik 2001)

2.3.2.2 *Gabaergic drugs*

GBP is indicated as adjunctive therapy in partial and generalized epilepsies. The interactions and side effects are few. Potentially severe side effects have not been reported. (Chadwick & Browne 1997, Leppik 2001) The lack of hepatic metabolism is a major advantage, and GBP does not have any drug interactions. (Chadwick & Browne 1997, Leppik 2001)

TGB may be used as an adjunctive therapy in partial epilepsies. It is not a hepatic enzyme inducer or inhibitor and it does not affect the kinetics of other drugs. However, concomitant enzyme-inducing AEDs markedly increase the clearance of TGB. Some clinical observations suggest that TGB could trigger status epilepticus. (Sommerville 1997, Leppik 2001)

Vigabatrin has high efficacy and low interaction profile. However, its propensity to cause asymptomatic peripheral visual field failure severely limits the use (Ben-Menachem & French 1997).

2.3.2.3 *Mixed mechanisms*

The mechanism of action of VPA is still uncertain, but it is known to block voltage dependent sodium channels, affect calcium (T) conductance and modify GABA receptors (Loscher 1981, Franceschetti *et al.* 1986). It has a number of complex interactions with antiepileptic and other drugs (Levy & Koch 1982, Perucca *et al.* 1984). VPA is the drug of choice in generalized epilepsies and it is also efficient in partial epilepsies (Davis *et al.* 1994, Morton & Pellock 1996). In general, VPA is well tolerated (Leppik 2001). The most problematic side effects may be the reproductive endocrine disorders, i.e. weight gain, menstrual disorders, polycystic ovaries, and hyperandrogenism in female patients (Isojärvi *et al.* 1993, Isojärvi *et al.* 1998). Hyperinsulinemia has also been reported (Pylvänen *et al.* 2003).

TPM has multiple modes of action. It does not have any significant interactions with concomitant AEDs, but other AEDs may change TPM concentrations. TPM is indicated in partial and generalized epilepsies as adjunctive therapy and as monotherapy if epilepsy is refractory to commonly used AEDs. Hypersensitivity or idiosyncratic effects have not been reported. (Kramer & Reife 1997, Leppik 2001)

2.3.2.4 *Other antiepileptic medications*

LEV is a novel AED recently licensed. It expresses significant anticonvulsant activity against partial seizures. LEV has been regarded as a new AED with ideal pharmacokinetics (Isoherranen *et al.* 2001). The mechanisms of action are still unsettled, but the existing experimental data show that LEV might be a selective blocker of N-type calcium channels (Lukyanetz *et al.* 2002), which is a unique mode of antiepileptic

function in AEDs. LEV is usually well tolerated and the incidence of hypersensitive reactions is similar to that of placebo (French *et al.* 2001).

Certain benzodiazepines are mainly used to suppress acute seizures, and as additional therapy to control seizures, for example during certain phases of menstrual cycle in female patients and in severe childhood epilepsies (Ko *et al.* 1997).

Ethosuximide is only indicated in generalized absence seizures and it is widely used in the world. It has an effect on calcium T-channel conductance, and side effects are common. (Leppik 2001)

Piracetam is used in cortical myoclonus of various etiologies. It is closely related to LEV, but piracetam may be useful particularly in patients with refractory myoclonus.

2.3.3 Surgery

In partial epilepsies such as TLE, resection of the epileptic focus can sometimes be performed to control the epileptic seizures refractory to pharmacotherapy. If the patients are carefully selected for the surgery, the outcome is good, as majority of patients become seizure-free, improve in their cognitive capacity and have remarkable improvement in the quality of life as a whole. The risks of modern epileptic surgery are acceptably low, with overall mortality being less than 0.5% and morbidity less than 5%. Increased mortality rates are associated with intractable epilepsy and there are indications that this risk might be reduced by epileptic surgery. (Engel Jr 1996, Duchowny *et al.* 1997)

In patients with refractory idiopathic generalized epilepsy, only palliative epilepsy surgery may be performed. (Larsen & Iivanainen 1994). International recommended standards of neurosurgery have recently been published (Binnie & Polkey 2000).

2.3.4 Vagal nerve stimulator

A new approach to the treatment of epilepsy is vagal nerve stimulator (VNS). It is a device that has been designed to electrically stimulate the left branch of the 10th cranial nerve, the vagus nerve, in constant frequency. The basic mechanisms of VNS are not completely understood. The experimental data suggest that the antiepileptic actions of vagal stimulation are largely mediated by projections from the nucleus of the solitary tract (NTS) to the reticular formation and the amygdalohippocampal complex and by diffuse projections to the cortex. It also seems to modify the concentrations of various amino acids of the brain, e.g. GABA. It can be used as a treatment to those refractory patients who are not candidates for surgery and the results are comparable to those of the new AEDs as add-on treatment. Side effects seem to be few. (Wilder 1997)

2.4 Autonomic nervous system

2.4.1 General aspects

ANS controls visceral functions demanded for maintaining the homeostasis of the organism. ANS regulates the functions of the heart muscle, smooth muscle, secretory glands and hormone secretion (Appenzeller 1990, Ravits 1997). The peripheral part of the ANS consists of two different functional and anatomical divisions, the sympathetic (SNS) and parasympathetic (PNS) nervous systems (Shields 1993, Harati & Machkhas 1997). The SNS and PNS regulate visceral functions as an interactive, dynamic network to meet the requirements of the outer and inner environment and to maintain the homeostasis of the body (Appenzeller 1990). Both the SNS and PNS consist of a two-neuron chain. Between the neurons lies the ganglio that divides the chain into pre- and postganglionic parts, and where these neurons synapse (Figure 1.).

All the preganglionic neurons and postganglionic parasympathetic neurons release acetylcholine as a chemical transmitter, whereas postganglionic sympathetic neurons release norepinephrine. The sweat glands innervated by sympathetic fibers releasing acetylcholine are an exception of this pattern. It has been shown histologically that postganglionic neurons of both SNS and PNS also contain several immunoreactive peptides. (Collins 1999, Jänig & McLachlan 1999, Van Zwieten 1999)

The preganglionic neurons of the SNS are located in the lateral horn of the gray matter at the T1-L4 of the spinal cord called intermediolateral cell column. The myelinated axons of the preganglionic neurons synapse with the paravertebral ganglio located laterally to spinal cord. This pearl-chain-like ganglionic chain is called truncus sympathicus. The axons of the postganglionic neurons travel to the target organs with blood vessels. From the target organs axons travel back to the spinal cord and part of them travel on to the skin and muscles with the spinal nerves. (Collins 1999, Jänig & McLachlan 1999, Van Zwieten 1999)

The PNS consists of two parts: the cranial part in the brain stem (cranial nerves III, VII, IX, X) and the sacral part in the spinal cord at the level of S2-S4 in the intermediolateral cell column. On the contrary to the SNS, the parasympathetic postganglionic neurons form ganglia located near the target organ. (Gibbins 1990, Reid 1990, Jänig & McLachlan 1999)

The heart is one of the most important target organs of the peripheral ANS. Sympathetic innervation of the heart arises from the cervical and upper thoracic (stellate) ganglia, whereas the PNS innervates the heart via the vagal nerve. The SNS increases conduction, excitability and contractility of the heart, and opposite to this, activation of the PNS decreases these cardiac functions. There are important interactions between vagal and sympathetic influences on the heart, and an imbalance in the autonomic cardiovascular regulation may result in cardiac arrhythmias and other complications. (Benarroch *et al.* 1997c) Cardiovascular regulation is discussed in detail in the chapter 2.4.3.

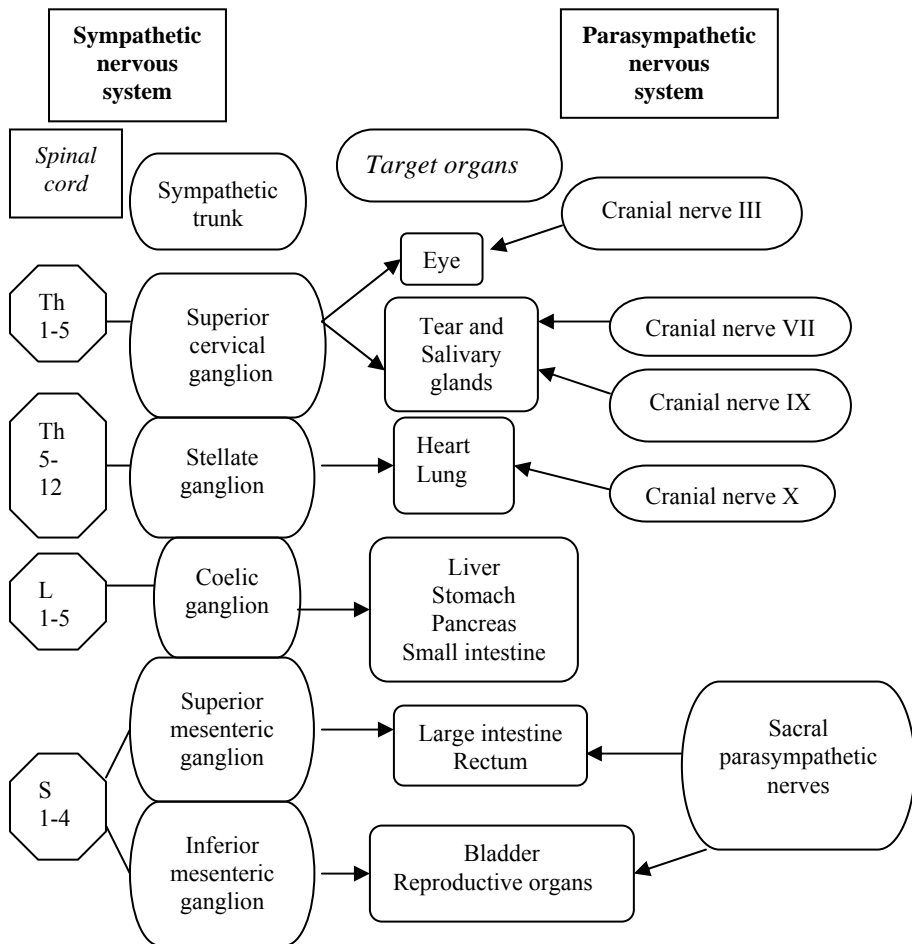


Fig. 1. The peripheral divisions of autonomic sympathetic and parasympathetic nervous systems.

2.4.2 Central autonomic network

Peripheral ANS is controlled by the CNS via complex neuronal interconnections functioning in relation to each other to form a functional entity called central autonomic network (CAN). The CAN has tonic, reflex and adaptive control over autonomic functions (Loewy 1990, Spyer 1990, Benarroch 1993, Benarroch 1997a). In addition, it regulates endocrine (Swanson 1991), behavioral motor (Bandler *et al.* 1991) and pain-

controlling responses (Lovick & Li 1993) and contributes to the regulation of attention and emotional behaviour (Bechara *et al.* 2000) as well.

During the past several years, the rapid development of research techniques has provided the framework for the current understanding of the functional anatomy of the CAN. Neuronal activity within the CAN both controls and is affected by arterial pressure, respiration and other physiologic variables (Day & Sibbald 1989, Saper 1990). Activity within the CAN is state dependent and affected by the sleep-wake cycle, attention, and other internal influences (Ruggiero *et al.* 1987, Hosoya *et al.* 1991).

Transmission of information within the CAN involves virtually all neuroactive chemical substances so far described. In general, excitatory (e.g. L-glutamate) and inhibitory (e.g. GABA) substances mediate rapid communication within the central autonomic circuits e.g. baroreflex pathways (Sun 1985). Monoamines exert a more diffuse neuromodulatory effect, whereas neuropeptides commonly coexist with other neurotransmitters both in local and diffuse projecting pathways and may be involved in longer-term modulation and function as circulating signals (Gardiner & Bennet 1989). Nitric oxide has been recognised as an important intercellular messenger (Snyder & Brecht 1991, Togashi *et al.* 1992). On the other hand, steroid hormones rapidly cross the blood-brain barrier and have access to specific receptors abundantly distributed throughout the CAN (Stumpf 1990).

Disorders involving the CAN may manifest themselves as autonomic hyperactivity, e.g. hypertension, arrhythmias, hyperhidrosis, or as autonomic failure, e.g. orthostatic hypotension, impotence, gastrointestinal tract dysmotility and neurogenic bladder. Some of these manifestations may be asymptomatic and detectable only on clinical examination or autonomic testing. Moreover, others may be life threatening such as ventricular arrhythmias or produce severe impairment in daily activities such as orthostatic hypotension. In general, autonomic hyperactivity tends to occur in the context of acute neurologic disease, whereas neurodegenerative disorders are most commonly associated with autonomic failure. (Benarroch 1997a)

2.4.2.1 *Insular cortex*

The insular cortex, lying deep in the temporal lobe is mainly a viscerosensory cortex. Electrical stimulation of the insular cortex in a variety of mammals elicits changes in BP, HR, respiration, gastrointestinal activity and epinephrine secretion as well as piloerection and pupillary dilatation (Cechetto & Chen 1990). In fact, in one experimental study with rats, prolonged stimulation of the insular cortex generated progressive degrees of heart block, increased plasma norepinephrine, and asystole resulting in death (Oppenheimer *et al.* 1991). Accompanying cardiac structural changes, myocytolysis and subendocardial hemorrhages, suggested that increased cardiac sympathetic activity was the reason for the observed changes (Oppenheimer *et al.* 1991).

Recently, functional MRI was used to identify regions of the human brain that were activated in response to tests designed to activate cardiovascular receptors (King *et al.* 1997). These tests included maximum inspiration, Valsalva's maneuver, and maximum

handgrip to elevate arterial BP. These maneuvers consistently resulted in discrete changes in activity in the anterior insular cortex with a time-course corresponding to the changes in arterial BP and HR they produced (King *et al.* 1997). There is also some evidence that stimulation of the insular cortex in humans elicits different results from each hemisphere (Oppenheimer *et al.* 1992a). Left insular cortex seems to be predominantly responsible for parasympathetic effects, whereas right insular cortex is more likely to produce sympathetic responses (Oppenheimer *et al.* 1992b).

2.4.2.2 Prefrontal cortex

Autonomic regions of the prefrontal cortex include ventromedial prefrontal cortex and the anterior cingulate gyrus. The ventromedial prefrontal cortex is involved in the regulation of high level emotional and cognitive functions whereas the anterior cingulate (infralimbic) cortex may constitute an autonomic premotor area (Cechetto & Saper 1990, Damasio *et al.* 1990).

The specific role of the prefrontal cortex in autonomic control is incompletely understood. However, various experimental studies suggest bradycardia and hypotension as the main results of the stimulation of the infralimbic cortex, and even a complete cessation of heart beat may occur in monkeys during stimulation of the cingulate gyrus (Cechetto & Saper 1990).

2.4.2.3 The amygdala

In the midbrain amygdala with adjacent areas (extended amygdala) integrates autonomic responses with emotional factors. Its functions are to interpret the emotional significance of incoming sensory information and to generate the appropriate autonomic, behavioral, motor, endocrine, and pain-suppressing responses to environmental stimuli (Amaral *et al.* 1992, Davis 1992, LeDoux 1992).

The amygdala receives cardiopulmonary information and has direct projections to autonomic control sites, such as hypothalamus, parabrachial nucleus, NTS and the dorsal motor nucleus of the vagus which may be the anatomical substrate for descending control over the ANS (Cechetto 2000). The amygdala is also an important cardiovascular control center within the limbic system with reciprocal connections with the insular cortex and direct projections to other autonomic control centers in the hypothalamus, pons and medulla (Cechetto 2000).

Stimulation of the central nucleus of the amygdala produces changes in BP, HR, respiration and gastric secretion and motility (Al Maskati & Zbrozyna 1989, Davis 1992). In humans, electrical stimulation of the amygdala has been shown to produce fear sensations, and seizures involving amygdala and its connections may result in various autonomic manifestations, including serious cardiac arrhythmias (Benarroch 1997b).

2.4.2.4 *The hypothalamus*

The preoptic region and the hypothalamus form an anatomicofunctional unit essential for integration of autonomic, endocrine, and behavioral responses critical for homeostasis and reproduction (Swanson 1987).

In hypothalamus, the periventricular area controls neuroendocrine functions as well as biological rhythms. The medial area has regulatory function over homeostasis and reproduction, and the dorsomedial nucleus especially contributes to the integration of cardiovascular responses to stress. The lateral area of the hypothalamus regulates behavioral functions, as well as vagal functions including cardiovascular regulation, gastrointestinal motility, and secretion, and insulin release. The zona incerta merging ventromedially with the lateral hypothalamic area has been implicated in arousal, locomotion, and autonomic regulation. (Benarroch 1997b)

The paraventricular nucleus has been called the "master controller" of the autonomic system because it innervates all autonomic centers (Swanson 1987, Holstege 1990). It is a critical site for integrated responses to stress and it exerts multiple actions, including regulation of the cardiovascular function, energy metabolism and immune responses (Benarroch 1997b). The circumventricular organs located in the anterior wall of the third ventricle region are an integral component of the hypothalamic control of autonomic and endocrine function (Brody & Johnson 1980). These special sites of the ventricle walls lack blood-brain barrier and are highly vascularized (Brody & Johnson 1980).

2.4.2.5 *Other components of the central autonomic network*

All the midbrain areas are in connection with the autonomic centers in the brain stem and spinal cord. Periaqueductal gray matter in the midbrain integrates autonomic responses with antinociceptive and behavioural reactions. The parabrachial region in the pons functions as a mediator in processing visceral and somatosensory information and it plays a major role in cardiorespiratory regulation, and stimulation of it produces an increase in arterial BP and inhibition of the baroreflex. The lateral part of the parabrachial nucleus has connections to cerebellum, and the cerebellar uvula has been implicated in the control of cardiovascular and respiratory function, particularly in the setting of alerting or orienting responses. (Feldman 1986, Paton & Spyer 1992)

A5 group of the ventrolateral pons may be important in the integration of somatosensory and autonomic responses. Stimulation of the norepineprine-synthesizing neurons of the A5 group produces complex cardiovascular responses. (Huangfu *et al.* 1992)

In the medulla oblongata nucleus of the solitary tract (NTS) plays a critical role in medullary reflexes, and relays viscerosensory information to all regions of the CAN (Loewy 1990). Afferents from arterial, cardiac and pulmonary baroreceptors and carotid and aortic chemoreceptors are carried by branches of glossopharyngeal and vagus nerves, and relay in the NTS. The dorsolateral subnucleus of the NTS contains neurons that discharge in phase with the cardiac cycle and initiate vasodepressor and bradycardiac

responses. The nucleus ambiguus also contributes to the innervation of the heart. (Anderesen & Kunze 1994)

There are several areas in the medulla that participate in the control of vasomotor tone, cardiac function and respiration. Neurons of the rostral ventrolateral medulla constitute an important station for various influences affecting central sympathetic activity (Benarroch 1997b). Stimulation of these neurons increases arterial BP, HR, sympathetic nerve activity, and releases adrenomedullary catecholamines (Amaral *et al.* 1992). On the other hand, the caudal ventrolateral medulla is a "depressor" area containing sympathoinhibitory neurons and thus being an integral component of the baroreflex arc (Willette *et al.* 1984).

2.4.3 The physiology of cardiovascular regulation

The CNS controls cardiovascular functions via the ANS regulatory system consisted of the SNS and PNS as its peripheral part and the CAN as its central part (Talman & Kelkar 1993). The balance of the SNS and PNS influences is critical for the control of cardiac functions, such as excitability and contractility (Benarroch 1997c).

Beat-to-beat control of HR is determined largely by the level of vagal innervation to the sinus node. Cardiovagagal cholinergic motoneurons are located in the nucleus ambiguus and in the dorsal vagal nucleus in the medulla oblongata. The peripheral afferent control is supplemented by central inputs that promote adjustments of HR during specific adaptive behavior. (Benarroch 1997c) The effectiveness of both reflex and behavioral influences on cardiovagagal motoneurons is strongly modulated by respiration to maintain a balance between cardiac output and respiratory minute volume and to optimize tissue respiration (Spyer *et al.* 1994). Cardiovagagal motoneurons of the nucleus ambiguus are an integrative element in the central control of circulation and they are excited by baroreflex and inhibited by hypothalamic and inspiratory influences (Benarroch 1997c). Figure 2 presents the main neural components participating in the regulation of the cardiovagagal motoneurons.

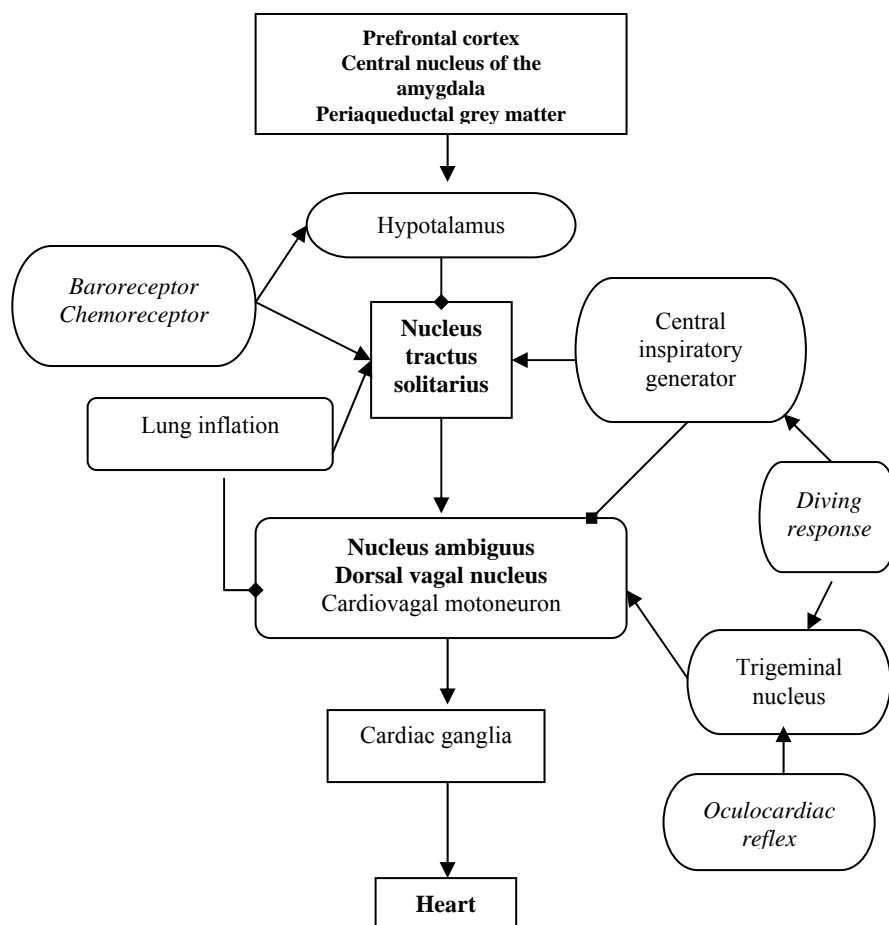


Fig. 2. Schematic diagram of the main neural components participating in the vagal control of the heart rate. The arrowheads indicate stimulation and the diamondheads inhibition of the cardiovagal motoneurons (Modified after Benarroch 1997c).

In humans, most cardiac branches of the vagus are given off in the thorax, near the origin of the recurrent nerve (Rossi 1994). There is an anatomicofunctional separation of the innervation of the SA and AV nodes. Therefore, the CNS is able to selectively influence the SA or the AV node either together or independently. The cardiac ganglia, however, are not merely relay stations for vagal inputs. Previous studies (Randall & Wurster 1994) have shown a complex organization in intracardiac ganglia, giving rise to a "cardiac brain" hypothesis. Studies in mammals have shown the presence of different functional cell types and thus, within the intracardiac ganglia there is a rich potential for complex interactions among vagal preganglionic neurons, primary afferents, local neurons, and collaterals from sympathetic fibers that control cardiac function (Loffelholz & Pappano 1985).

The parasympathetic innervation is more dense in the SA and AV nodes than in the surrounding myocardium, and the right and left vagal fibers provide partial bilateral innervation to both the SA and AV nodes (Loffelholz & Pappano 1985). In general, parasympathetic outflow decreases automatism of the SA node decreasing HR, hyperpolarizes the AV node decreasing AV conduction, inhibits atrial and ventricular contractility and exerts complex effects on cardiac excitability by shortening the refractory period in the atria and prolonging that of ventricles, Purkinje system, and accessory AV pathways. Thus, vagal input has an antiarrhythmic effect (Benarroch 1997c).

Similarly, there is a lateralized influence of the sympathetic system on cardiac function. The right sympathics predominantly innervate the SA node and increase HR, whereas the left sympathics mainly innervate AV node and ventricles increasing AV conduction, excitability within the His-Purkinje system node, cardiac contractility and oxygen consumption (Levy & Martin 1979). They receive inputs from the periventricular nuclei, ventrolateral medulla, lateral hypothalamic area, zona incerta and the periaqueductal gray matter (Benarroch 1997c).

In the intact animal, parasympathetic responses are of shorter latency and duration than those mediated by the sympathetics (Talman & Benarroch 1993). The complex interactions between the sympathetic and parasympathetic outflows to the heart not only control normal cardiac function, but also modulate the susceptibility to cardiac arrhythmias (Benarroch 1997c). Figure 3 presents the main neural components participating in the sympathetic control of the HR.

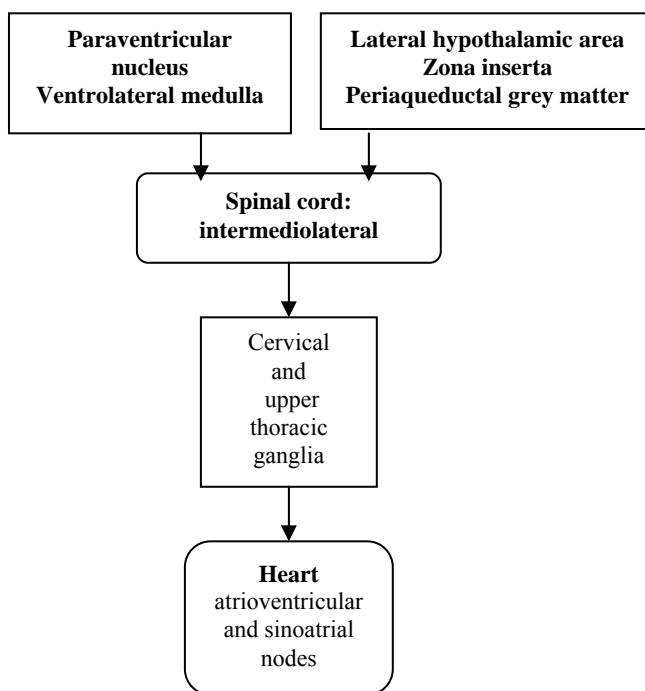


Fig. 3. Schematic diagram of the sympathetic control of the heart rate.

The baroreflex control of cardiovagal outflow appears to result from the algebraic sum of the effects of carotid and aortic receptors, unlike the redundant control of sympathetic vasomotor and cardiomotor outflows by these two receptors (Thames *et al.* 1994, Somer & Abboud 1994). The arterial chemoreflex in response to hypoxia is triggered primarily by stimulation of the carotid body chemoreceptors. This produces an increase in ventilation and selective, sympathetically mediated vasoconstriction and vagally mediated bradycardia (Somer & Abboud 1994).

Figure 4 presents the main neural components participating in the control of arterial BP.

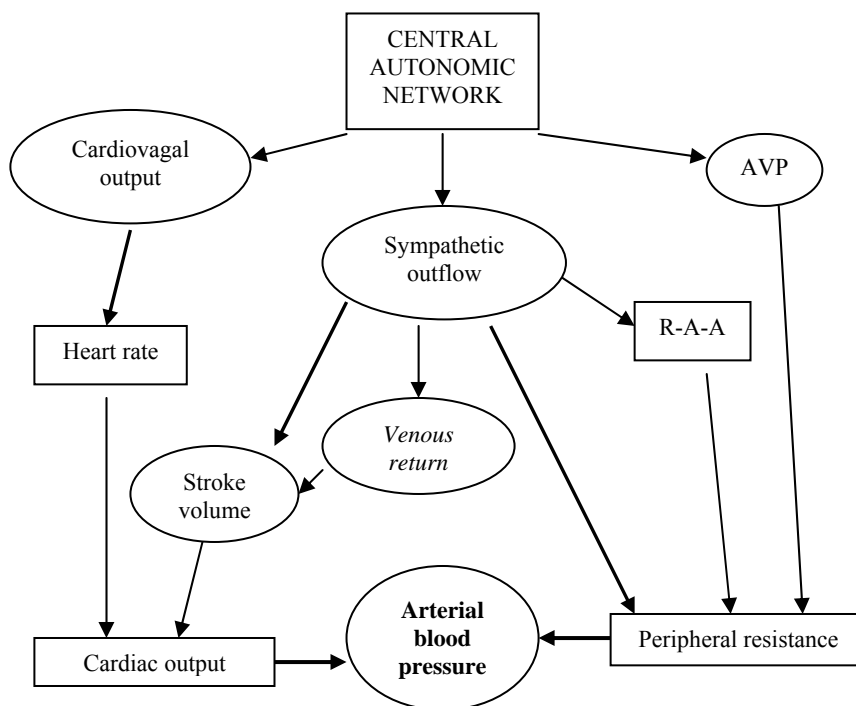


Fig. 4. Schematic diagram of the components regulating arterial blood pressure (Modified after Benarroch 1997e). AVP, natriuretic peptide; R-A-A, renin-angiotensin system.

2.5 Evaluation of autonomic nervous system function

2.5.1 General aspects

In a patient with a suspected autonomic disorder the major aims of the investigation are to determine the normality of autonomic function, to assess the degree of dysfunction with an emphasis on the site of the lesion and on the functional deficit, and also to ascertain whether the abnormality is of the primary variety or secondary to recognized disorders, as the prognosis and management may depend on the diagnostic category. Investigatory methods are available for recording cardiovascular, sudomotor, gastrointestinal, genitourinary, respiratory and pupillary autonomic functions. They are in routine clinical as well as in research use to study both central and peripheral ANS functions.

It has been observed that the heart is one of the most delicate organs reflecting cardiovascular autonomic regulatory function. It is well known that the HR is not

uniform but the interval between the two R spikes in the ECG fluctuates. Respiration, neurohumoral factors and cardiovascular regulation are the main effectors on the RR interval. HRV reflects the competence of this regulatory system, diminished HRV being a sign of dysfunction of the ANS. During the past decades, noninvasive bedside techniques have been developed to study the regulation of HR and BP. (Benarroch 1997c)

Table 5. The methods used to study autonomic failure (Bannister & Mathias 1999).

Target organ system	Method
Cardiovascular	
Physiological	Head-up tilt (45°): Standing, Valsalva maneuver Pressor stimuli: Isometric exercise, cutaneous cold, mental arithmetic Heart rate responses: deep breathing, hyperventilation, standing, head-up tilt, 30:15 ratio Liquid meal challenge Exercise testing Carotid sinus massage Heart rate variation measures from 24 h ECG-recording
Biochemical	Plasma noradrenaline: supine and head-up tilt or standing Urinary catecholamines Plasma renin activity and aldosterone
Pharmacological	Norepinephrine: α -adrenoceptors – vascular Isoprenaline: β -adrenoceptors – vascular and cardiac Tyramine: pressor and norepinephrine responses Edrophonium: norepinephrine responses Atropine: parasympathetic cardiac blockade
Sudomotor	Central regulation: thermoregulatory sweat test Sweat gland response. Intradermal acetylcholine, quantitative sudomotor axon test (Q-SART), localized sweat test, sympathetic skin response
Gastrointestinal	Barium studies, videofluoroscopy, endoscopy, gastric emptying studies
Renal function and Urinary tract	Day and night urine volumes and sodium/potassium excretion Urodynamic studies, intravenous urography, ultrasound examination, spinchter electromyography
Sexual function	Penile pletysmography Intracavernosal papaverine
Respiratory	Laryngoscopy Sleep studies to assess apnoea/oxygen desaturation
Eye	Schirmer's test Pupil function: pharmacological and physiological

2.5.2 Cardiovascular autonomic reflexes

Assessment of cardiovascular autonomic reflexes is a critical element in evaluation of autonomic function in humans. Cardiovascular autonomic reflexes in humans are

essential for the maintenance of arterial BP during the orthostatic stress adopting a standing posture, and for preventing wide fluctuations of arterial BP in response to stress, exercise, and other adaptive responses. (Benarroch 1997d). To examine cardiovascular reflexes, a standardized laboratory test pattern, in which HR and BP responses at rest and to certain stimuli are measured, is often used. The method is easy to perform, standardized measures make interindividual comparisons possible and it has indeed an established role as the most used method assessing autonomic functions. The test pattern includes measurement of HR and BP during normal and deep breathing, the Valsalva maneuver, the tilt test and the isometric work test.

The arterial baroreflexes exert buffering influence on the magnitude of centrally induced variations of arterial pressure during day and night. They act by reducing arterial BP oscillations, and their activity is manifested by beat-to-beat variations of the HR opposite in direction to the changes in arterial BP (Shepherd & Mancia 1986). If the arterial baroreflex is acting normally, there are small arterial BP oscillations and large HR oscillations, whereas the opposite occurs in patients with baroreflex failure.

Assumption of an upright posture produces blood to shift downwards, creating a decrease in stroke volume. The circulatory adjustment to orthostatic stress is rapid in healthy subjects. Several mechanisms including the arterial baroreflexes, cardiopulmonary reflexes, venoarteriolar reflexes, and the vasopressin (AVP) and renin-angiotensin systems contribute to the maintenance of postural normotension (Wieling & Van Lieshout 1993). Mechanoreceptors in the atria and ventricles innervated by vagal afferents exert tonic inhibitory influence on sympathetic outflow and AVP release (Shepherd & Shepherd 1992).

The respiratory sinus arrhythmia is evaluated while at rest and during deep breathing at a rate of 6 breaths per minute that produces the maximum sinus arrhythmia (Angelone & Goulter 1964, Borgdorff 1975, Hirsch & Bishop 1981, Piha *et al.* 1988). The registration of HR fluctuation during normal and deep breathing is a sensitive detector of autonomic dysfunction (Mackay *et al.* 1980).

In the Valsalva maneuver the respiratory strain increases intra-thoracic and intra-abdominal pressure altering hemodynamic and cardiac functions (Nishimura & Tajik 1986, Benarroch 1991). The Valsalva ratio is the most commonly used test parameter that calculates the ratio of the longest RR interval after the blowing and to the shortest RR interval during the blowing (Levin 1966). Both SNS and PNS control autonomic responses during the Valsalva maneuver (Sandroni *et al.* 1991) and continuous BP monitoring increases the sensitivity of the test (Ravits 1997).

Normally, orthostatic stress produces an increase in HR, increase in diastolic and decrease in systolic BP accompanied by increase in plasma norepinephrine and muscle sympathetic activity. Thereafter a relative bradycardia follows due to vagal reflexes (Ewing *et al.* 1978, Borst *et al.* 1982). The HR changes to standing are expressed as the 30:15 ratio (Ewing *et al.* 1980). The BP is monitored during the test continuously or serially and the largest drop (or lowest increase) is quantified. Orthostatic hypotension means a reduction of systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg within 3 minutes (Consensus Statement 1996). Even though the physiological responses to passive tilting are not identical to standing up, the pulse response is seen if the tilting is quick and extended up to 90° (Sundquist *et al.* 1980, Myllylä *et al.* 2000).

During the isometric work test the BP reaction to sustained handgrip is measured. The mechanism involves the exercise reflex that withdraws parasympathetic activity and increases sympathetic tone. Normally the diastolic BP raise is more than 15 mmHg. The participant's age does not affect the BP responses to isometric work (Goldstraw & Warren 1985), but the responses are greater in male than female (Piha 1993, Khurana & Setty 1996).

The cardiovascular reflex parameters based on HR fluctuation are age and HR dependent and must therefore be adjusted for age and baseline RR interval. The results of two subtests outside the 95% confidential limits of the control subjects has been considered as a clinically abnormal finding, but also a marked decrease of BP with fainting after standing or tilting, as a sole finding, is enough for the diagnosis.

Abnormalities in the cardiovascular reflexes have been detected in a majority of patients with multisystem atrophy and primary autonomic failure (Cohen *et al.* 1987, Ravits *et al.* 1995). Cardiovascular responses have also been used to evaluate autonomic dysfunction in diabetic, uremic and hereditary neuropathies (Bennet *et al.* 1977, Ewing *et al.* 1978, Ewing *et al.* 1981, Low *et al.* 1986, Shahani *et al.* 1990, Wang *et al.* 1994), pulmonary diseases (Pagani *et al.* 1996), amyotrophic lateral sclerosis (Pisano *et al.* 1995), cerebellar and extrapyramidal disorders (Turkka *et al.* 1987, Sandroni *et al.* 1991, Haapaniemi *et al.* 2000), stroke (Korpelainen *et al.* 1994), migraine (Havanka-Kanniainen *et al.* 1988), multiple sclerosis (Senaratne *et al.* 1984, Vita *et al.* 1993) and chronic alcoholism (Yokohama *et al.* 1991, Monforte *et al.* 1995).

Power spectral analysis of HR and arterial BP variations, including analysis of signal coherence both at rest and in response to tilt, and other maneuvers, provides additional information on the sympathetic and cardiovagal components of cardiovascular reflex responses.

2.5.3 Ambulatory ECG and analysis of heart rate variability

Although respiratory sinus arrhythmia has been noticed already in 1733 by Hales (Singer & Underwood 1962), only the development of high resolution ECG and digital computers has made it possible to measure more subtle fluctuations of HR and BP. The HRV analysis from ambulatory ECG recording is now an important tool in evaluating cardiovascular autonomic regulation. Information about tonic autonomic effects on the heart can be obtained by the traditional time and frequency domain measures based on linear fluctuations of HR (Huikuri *et al.* 1995). However, as the behaviour of the heart is not only linear but also chaotic, new methods based on non-linear dynamics and fractal analysis have been developed (Goldberger & West 1987, Denton *et al.* 1990, Pincus & Goldberger 1994).

Diminished HRV and loss of its circadian oscillation are particularly associated with cardiac arrhythmogenic death in patients with prior heart problems, but the predictive value is not very good, with the sensitivity being 50%-80% and the specificity 60-90% in an individual patient (Huikuri *et al.* 1995c). Age, gender, physical activity and certain drugs affect HRV (Huikuri *et al.* 1995c, Task Force 1996).

The time domain analysis of HR fluctuation is conventionally based on indices on statistical operations on RR intervals. The most widely used index is the standard deviation of all normal to normal RR intervals (SDNN) over a 24-hour period, reflecting primarily the very low frequency (VLF) fluctuation in HR behaviour (Rosenbaum & Race 1968). It has been used as a predictor of mortality in post myocardial infarction patients (Kleiger *et al.* 1987).

Spectral analysis of HRV inspects the frequency-specific oscillations of HR fluctuation and decomposes a series of sequential RR intervals into a sum of sinusoidal functions at different amplitudes and frequencies (Akselrod *et al.* 1981). The amplitude of the HR fluctuations at different oscillation frequencies is presented as power spectrum.

The Fast Fourier transformation and autoregressive analysis are the most commonly used methods for transforming signals to the frequency domain. The power spectrum is usually divided into three or four frequency bands as follows: ultra low frequency (ULF) <0.0033 Hz, VLF from 0.0033–0.04 Hz, low frequency (LF) from 0.04-0.15 Hz and high frequency (HF) from 0.15-0.4 Hz (Task Force 1996). The HF fluctuation of RR intervals mainly reflects the cardiovagal modulation and the inspiratory inhibition of vagal tone and the LF and VLF bands reflect sympathetic excitation, sympathovagal balance, and arterial BP oscillations and thermoregulation (Rosenbaum & Race 1968, Dwain & Eckberg 1997, Pagani *et al.* 1997).

The Poincaré plot is a geometrical method of HRV analysis. It is a diagram (scattergram) that plots each RR interval as a function of the previous RR interval. These plots can be interpreted visually and quantitatively, where the instantaneous beat to beat RR interval variability (SD1) and the SD of continuous long-term RR interval variability (SD2) are analysed (Huikuri *et al.* 1996, Tulppo *et al.* 1996). SD1 describes the magnitude of beat to beat RR interval variability reflecting vagal modulation of the HR. SD1 correlates with the HF spectral component relatively strongly. On the other hand, SD2 has correlations with the magnitude of the LF and VLF spectral components and it describes the long-term RR interval fluctuations. Unlike the spectral analysis, the Poincaré plot method is not interfered by stationary irregularities and trends in the RR intervals, and it may therefore be more suitable for HRV analysis from uncontrolled ambulatory ECG recordings (Tulppo *et al.* 1996).

Analysis of non-linear dynamics based on chaos theory and fractal mathematics have opened new approaches for studying and also understanding the HR behaviour (Goldberger & West 1987, Goldberger 1996). With these methods, estimation of the correlation properties and complexity of HRV can be performed. Analysis of fractal-like properties have been used to detect abnormalities of HR dynamics in various cardiovascular disorders (Bigger *et al.* 1996, Huikuri *et al.* 1998, Mäkikallio *et al.* 1998, Mäkikallio *et al.* 1999a, Mäkikallio *et al.* 1999b). Analysis of 1/f characteristics i.e. the inverse power-law slope has been shown to be an independent predictor of survival in the elderly as well as in patients with impaired left ventricular function (Brouwer *et al.* 1996, Ho *et al.* 1997, Huikuri *et al.* 1998). The physiological background for this method is not completely understood, but it is influenced by the autonomic input to the heart, as the slope of the power law relation is especially deep in denervated, transplanted hearts (Bigger *et al.* 1996).

The parameter approximate entropy (ApEn) quantifies the regularity or predictability of time series data. This reduced complexity of HR dynamics has been found in sickness

of the neonates and in patients with postoperative complications after cardiac surgery, as well as in patients with chronic liver disease (Pincus & Viscarello 1992, Fleisher *et al.* 1993, Fleisher *et al.* 2000). The decrease of these dynamic parameters, especially the value of ApEn, are also suggested to be associated with spontaneous onset of paroxysmal atrial fibrillation (Vikman *et al.* 1999).

Altered HRV may also be associated with certain neurological diseases. Acute cerebrovascular diseases and brain injuries frequently cause cardiovascular complications and also decrease HRV. It has been shown that all the spectral components of HRV are suppressed after hemispherical and brainstem cerebral infarctions, and this may be long lasting (Korpelainen *et al.* 1996a, Korpelainen *et al.* 1996b). A similar pattern of HRV is also seen in brain-dead patients (Kita *et al.* 1993, Freitas *et al.* 1996) and in patients with severe brainstem injury (Novak *et al.* 1995). Moreover, it has been shown that circadian fluctuation of HR variability is reversibly abolished in the acute phase of ischaemic stroke. This reversible abolition and the loss of the relative nocturnal dominance of the HR variability may contribute to the high incidence of cardiac arrhythmias and other cardiovascular complications after acute stroke (Korpelainen *et al.* 1999). Altered HRV has also been observed in Parkinson's disease (Haapaniemi *et al.* 2001), and multiple sclerosis (Frontoni *et al.* 1996). In addition, there is also evidence that HRV is altered in neonates who later experience sudden infant death (Rosenstock *et al.* 1999).

2.6 Epilepsy and autonomic nervous system

2.6.1 General aspects

Epilepsy may be associated with a variety of changes in the ANS function. During acute epileptic seizures, there may be autonomic symptoms present and epileptic seizures may manifest themselves as ANS dysfunction only (Marshall *et al.* 1983, Gilchrist 1985, Wannamaker 1985, Blumhardt *et al.* 1986, Schraeder & Lathers 1989, Vaughn *et al.* 1996, Messenheimer *et al.* 1997). It is also known that long term ANS abnormalities may arise in epilepsy but the clinical significance of these signs and symptoms of chronic dysregulation of ANS function is not completely understood (Kälviäinen *et al.* 1990, Frysinger *et al.* 1993, Devinsky *et al.* 1994, Faustmann & Ganz 1994, Massetani *et al.* 1997, Tomson *et al.* 1998, Druschky *et al.* 2001). In addition, means to treat or prevent them are not yet known. Although the significance of subclinical ANS dysfunction is incompletely understood, it may sometimes be associated with events that, under unfavourable circumstances, may even be fatal to a patient.

2.6.2 Ictal autonomic dysfunction

Various symptoms and signs of ANS dysfunction may be present during epileptic seizures. These common and dramatic cardiorespiratory accompaniments have raised the question of how the patients can survive such an overwhelming event. Nonetheless, almost invariably the patients awake without sequelae.

Autonomic changes during epileptic seizures have been studied during electroshock therapy (ECT) (Brown *et al.* 1953). In this study patients received only subparalyzing doses of curare so that the convulsions could be monitored. At the onset of the ECT response, the average systolic and diastolic BP decreased 20 to 50 mmHg below control and in contrast to expected tachycardia in response to fall of BP, the HR slowed by over 50 beats/min. At the same time respiratory arrest appeared and lasted an average of 52 seconds. As convulsions continued, both the BP and HR increased only to fall again below control levels after the convulsions ceased. This second decrease in BP was followed by yet another elevation above control level, which gradually waned. Bradycardia persisted throughout the postictal period. In a second subgroup of experiments, subconvulsive shocks failed to produce apnea, but the variations of BP and HR was observed. (Brown *et al.* 1953) Later, other investigators have confirmed these ictal cardiorespiratory changes, which are correlated with generalized seizures, even when clinical seizure activity is prevented by neuroblocking agents (Mosier *et al.* 1957, McKenna *et al.* 1970).

Especially temporal partial seizures are associated with autonomic dysregulation. Seizures may only manifest themselves as burping, pallor or blushing, feeling of fear or panic, rising gustatory sensation including dyspepsia and cardiac arrhythmia or apnea. Based on various studies of focal temporal epileptic discharges and simultaneous ECG-recording it seems that especially tachyarrhythmias are a common phenomenon and that localized discharges in the temporal lobe and medial frontal cortex are often associated with major cardiorespiratory and cardiovascular changes similar to changes during generalized seizures (Marshall *et al.* 1983, Gilchrist 1985, 1996 Wannamaker 1985, Blumhardt *et al.* 1986, Schraeder & Lathers 1989, Vaughn *et al.* 1996, Messenheimer *et al.* 1997) It is noteworthy also that acceleration of HR often occurs around the time or even before the earliest scalp electroencephalographic or clinical change (Zijlmans *et al.* 2002).

Typical abnormal function of the ANS occurs with prolonged seizures. Hypotension develops in the course of a prolonged seizure and neurogenic pulmonary oedema is a well described phenomenon in status epilepticus (Lathers *et al.* 1997). Especially status epilepticus may be associated with ECG changes within 48 hours of the onset of the ictal phenomenon, and ischemic patterns and QT interval prolongation are the most typical findings. In an autopsy series of status epilepticus patients myofibrillar necrosis of the heart, a sign of high catecholamine state, was a common finding (Boggs *et al.* 1993).

2.6.3 Long-term autonomic dysfunction

The long term alterations of autonomic cardiovascular regulation may be subtle and only manifest themselves as changes in HR and BP regulation. Based on experimental work, it has been concluded that even minimal epileptogenic activity can be associated with altered cardiac neural discharge and arrhythmias (Lathers *et al.* 1997). It is possible, therefore, that even subclinical epileptogenic activity alters the function of different areas of the brain, resulting in changes in HR and BP and cardiac neural discharge as cardiovascular regulation is, in fact, a function of neuronal activity in the cerebral cortex, the amygdala and the medullary reticular formation.

There are only a few previous studies on interictal autonomic function in epilepsy. Devinsky and his colleagues (Devinsky *et al.* 1994) found essentially normal autonomic function in patients with epilepsy using a conventional pattern of autonomic reflex testing. However, epilepsy patients showed a greater variability in BP and HR in response cardiovascular reflex test procedures than the control subjects. This was thought to be partly attributable to CBZ treatment. In a recent study, a time and frequency domain analysis of HR variation and post-ganglionic innervation of the heart by the means of [¹²³I]metaiodobenzylguanide (MIGB)-SPECT was studied in TLE patients (Druschky *et al.* 2001). The results revealed predominant parasympathetic activity in patients with TLE compared to the control subjects and significantly decreased cardiac MIGB uptake, reflecting altered post-ganglionic sympathetic innervation of the study patients compared to the control group. Faustmann & Ganz studied the structure of HR dynamics by estimation of the Largest Lyapunov Exponent (LLE) in patients with idiopathic generalized epilepsies (Faustmann & Ganz 1994). HR dynamics in patients with normal EEG did not differ from that of the control subjects, whereas patients with interictal epileptiform discharges in EEG had significantly lower LLE of the HR dynamics. Frysinger and his co-workers studied spectral analysis of HRV in TLE patients prior to resective surgery (Frysinger *et al.* 1993). TLE patients had significantly lower low frequency bands of HRV compared to the control subjects. However, these study patients were confined to bed, whereas the control subjects continued with normal daily living during the ambulatory ECG recording, which may have affected the results. Cardiovascular reflex tests were performed in patients with progressive myoclonus epilepsy, a neurodegenerative disease characterized by generalized tonic clonic and sometimes absence seizures and progressive myoclonus (Kälviäinen *et al.* 1990). The majority of these patients complained various symptoms suggesting ANS dysfunction. Yet, HRV during deep breathing was the only significantly altered parameter in this study. However, it was concluded that this might be an early sign of ANS dysfunction in these young adult patients.

Spectral analysis of HR variability from ambulatory ECG and after certain stimuli (e.g. supine position and passive tilt position) was studied by Massetani and his co-workers in TLE patients (Massetani *et al.* 1997). The results of this study suggested that patients with TLE had a significant decrease in the total HRV in the supine position, and of the low frequency/high frequency ratio in the orthostatic position. These findings seemed to be associated particularly with right sided epileptic focus in EEG. Moreover, no correlation between the results and pharmacotherapy was seen. Finally, spectral

analysis of HRV from ambulatory 24-hour ECG recording was also studied by Tomson and his colleagues in patients with JME and TLE (Tomson *et al.* 1998). In this study, patients with TLE had significantly lower values of various measures than their control subjects. Also patients with JME had decreased value of low frequency/high frequency ratio compared to the control subjects reflecting the predominance of altered HRV in TLE. Patients with CBZ medication also had decreased values of the spectral analysis of HRV. However, most of the patients with CBZ had TLE, and therefore the authors were not able to conclude whether the observed changes were more likely due to TLE or CBZ.

Based on the above described studies altered autonomic regulation seems to be present in patients with epilepsy. However, it is not yet known how these observed changes affect the well being of an individual or whether these abnormalities progress with the continuation of epilepsy.

2.6.4 Sudden unexpected death in epilepsy (SUDEP)

The increased mortality of patients with epilepsy compared to the general population is partly due to the co-morbidity in epilepsy since there is a variety of progressive diseases that lead to epilepsy and eventually to death (Hauser *et al.* 1993, O'Donoghue & Sander 1997). However, sudden death is substantially more common in patients with epilepsy than in the general population. Its incidence varies from 1/100 patient years in patients with severe intractable epilepsy to 1/1000 patient years in patients with well controlled epilepsy (Hirsch & Martin 1971, Leestma *et al.* 1984, Leestma *et al.* 1989, Devinsky *et al.* 1994, Donoghue & Sander 1997, Nashef *et al.* 1998, Nilsson *et al.* 1999, Sperling *et al.* 1999, Walczak *et al.* 2001, Langan *et al.* 2002). In the most comprehensive population-based study so far published the incidence of SUDEP was 0.35/1000 person-years, exceeding the expected rate of sudden death in the general population by nearly 24 times (Ficker *et al.* 1998). In Finland, there are no statistics available to survey the incidence of this phenomenon.

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death of an epilepsy patient with or without evidence for seizure and excluding documented status epilepticus. Autopsy may reveal pulmonary oedema and congestion of other organs, as well as scattered microscopic injury of the heart muscle, but not the cause of death (Earnest *et al.* 1992, Devinsky *et al.* 1994, Nashef 1997, Shorvon 1997, Nashef *et al.* 1998, Sperling *et al.* 1999). The risk factors for SUDEP seem to be multiple. SUDEP has been suggested to affect mostly young patients, aged 20-40 years, to associate with alcohol abuse, psychiatric co-morbidity, related medication, noncompliance and male gender in uncontrolled studies, but later it has been shown that these risk factors are not mandatory, but a healthy, compliant patient may also die suddenly (Tennis *et al.* 1995, Hanna 1997, Leestma *et al.* 1997, Nashef 1997, Nashef *et al.* 1998, Nilsson *et al.* 1999, Walczak *et al.* 2001). Moreover, it has been suggested that carbamazepine may be associated with increased risk for SUDEP, but this has not yet been confirmed (Kennebäck *et al.* 1997, Timmings 1998). However, refractory epilepsy

and polytherapy with AEDs seem to be important individual risk factors as shown in few case-control studies (Shorvon 1997, Nilsson *et al.* 1999).

The pathophysiology of SUDEP is not yet completely understood. It has been suggested that the utmost pathology lies on cardiorespiratory dysregulation that predisposes a patient to potentially fatal cardiac arrhythmia and central hypoventilation or apnea. The few experimental studies published so far on SUDEP have not given any conclusive results. (Schraeder & Lathers 1989, Oppenheimer & Cechetto 1990, Oppenheimer *et al.* 1990, Oppenheimer *et al.* 1992, Johnston *et al.* 1995, Johnston *et al.* 1997, Lathers *et al.* 1997, Nashef *et al.* 1998)

One possible mechanism for autonomic dysfunction and possible risk of SUDEP may relate to the experimental finding in which simultaneous recordings of cardiac autonomic neural discharges and cerebral epileptiform discharges revealed a “lockstep phenomenon”, defined as the occurrence of cardiac sympathetic and vagal cardiac neural discharges intermittently synchronized with epileptogenic discharge (Lathers *et al.* 1983, Lathers *et al.* 1987). With the disappearance of constant interdischarge intervals (e.g. stable lockstep phenomenon) and the appearance of variable interspike intervals (e.g. unstable lockstep phenomenon), precipitous changes in BP and incidence of ECG changes occurred more frequently (Stauffer *et al.* 1989). It has been postulated that the development of abnormal rhythmic activity of the unstable lockstep phenomenon may alter neurotransmitter release and initiate autonomic dysfunction thereby possibly contributing to the occurrence of SUDEP (Lathers *et al.* 1997).

It is well known that neuroanatomic connections between the brain and the heart provide links that allow cardiac arrhythmias to develop in response to activation of discrete areas in the brain. The neural aberration may then initiate other biological events, such as secretion of catecholamine that may contribute to the induction of cardiac arrhythmias or damage (Lathers *et al.* 1997). In one experimental work, epileptiform discharge in hypothalamic and mesencephalic neurons triggered various alterations of conduction system of the heart and bundle branch blocks (Mameli *et al.* 1993). In humans, on the other hand, various alterations in cardiovascular and respiratory regulation have been demonstrated in association with epileptogenic discharges and the phenomenon of apnea in association with seizures is well known to occur in children, especially in association with bradycardia (Lathers *et al.* 1997). It can be concluded that risk factors of SUDEP appear to be multiple, and a generalized autonomic storm leading to death, will have both sympathetic and parasympathetic effects.

3 Aims of the research

The aims of this study were

1. to investigate whether epilepsy is associated with changes of cardiovascular autonomic regulation by using cardiovascular reflex tests and analysis of HRV from an ambulatory ECG-recording.
2. to elucidate the effects of TLE on cardiovascular autonomic regulation.
3. to evaluate the association of the severity of TLE on cardiovascular autonomic functions.
4. to study the association of structural changes of the temporal lobes with changes in HRV in patients with TLE.
5. to compare the two methods, cardiovascular reflex tests and analysis of HRV, in the assessment of autonomic dysfunction in patients with epilepsy.

4 Subjects and methods

4.1 Subjects

The study was carried out in the Departments of Neurology, Clinical Neurophysiology, Radiology and division of Cardiology, University of Oulu during the years 1994-2003. The study was approved by the Ethics committee of the Medical Faculty of University of Oulu and carried out according to the principles of the Declaration of Helsinki. All patients and control subjects gave their informed consent before their inclusion in the study. 128 patients seen in the outpatient clinic of the Department of Neurology, Oulu University Hospital were included in the study. Manifestations of illness any other than epilepsy (e.g. diabetes mellitus, cardiopulmonary diseases, alcoholism, or renal failure) or medication known to affect the ANS were used as exclusion criteria. Similarly female patients who were pregnant or lactating were excluded. The clinical characteristics of the patients and control subjects in the individual studies are presented in Tables 6 and 7. In Table 8 (page 58) the number of patients with various types of epilepsy in different substudies participating in various examinations is shown.

Eighty four epilepsy patients participated in study I. Sixty patients had partial epilepsy whereas 24 patients suffered from idiopathic generalized epilepsies. Thirty-seven were previously untreated patients referred to the Outpatient Clinic for diagnosis and treatment because of experiencing at least two epileptic seizures. Forty seven patients were already diagnosed with epilepsy. Of these, 29 patients had been seizure-free for at least one year before the study and 18 patients had recurrent seizures. However, all 47 patients had been seizure-free at least one week before the study.

Thirty-eight patients with TLE participated in study II. Nineteen patients had well controlled TLE and most of them had been seizure free since starting antiepileptic medication. Nineteen patients had refractory TLE and suffered from recurrent monthly seizures despite the regular use of AEDs.

Fourty four TLE patients participated in study III. Of these, 25 patients had well controlled TLE, and 19 patients had refractory TLE.

Thirty nine patients with TLE participated in study IV. Of these patients 8 had hippocampal sclerosis and 31 had normal imaging of the brain.

The control population consisted of 84 healthy age and sex matched subjects who were members of the hospital staff, people recruited by the members of the hospital staff or healthy persons randomly selected by social code from the general population of Oulu. None of them had symptoms or signs of disease or medication affecting the ANS in their medical history and they had normal bodyweight.

Table 6. The demographics of the study patients and the control subjects.

Studies	Male/Female/Total	Age	Duration of epilepsy (years \pm SD)	Number of patients by the type of epilepsy P/GE
Study I				
Untreated	23/14/37	31 \pm 10	-	24/13
Patients taking AED(s)	31/16/47	31 \pm 8	12 \pm 9	36/11
Control subjects	33/17/50	39 \pm 29	-	-/-
Study II				
Patients with refractory TLE	4/15/19	33 \pm 7	22 \pm 11	19/-
Patients with well controlled TLE	4/15/19	34 \pm 7	14 \pm 10	19/-
Control subjects	8/30/38	33 \pm 8	-	-/-
Study III				
Patients with refractory TLE	5/14/19	33 \pm 7	22 \pm 10	19/-
Patients with well controlled TLE	11/14/25	33 \pm 6	16 \pm 10	25/-
Control subjects	9/25/34	33 \pm 10	-	-/-
Study IV				
Patients with HS	2/6/8	36 \pm 5	27 \pm 10	8/-
Patients without HS	11/20/31	31 \pm 7	16 \pm 9	31/-
Control Subjects	12/50/72	34 \pm 8	-	-/-

P, partial epilepsy; GE, idiopathic generalized epilepsies; HS, hippocampal sclerosis.

Table 7. The antiepileptic medication of the study patients

AED(s)	Study I P/GE	Study II rTLE/wTLE	Study III rTLE/wTLE	Study IV HS/No-HS
CBZ	17/2	-/9	-/14	3/8
OXC	-/-	5/8	4/8	-/11
PHT	9/1	-/1	-/1	-/1
VPA	-/6	1/-	1/-	-/-
LTG	-/-	-/1	-/1	-/1
CBZ with other AED(s)	2/2	6/-	7/1	3/5
OXC with other AED(s)	-/-	6/-	7/-	2/5

P, partial epilepsy; GE, idiopathic generalized epilepsies; rTLE, refractory temporal lobe epilepsy; wTLE, well controlled temporal lobe epilepsy; HS, hippocampal sclerosis; No-HS, no hippocampal sclerosis; CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; VPA, valproate; LTG, lamotrigine.

4.2 Methods

4.2.1 *Clinical evaluation*

All patients were carefully interviewed and clinically examined and the epilepsy type was classified according to the recommendations of the International League Against Epilepsy (ILAE 1989). In an interview of each patient, clinical manifestations of ANS dysfunction such as arrhythmias, dizziness due to orthostatic hypotension, sweating, abnormalities of urine and bowel function and sexual malfunction were evaluated in particular. Laboratory screening (liver and renal function, serum electrolytes, basic hematologic parameters) was normal in all the study patients. In general, the patients had neither excessive body weight nor elevated BP. EEG-recording was obtained from all the patients.

The exclusion criteria were met in male patients more often than in female patients which resulted in a smaller number of male patients in the study.

4.2.2 *Cardiovascular autonomic reflex tests*

Cardiovascular autonomic reflex tests, based on HR and BP responses at rest and after various stimuli were performed in 122 study patients and 88 control subjects under standardized conditions, in a silent room with a temperature from 20 to 23°C between 9 a.m. and 12 a.m (Braune *et al* 1996, Suominen 1997). First, with the patient in a supine position on the tilt table, the maximum contraction power (handgrip) of the patient's dominant hand was measured three times with a dynamometer for the isometric work test. At the end of a 30-minute resting period, the baseline BP was measured three times using an automatic arm sphygmomanometer. Thereafter, the following five tests were performed: normal breathing, paced breathing at six breaths per minute (deep breathing), the Valsalva maneuver, upright tilting (2 seconds, 90°) and isometric work. The interval between the various tests was standardized so that the next test was not started until the HR and BP had returned to the baseline level after the previous test. In the analyses of the deep breathing test, the thermistor signal ascertained that the paced deep but not maximum breathing was evenly performed. A small hole in the mouthpiece attached to a mercury manometer during the Valsalva maneuver guaranteed that thoracic pressure had to be used for blowing. The blowing pressure was monitored and only steadily maintained blowings were accepted. In the isometric work test the contraction power on the dynamometer was monitored graphically and thereby maintained at the optimal level. The ECG and breathing (nasal thermistor) signals were conveyed through an A/D converter with a sampling frequency of 320 Hz to a PC computer and were analyzed off-line using an automatic program package which allowed visual checking of the raw ECG and breathing signals. Test performances in deep breathing, the Valsalva maneuver and the isometric work tests were checked on-line and off-line, and only adequately

accomplished test performances were accepted for analysis. (Suominen 1997, Myllylä *et al.* 2002)

In the normal breathing test the consecutive RR intervals for a period of one minute were measured from the ECG, and the standard deviation (SD) of the intervals was used as the test variable. Successive RR intervals were measured and the square root of the mean squares of the differences between successive intervals (rMSSD) was calculated, so reflecting the true beat-to-beat variation. (Myllylä *et al.* 2002)

In the deep breathing test the mean ratio of the longest (expiration) to the shortest (inspiration) RR interval of five consecutive breathing cycles was calculated. The test was performed twice and the higher RR interval ratio was used as the "maximum-minimum (max-min) ratio". (Myllylä *et al.* 2002)

In the Valsalva maneuver the ratio of the longest RR interval after blowing (at the pressure of 40 mmHg for 15 sec) to the shortest RR interval during blowing or immediately after it was calculated. The highest ratio of three maneuvers was used as the "Valsalva ratio". (Myllylä *et al.* 2002)

In the tilting test the ratio of the longest RR interval around beat 30 (beats 20 to 40) to the shortest RR interval around beat 15 (beats 10 to 20) after quick passive upright tilting was used as the "30:15 ratio". The systolic and diastolic BP responses were measured at rest, immediately after tilting, and at 2, 5, and 7 minutes after tilting. The difference between the BP at rest and the lowest BP after tilting was recorded. (Myllylä *et al.* 2002)

In the isometric work test the largest increase in systolic and diastolic BP during a 5-minute period of sustained handgrip with a dynamometer at 30% of the maximum voluntary power was recorded. BP was measured at 1, 2, 3, 4 and 5 minutes of work and the result was compared with the BP at rest. Male and female subjects were analysed separately. (Myllylä *et al.* 2002)

4.2.3 Heart rate variability analysis

4.2.3.1 ECG recordings

A two-channel 24-hour ambulatory ECG recording (Delmar Avionics electroscanner) was performed in patients and control subjects in studies III-IV (Task Force 1996). During the recording they continued to perform their normal daily activities. They were also asked to keep a diary of all the activities and possible seizures during the recording.

The ECG data from the recordings were sampled digitally and transferred from the Oxford Medilog scanner to a microcomputer for analysis of HRV. All RR interval time series were first edited automatically, after which careful manual editing was performed by visual inspection of the RR intervals. Each RR interval time series was passed through a filter that eliminates premature beats and artifacts and deletes the filling gaps (Huikuri *et al.* 1993, Huikuri *et al.* 1994, Huikuri *et al.* 1996). In the final analysis of linear components of HRV, 24-hour measurements were divided into segments of 3600 RR intervals, and in the analysis of non-linear components of HRV, 24-hour measurements

were divided into segments of 8000 and only segments with >85% sinus beats were included. (Myllylä *et al.* 2002)

4.2.3.2 *Time domain and spectral analysis*

The mean length of all RR intervals and standard deviation (SDNN) of all RR intervals were computed as time domain measures of HRV. The power spectra of HRV (Figure 1) were quantified by measuring the area in 3 frequency bands: 0.005 to 0.04 Hz, VLF, 0.04 to 0.15 Hz, LF and 0.15 to 0.4, HF. (Myllylä *et al.* 2002)

4.2.3.3 *Poincaré plot analysis*

For quantitative two-dimensional vector analysis, the standard deviation of instantaneous beat-to-beat RR interval variability (SD1) and continuous long-term RR interval variability (SD2) were analysed, and visually presented as Poincaré plot scattergrams (Figure 2), in which each RR interval is plotted as a function of the previous one (Tulppo *et al.* 1996, Korpelainen *et al.* 1999). In the computerised analysis, the Poincaré plot was first turned clockwise, and then standard deviation of the plot data was then computed around the horizontal axis, passing through the data centre (SD1). The SD of the continuous long-term RR intervals was quantified by turning the plot 45° counterclockwise (SD2) and by computing the data points around the horizontal axis, passing through the centre of the data. (Myllylä *et al.* 2002)

4.2.3.4 *Approximate entropy analysis*

A value of ApEn is a measure that quantifies the regularity of time series data. It measures the logarithmic likelihood that runs of patterns (beat to beat difference of RR interval length) are close in the next incremental comparison. A time series containing many repetitive patterns has a relatively small ApEn, whereas more random data produce higher values. Two input variables, m and r , must be fixed to compute ApEn, and $m = 2$ and $r = 20\%$ of the SD of the data sets were chosen as suitable values on the basis of previous findings of good statistical validity. (Pincus 1991, Pincus & Viscarello 1992, Pincus & Goldberger 1994, Myllylä *et al.* 2002)

4.2.3.5 Fractal correlation analysis

To quantify fractal correlation properties of HR, the detrended fluctuation analysis technique, which is a modified root-mean-square analysis of random walk, was used. The HR correlation properties were defined separately for short-term (≤ 11 beats, α_1) and for long-term (> 11 beats, α_2) correlations of RR interval data (short- and long-term scaling exponents). (Peng *et al* 1995, Iyengar *et al* 1996, Mäkikallio *et al* 1997, Myllylä *et al.* 2002)

4.2.3.6 Power-law relationship analysis

The power-law relationship of RR interval variability, a spectral measure reflecting the distribution of the spectral characteristics of the RR interval oscillations, was calculated from the frequency range of 10^{-4} to 10^{-2} . The point power spectrum was logarithmically smoothed in the frequency domain, and the power was intergrated into bins spaced $0.0167 \log(\text{Hz})$ apart. A robust line fitting algorithm of $\log(\text{power})$ on $\log(\text{frequency})$ was then applied to the power spectrum between 10^{-4} and 10^{-2} , and the slope of this line was calculated. This frequency band was chosen on the basis of previous observations regarding the linear relationship between $\log(\text{power})$ and $\log(\text{frequency})$ in this frequency band. (Saul *et al* 1987, Bigger *et al* 1996, Myllylä *et al.* 2002)

4.2.4 Magnetic resonance imaging

In Studies II - IV, MRI was performed in all except three patients with well-controlled TLE who had claustrophobia. CT was performed in those three patients. In Study I CT was performed in all patients to exclude symptomatic epilepsy. MRI was performed on a 1.0 Tesla unit (Magnetom SP 42, Siemens, Erlangen Gemany). The protocol consisted first of sagittal, T1-weighted scans with a 5.0-mm section thickness. TR = 570 msec, TE = 15 msec, 2 acquisitions. Second, a fast spin-echo with TR of 6000 msec, effective TE of 90 ms, 8 echoes and FOV of 230 mm was used to image axial slices. Third, a coronal, three-dimensional (3-D) gradient-echo fast low-angle shot (FLASH) acquisition was performed. Parameters of the sequence were 30/5/1 (TR/TE/excitations), field of view was 25 cm and matrix size was 256 x 256. Section thickness was 3 mm and the slices were contiguous. Fourth, coronal multiple spin-echo (SE) imaging with 8 echoes was performed with TR of 2000 msec and TE from 20 msec to 125 msec with 15 ms interval. the field of view was 230 mm and section thickness was 5.0 mm with a 1.0 gap. Contrast was not routinely used.

The images were transferred to a HP 9000/730 workstation. Volumetric measurements were performed using a custom made software. Hippocampal volume was measured on sections of the coronal 3-D FLASH acquisition that was not perpendicular to the axis of the hippocampal formation. The images were magnified and the area of the hippocampal

formation was zoomed. The structures to be measured were outlined manually with a mouse-driven cursor. The measurements included entire rostrocaudal extent of the hippocampus. The landmarks used for the definition of the hippocampus have been described in detail (Lehericy *et al* 1994, Hasboun *et al* 1996).

Measurements of the hippocampal formations at the level of the body of the structure were usually easy. These measurements included Ammon's horn, the subiculum, the dentate gyrus, and the white-matter tracts of the alveus and the fimbria. The border between the subiculum and parahippocampal gyrus was arbitrarily defined as the most medial extent of the junction of subiculum and the parahippocampal gyrus. Measurements at the level of the head and tail were more difficult. The delineation was guided by the band of high signal intensity generated by the alveus. If the alveus was not clearly visible the most accurate anterior limit was confirmed with the 3-D sagittal plane. Caudally, the posterior boundary of the hippocampal formation was chosen as the last section containing Ammon's horn, which corresponded to the section where the crus of the fornix was visible.

After the segmentation process, the hippocampus was marked with colour and the entire hippocampus was portrayed with the 3-D cursor in the sagittal plane. Reformatting in this fashion allowed confirmation of the anterior coordinates of the hippocampus and correlation with the original coronal images to ensure accuracy of measurements. The hippocampal area in one section was then calculated by pixel counting. The volumes were calculated by adding areas and multiplying by section thickness. Volume measurements were performed by one operator unaware of the clinical diagnosis.

Table 8. Number of patients epilepsy participating in various examinations in different substudies.

Substudies	Cardiovascular reflex tests*	Analysis of HRV from ambulatory 24 hour ECG recordings#	CT	MRI
Study I				
Untreated patients	37	-	37	
Patients with idiopathic generalized epilepsies taking AED(s)	11	-	11	
Patients with partial epilepsies taking AED(s)	36	-	36	
Study II-III				
Patients with refractory TLE	19	19		19
Patients with well controlled TLE	25	25	3	22
Study IV				
Patients with hippocampal sclerosis	8	8		8
Patients without hippocampal sclerosis	31	31		31

*, SD of RR intervals, max-min ratio, Valsalva ratio, 30:15 ratio, isometric test; #, spectral analysis, dynamic measures.

4.2.5 *Statistical analysis*

The demographic data of the patients and control subjects were analysed with Student's unpaired or paired t-test in the case of normal distribution when comparing quantitative data between different groups. The Mann-Whitney two-sample test and the Kruskal-Wallis test (comparison of three groups) were used in analysing unevenly distributed data or ordinal variables.

In the analyses of the cardiovascular reflex tests, analysis of covariance was used to determine the significance levels in comparison between the patients and the control subjects. Cardiovascular autonomic reflexes have been shown to be dependent upon both age and baseline HR (Bannister & Mathias 1988, Kajser *et al* 1985, McLeod & Tuck 1987, O'Brien *et al* 1986, Robinson *et al* 1983, Vargas & Lye 1980, Vita *et al* 1986, Yokohama *et al* 1991). Therefore, the values of the HR and BP responses (after logarithmic transformation) were corrected for age and baseline HR separately for the patients and the control subjects using multiple regression. The significance levels for the comparison between the patients and the controls were obtained using analysis of covariance (ANCOVA). The values of the HR responses in all groups were separately adjusted both for the mean age and for the mean baseline RR interval (880 ms) of the patients by multiple regression analysis, and the differences between the results of the regression analysis and those between the regression values were compared by ANCOVA. Statistical evaluation of the various HR variability analyses was performed with using the Kruskal-Wallis test and the Mann-Whitney two-sample test to compare the values of the control subjects and those of the patients.

Correlations between ApEn, the slope of the powerlaw relationship of the HR variability and the traditional spectral measures of HR variation in patients with TLE (Study III) and correlations between the measures of HR responses and measures of HR variability (Study IV) were assessed with Pearson's bivariate correlation test. Values $p < 0.05$ were considered significant. All analyses were made on observed cases and calculated using the SPSS Windows.

The mean (\pm SD) values of the volumetric measures of the hippocampi and amygdalas were calculated using with Student's t-test.

5 Results

5.1 Clinical findings

The patients did not complain any particular symptoms referring to ANS dysfunction. In the clinical examination, signs of autonomic disturbances could not be found. The clinical cardiorespiratory findings, including baseline BP and neurological examinations, were normal in all patients. None of the patients had severe cardiac arrhythmias in the ECG recordings. The patients were not under- or overweight. The basic laboratory screening and serum drug levels were within usually recommended ranges in all patients.

5.2 Cardiovascular reflex tests (Studies I-II and IV)

The main results of the Study I are presented in Tables 9 and 10. The mean HR and BP responses in patients with untreated recently diagnosed epilepsy did not differ from those of the control subjects. The SD of RR intervals ($p < 0.05$) and the maximum systolic BP increase in isometric work ($p < 0.05$) were diminished in patients who had been treated with AEDs for epilepsy for a long time. The diminished max-min ratio ($p < 0.05$), Valsalva ratio ($p < 0.001$) and BP responses during isometric work ($p < 0.001$) were noted only in patients treated with CBZ. In relation to the type of epilepsy, the patients with idiopathic generalized epilepsies had diminished SD of RR interval ($p < 0.05$), whereas patients with partial epilepsies had diminished BP responses during isometric work ($p < 0.05$).

Two (5.4%) patients with recently diagnosed untreated partial epilepsies had two measurements of cardiovascular reflexes outside the reference range obtained in our control subjects (mean \pm 2 SD). One had diminished SD of RR interval and Valsalva ratio, and the other had abnormal BP responses 2 and 7 min after tilting (30:15 ratio). One patient (2.1%) receiving long-term monotherapy (CBZ) for partial epilepsy had two

tests (max-min ratio and Valsalva ratio) outside the normal range. None of the control subjects had two or more abnormal test.

In Study II the SD of RR interval ($p < 0.001$) and 30:15 ratio ($p < 0.05$) were lower in patients with refractory TLE than in the control subjects. The 30:15 ratio ($p < 0.05$) was also diminished in patients with well controlled TLE compared to the control subjects. Patients with refractory TLE had lower SD of RR interval compared to the patients with well controlled TLE ($p < 0.05$). The BP responses (to tilting and isometric work) showed no differences between the patients and the control subjects (Table 11).

A decreased max-min ratio was found in patients taking CBZ as either monotherapy or polytherapy, compared to the control subjects (patients 1.26 ± 0.03 , control subjects 1.37 ± 0.03 , $p < 0.01$). They also had lower 30:15 ratio than the control subjects (1.10 ± 0.02 versus 1.21 ± 0.02 respectively, $p < 0.01$). The patients taking CBZ only as monotherapy showed a trend to the lower SD of the RR interval (31.13 ± 6.90 versus 46.25 ± 5.67 respectively, $p = 0.127$), the max-min ratio (1.39 ± 0.03 versus 1.30 ± 0.05 respectively, $p = 0.217$), the Valsalva ratio (2.16 ± 0.09 versus 1.91 ± 0.20 respectively, $p = 0.217$), and the 30:15 ratio (1.19 ± 0.03 versus 1.13 ± 0.04 respectively, $p = 0.207$) (Table 11).

The values of the measured parameters did not differ between patients taking other AEDs as monotherapy or polytherapy and the control subjects, or between patients taking different AED regimens, lateralization of epileptic focus, or interictal EEG findings.

Three patients with refractory TLE (15.8%) and two patients with well controlled TLE (10.5%) had two values of the measurements of cardiovascular responses below the reference range obtained in our control subjects (mean ± 2 SD). These patients did not show any characteristic pattern of antiepileptic medication, drug dosage or serum concentration, type or frequency of seizures, duration of TLE or lateralization of epileptic focus in EEG-registration compared to the patients with cardiovascular responses within normal range. However, four out of five patients with clinically significant abnormalities of cardiovascular reflexes were men.

Table 9. The heart rate and blood pressure responses in patients with untreated epilepsy and in epilepsy patients with carbamazepine medication compared to the control subjects.

Cardiovascular Reflexes	Untreated patients (n = 37)	Patients with CBZ monotherapy (n = 19)	Patients with CBZ polytherapy (n = 12)	Control subjects (n = 50)
SD of RR intervals	46.9 ± 3.4	37.0 ± 5.3	37.9 ± 4.4	48.3 ± 3.4
Maximum-minimum ratio	1.38 ± 0.03	1.37 ± 0.05	$1.28 \pm 0.03^*$	1.37 ± 0.02
Valsalva ratio	2.20 ± 0.08	$1.74 \pm 0.09^{**}$	2.08 ± 0.08	2.16 ± 0.08
Isometric test				
Maximum SBP	$+26.3 \pm 1.8$	$+24.9 \pm 2.0$	$+22.4 \pm 4.9^*$	$+31.6 \pm 2.1$
Maximum DBP	$+22.1 \pm 1.8$	$+14.2 \pm 2.2^{**}$	$+23.1 \pm 4.3$	$+23.9 \pm 1.6$

Values are mean (\pm SD). *, $p < 0.05$ compared to the control subjects; **, $p > 0.001$ compared to the control subjects.

Table 10. The heart rate and blood pressure responses in patients with partial and primary generalized epilepsy compared to the control subjects.

Cardiovascular reflexes	Patients with refractory TLE (n = 19)	Patients with well controlled TLE (n = 19)	Control subjects (n = 38)
SD of RR intervals	33.36 ± 2.59** ϕ	44.75 ± 4.53	48.11 ± 4.23
Maximum-minimum ratio	1.29 ± 0.02	1.32 ± 0.02	1.36 ± 0.03
Valsalva ratio	2.02 ± 0.08	2.06 ± 0.12	2.16 ± 0.09
30:15 ratio	1.14 ± 0.03*	1.15 ± 0.02*	1.21 ± 0.02

Values are mean (\pm SD). *, $p < 0.05$; **, $p < 0.001$; compared to the control subjects; ϕ , $p = 0.02$ compared to the patients with well controlled TLE.

Table 11. The heart rate responses in patients with refractory and well controlled temporal lobe epilepsy and in temporal lobe epilepsy patients with CBZ medication compared to the control subjects.

Cardiovascular Reflexes	Patients with partial epilepsy (n = 60)	Patients with idiopathic generalized epilepsies (n = 24)	Control subjects (n = 50)
SD of RR intervals	43.6 ± 2.6	34.9 ± 6.8*	48.3 ± 3.4
Maximum-minimum ratio	1.37 ± 0.02	1.34 ± 0.05	1.37 ± 0.02
Valsalva ratio	2.05 ± 0.06	2.03 ± 0.11	2.16 ± 0.08
Isometric test			
Maximum SBP	+24.3 ± 2.0*	+28.7 ± 3.0	+31.6 ± 2.1
Maximum DBP	+19.3 ± 1.7	+24.4 ± 3.1	+23.9 ± 1.6

Values are mean (\pm SD). *, $p < 0.05$ compared to the control subjects; **, $p > 0.001$ compared to the control subjects.

In Study IV, the SD of the RR interval ($p < 0.05$), the max-min ratio ($p < 0.05$) and the 30:15 ratio ($p < 0.001$) of the HR responses were lower in the patients with TLE than in the control subjects. In patients with hippocampal sclerosis, the mean values of most of the parameters of the cardiovascular reflex tests were smaller than those of the patients without hippocampal sclerosis. However, the differences did not reach statistical significance (Table 12).

One patient with (12.5%) and three patients without (9.7%) HS had two values of the measurements of cardiovascular reflex tests below the reference range obtained in our control subjects (mean \pm 2 SD). These patients did not show any characteristic pattern of AEDs, type or frequency of seizures, duration of TLE, lateralization of epileptic focus in EEG-registration compared with patients with cardiovascular responses within normal range. Yet, three out of four patients with clinically significant abnormalities in cardiovascular reflexes were men.

Table 12. The heart rate responses in temporal lobe epilepsy patients with and without hippocampal sclerosis and the control subjects.

Cardiovascular reflex tests	Patients with HS (n = 6)	Patients with No-HS (n = 27)	All patients (n = 33)	Control subjects (n = 38)
SD of RR interval	40 ± 19	47 ± 31	46 ± 29	58 ± 67
Max-min ratio	1.30 ± 0.15	1.32 ± 0.13*	1.32 ± 0.13*	1.42 ± 0.34
Valsalva ratio	1.91 ± 0.27*	2.12 ± 0.45	2.08 ± 0.43*	2.26 ± 0.49
30:15 ratio	1.08 ± 0.37*	1.14 ± 0.10*	1.13 ± 0.09**	1.25 ± 0.15

Values are mean (± SD). HS, hippocampal sclerosis; *, $p < 0.05$ compared to the control subjects; **, $p < 0.001$ compared to the control subjects.

5.3 Heart rate variability analysis (Studies III - IV)

Six patients with refractory TLE reported having experienced simple and/or complex partial seizures during the recording. Their HRV profile did not, however, show any particular pattern different from HRV profiles of the other patients and were, therefore, included in the analysis. None of the patients reported generalized seizures. The mean value of RR interval was similar in the patients and the control subjects. No significant arrhythmias were seen during ECG-recordings.

In Study III the values of SDNN ($p < 0.05$) and the spectral components VLF ($p < 0.001$), LF ($p < 0.001$) and HF ($p < 0.001$) were lower in patients with TLE compared to those of the control subjects. The slope of the power-law relationship of the HRV ($p < 0.01$) was deeper in the patient group than in the control subjects (Table 13).

The mean value of the ApEn ($p < 0.05$) of the refractory TLE patients was lower than that of the well controlled TLE, and the long term fractal correlation value α_2 ($p < 0.05$) was smaller in patients with well controlled TLE. The values of the other HR measures among patients with refractory and well controlled TLE were similar (Table 13).

Altered HRV was not associated with any particular AED regimen, or the serum concentrations of different AEDs. Moreover, the duration of TLE did not correlate with the alterations of HRV.

Figures 5, 6 and 7 present examples of the power spectrum analyses of HRV, Poincaré plots and power-law relation slopes from a patient with TLE and from a healthy subject.

Table 13. Analysis of heart rate variation in patients with refractory and well controlled temporal lobe epilepsy and the control subjects.

Measure	Patients with refractory TLE (n = 19)	Patients with well controlled TLE (n = 25)	All patients (n = 44)	Control subjects (n = 34)	p Value (Mann-Whitney)
RRI	863 ± 103	819 ± 112	838 ± 109	850 ± 71	0.403
SDNN	154 ± 32	158 ± 51	156 ± 43	177 ± 44	0.039
VLF	1538 ± 762	1749 ± 1005	1658 ± 905	3256 ± 1765	<0.001
LF	905 ± 472	1038 ± 507	981 ± 491	1901 ± 1308	0.001
HF	604 ± 502	628 ± 365	681 ± 424	1710 ± 2050	0.011
ApEn	0.93 ± 0.21†	1.09 ± 0.32	1.02 ± 0.29	1.15 ± 0.21	0.045
α_1	1.22 ± 0.18	1.17 ± 0.18	1.19 ± 0.18	1.16 ± 0.1	0.292
α_2	1.03 ± 9.0	0.99 ± 7.64*	1.01 ± 6.13	1.01 ± 6.13	0.824
Slope of HRV	-1.32 ± 0.13	-1.37 ± 0.21	-1.35 ± 0.18	-1.20 ± 0.21	0.002

Values are mean (\pm SD); RRI, RR interval; SDNN, SD of all RRIs; VLF, very low frequency; LF, low frequency; HF, high frequency; SD1 instantaneous beat to beat RR interval variability; SD2, long-term continuous RR interval variability ApEn, approximate entropy; α_2 , long term scaling exponent; †, $p = 0.021$ compared to the patients with well controlled TLE; *, $p = 0.037$ compared to the patients with refractory TLE; **, $p =$ all patients compared to the control subjects

In Study IV the values of SD ($p < 0.001$), SDNN ($p < 0.05$), VLF ($p < 0.001$), LF ($p < 0.001$), HF ($p < 0.05$), SD1 ($p < 0.001$), SD2 ($p < 0.001$), ApEn ($p < 0.05$) and the slope of the power law ($p < 0.001$) of the analysis of HRV were lower in the patients with TLE than in the control subjects. In patients with hippocampal sclerosis (see chapter 5.5.) the mean values of nearly all the parameters of analysis of HRV were smaller than those of the patients without hippocampal sclerosis. However, the differences did not reach statistical significance (Table 14).

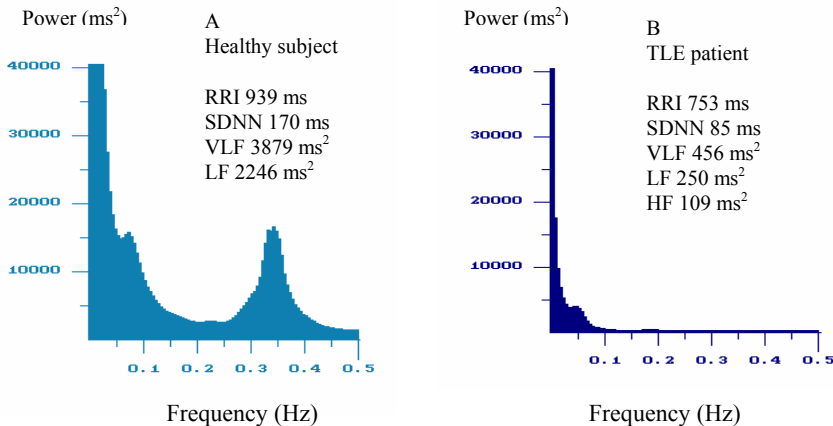


Fig. 5. Spectral analysis of HRV in a healthy subject (A) and in a TLE patient (B). The area from 0.005 to 0.04 Hz represents VLF power, the area from 0.04 to 0.15 Hz LF power, and the area from 0.15 to 0.4 Hz HF power (data from Study III).

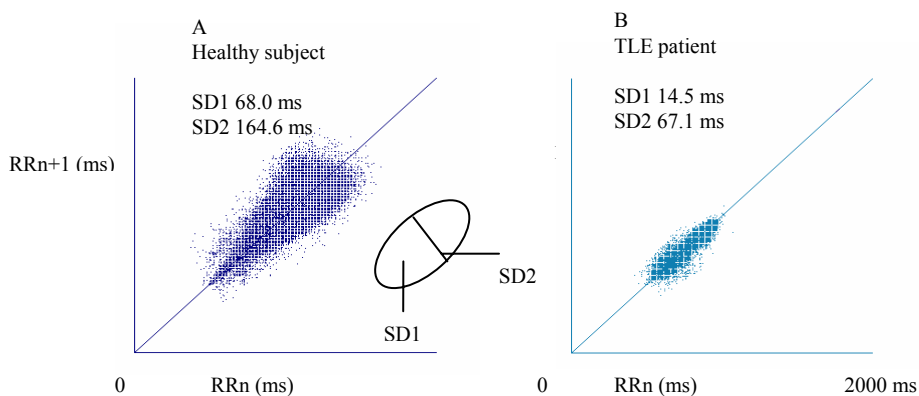


Fig. 6. Poincaré plot from a healthy subject (A) and a TLE patient (B). SD1 indicates SD of instantaneous RR interval variability measured from axis 1, and SD2 indicates SD of long-term continuous RR interval variability measured from axis 2 (data from Study III).

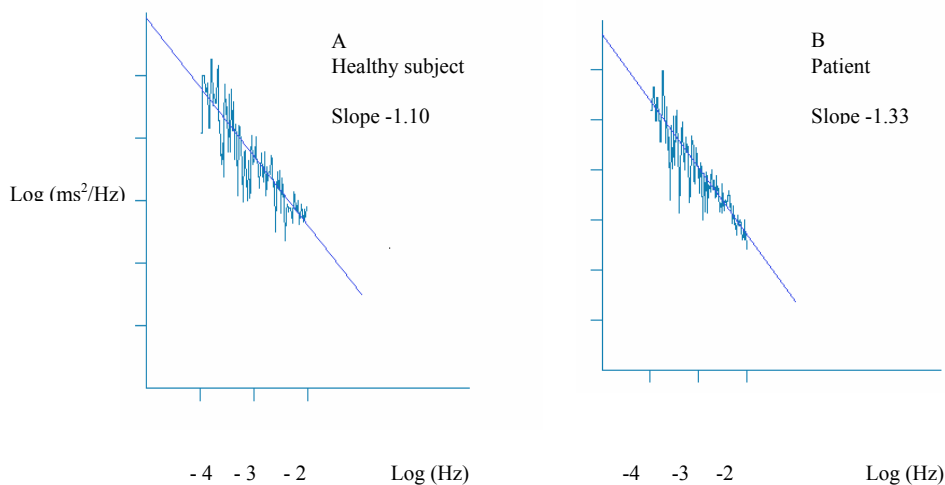


Fig. 7. Slopes of power-law relation of a healthy subject (A) and a TLE patient (B) (data from Study III).

Table 14. Analysis of heart rate variation in temporal lobe epilepsy patients with and without hippocampal sclerosis and the control subjects.

Measure	Patients with HS (n = 8)	Patients with No-HS (n = 31)	All Patients (n = 39)	Control Subjects (n = 34)
RRI	879 ± 153	834 ± 101	843 ± 113	850 ± 71
SD	92 ± 19*	92 ± 30**	92 ± 28 **	113 ± 30
SDNN	166 ± 69	154 ± 38	156 ± 45*	177 ± 44
VLF	1410 ± 694**	1714 ± 983**	1652 ± 935**	3256 ± 1765
LF	871 ± 407*	972 ± 488**	951 ± 469 **	1901 ± 1308
HF	600 ± 255	632 ± 488*	625 ± 448 *	710 ± 2050
SD1	30 ± 7	28 ± 10**	29 ± 10 **	42 ± 22
SD2	126 ± 27	128 ± 39**	128 ± 37 **	153 ± 38
$\alpha 2$	0.98 ± 0.10	1.03 ± 0.07	1.02 ± 0.10	1.0 ± 0.1
ApEn	1.08 ± 0.18	0.97 ± 0.31*	0.99 ± 0.29 *	1.15 ± 0.21
Slope of the HRV	-1.37 ± 0.29	-1.35 ± 0.15**	-1.35 ± 0.19**	-1.20 ± 0.2

For abbreviation see page 66. Values are mean (\pm SD). HS, hippocampal sclerosis; *, $p < 0.05$; **, $p < 0.001$.

5.4 Correlation of cardiovascular autonomic reflex tests and heart rate variability analysis (Study IV)

There was a strong correlation between HR responses in breathing tests and several traditional measures of HRV, whereas the correlation was weak between dynamic measures of HRV, the HR responses of the cardiovascular autonomic reflexes and traditional measures of HRV (Table 15).

Table 15. The correlation of cardiovascular reflex tests and heart rate variability analysis in patients with temporal lobe epilepsy.

Measures of HRV	SD of RR interval	Max-Min Ratio	Valsalva Ratio	30:15 Ratio
RRI	0.24	-0.06	-0.09	-0.03
SD	0.64**	0.45*	0.24	0.002
SDNN	0.18	0.35*	0.25	-0.29
VLF	0.63**	0.44*	0.27	0.08
LF	0.64**	0.40*	0.32	0.17
HF	0.58**	0.34	0.43*	0.04
SD1	0.60**	0.41*	0.40*	0.05
SD2	0.61**	0.42*	0.25	-0.03
$\alpha 2$	0.12	0.19	0.27	0.14
ApEn	0.34	0.29	0.17	0.20
Slope	-0.32	-0.19	-0.15	-0.10

For abbreviations see page 66. Values are mean (\pm SD). *, $p < 0.05$, **, $p < 0.001$.

5.5 MRI findings (Study IV)

Four patients had left-sided hippocampal sclerosis and three patients had right-sided hippocampal sclerosis in MRI, whereas one patient had hippocampal sclerosis and parahippocampal cortical dysplasia on the left in MRI. All other patients were defined as to have cryptogenic TLE, i.e. the etiology of epilepsy could not be ascertained.

The mean values of the hippocampus and amygdala are shown in Table 16. The hippocampal ($r = -.382$; $p = 0.016$) and amygdaloid ($r = -.228$; $p = 0.162$) volumes were smaller with the longer duration of epilepsy.

Table 16. The mean (\pm SD) volumes of the hippocampus and amygdalas in TLE patients with and without hippocampal sclerosis.

	Patients with hippocampal sclerosis (n = 8)	Patients without hippocampal sclerosis (n = 31)	All Patients (N = 39)
Hippocampus			
Right	2973 \pm 256	2955 \pm 256	2958 \pm 246
Left	2900 \pm 348	2917 \pm 353	2913 \pm 348
Min	2778 \pm 235	2836 \pm 296	2824 \pm 282
Amygdala			
Right	2195 \pm 250	2259 \pm 358	2246 \pm 337
Left	2183 \pm 504	2218 \pm 392	2211 \pm 410
Min	2051 \pm 421	2135 \pm 367	2118 \pm 374

Min, smaller hippocampus or amygdala. Values are mean (\pm SD).

6 Discussion

6.1 General aspects

Previous studies on autonomic regulatory system function have provided data that suggest altered autonomic function in patients with epilepsy. Ictal changes in HR and BP and other autonomic functions have been described in detail, but considerably less is known about the interictal alterations of cardiovascular regulation (Brown *et al.* 1953, Mosier *et al.* 1957, McKenna *et al.* 1970, Marshall *et al.* 1983, Gilchrist 1985, Wannamaker 1985, Blumhardt *et al.* 1986, Schraeder & Lathers 1989, Frysinger *et al.* 1993, Devinsky *et al.* 1994, Faustmann & Ganz 1994, Vaughn *et al.* 1996, Massetani *et al.* 1997, Messenheimer *et al.* 1997, Tomson *et al.* 1998, Druschky *et al.* 2001, Zijlmans *et al.* 2002). These previous studies have used either cardiovascular reflex tests or traditional analysis of HRV in assessing autonomic function in patients with epilepsy. However, it is known that cardiovascular reflex tests provide only a limited view of the cardiovascular autonomic control, since the responses are recorded under experimental conditions and for only a short period. Therefore, especially dynamic measures of HRV using ambulatory ECG recordings may reveal new aspects of cardiovascular control mechanisms and the pathophysiology which lead to autonomic dysfunction in various diseases (Mäkikallio *et al.* 1996).

The present study was designed to assess quantitatively the reflectory cardiac control with standard cardiovascular reflex tests, and the tonic autonomic cardiac regulation with HR fluctuation analysis from 24-hour ECG recording in epilepsy patients. Patients with previously untreated epilepsy, partial and idiopathic generalized epilepsies as well as refractory and well controlled TLE and TLE patients with or without hippocampal sclerosis were included in the substudies. The parameters of the cardiovascular reflex test were adjusted to the baseline RR interval, and the effect of age was taken into account in the statistical analysis. For the first time, the analysis of dynamic measures of HRV was used to study autonomic regulation in epilepsy. In addition, there was an attempt to resolve whether the cardiovascular reflex test and analysis of HRV from ambulatory ECG recordings can reveal similar alterations of autonomic function in epilepsy patients.

The effects of epilepsy and AEDs on cardiovascular autonomic regulatory functions are important because of the increased risk of SUDEP that accounts for approximately 10% of the deaths in epileptic population (Devinsky *et al.* 1994, Johnston *et al.* 1997, Ficker *et al.* 1998, Nashef *et al.* 1998, Nilsson *et al.* 1999, Sperling *et al.* 1999). Most likely this usually peri-ictal phenomenon is due to the autonomic regulatory system dysfunction presenting itself either as central apnea or cardiac arrhythmia (Devinsky *et al.* 1994, Johnston *et al.* 1997, Nashef *et al.* 1998, Nilsson *et al.* 1999, Sperling *et al.* 1999). Postmortal examination does not reveal the cause of death, but signs of neurogenic injury of various organs, especially heart and lungs are often present. (Devinsky *et al.* 1994, Johnston *et al.* 1997, Nashef *et al.* 1998, Sperling *et al.* 1999, Thom *et al.* 1999). However, the primary cause of SUDEP and its association with focal anatomic cerebral changes still remain unknown.

MRI is considered as the best modern technique to reveal epilepsy specific anatomic changes of the brain. MRI also makes volumetric measures of the structures of the inner temporal lobe, e.g. the hippocampus and the amygdala, possible. With this delicate method, neuronal loss associated with TLE leading to atrophy of the structures can be measured (Jackson 1994, Cascino 1997). It is not known whether these TLE specific anatomic changes contribute to the alterations of autonomic function in patients with TLE, and the subject has not been previously studied.

6.2 Clinical findings

Although ictal changes of autonomic function are frequently encountered in epilepsy, interictal changes may be more difficult to recognize. In this study, possible symptoms of autonomic dysfunction were screened with a questionnaire, and clinical examination with particular attention to signs of ANS dysfunction was performed on each patient. However, no clinical signs or symptoms of ANS dysfunction were detected.

6.3 Cardiovascular regulation

6.3.1 Untreated patients

In the present study, the values of cardiovascular reflex tests did not differ in patients with untreated recently diagnosed epilepsy from those of the control subjects. These patients had experienced at least two recent partial or generalized epileptic seizures and were otherwise healthy. However, in two patients, two measurements of cardiovascular reflex tests were outside the reference range, although they did not complain any symptoms of ANS dysfunction. This observation gives further evidence to the hypotheses that epilepsy related autonomic cardioregulatory dysfunction is associated with the

chronic nature of epilepsy, with the possible modifying effect of long-lasting antiepileptic medication on the ANS function (Quint *et al.* 1990).

6.3.2 Patients with idiopathic generalized epilepsies

In the present study, patients with idiopathic generalized epilepsies had diminished values of SD of RR intervals, whereas patients with partial epilepsy showed decreased BP responses in isometric tests in cardiovascular reflex tests compared to the control subjects. Patients with idiopathic generalized epilepsies were mainly using VPA as an AED, whereas the majority of the patients with partial epilepsy had CBZ as their AED. Based on these results, it can be concluded that patients with idiopathic generalized epilepsies seem to have mild alterations of autonomic cardiovascular regulation, but these changes may be more subtle than in patients with partial epilepsies. This apparent yet conclusive difference between idiopathic generalized and partial epilepsies may be due to the different nature of the two epilepsy types but may also relate to differences in AED therapy (Quint *et al.* 1990, Devinsky *et al.* 1994, Tomson *et al.* 1998).

Cardiovascular dysfunction has previously been demonstrated in a small group of patients with progressive myoclonus epilepsy (Kälviäinen *et al.* 1990). The majority of these young progressive myoclonus epilepsy patients complained symptoms of ANS dysfunction and had diminished values of the max-min ratio of the cardiovascular reflex tests compared to their controls. However, progressive myoclonus epilepsy is a degenerative disease of the CNS different from any other epilepsy type, which makes the comparison of the results difficult. Autonomic dysfunction has been demonstrated in patients with JME using traditional analysis of HRV from 24-hour ECG-registration (Tomson *et al.* 1998). In the same study, patients with TLE were also investigated, and altered autonomic control of the heart was more evident in TLE patients. Patients with JME were mainly on VPA therapy and patients with TLE were mainly on CBZ therapy. Patients with JME differed only little from the controls, showing reduced HF/LF ratio, suggesting decreased sympathetic, or alternatively an increased vagal tone, since LF oscillations are associated with negative feedback from the baroreflex arc mediated both by sympathetic and parasympathetic activity and HF power reflects respiratory sinus arrhythmia and is mainly related to parasympathetic activity (Tomson *et al.* 1998).

6.3.3 Patients with partial epilepsies

The major finding of the present study was that both cardiovascular reflexes and tonic autonomic cardiovascular regulation are altered in patients with partial epilepsy. There are few previous studies focusing on interictal ANS dysfunction in patients with partial epilepsy (Frysinger *et al.* 1993, Devinsky *et al.* 1994, Faustmann & Ganz 1994, Massetani *et al.* 1997, Tomson *et al.* 1998, Druschky *et al.* 2001). The methods and parameters used, as well as study designs, are different in these studies, and, therefore,

the results are difficult to compare. To our knowledge, this is the first study to evaluate the association between altered HRV and the severity of TLE. Moreover, dynamic measures that are able to describe long term tonic oscillations of HRV have not been previously used to evaluate autonomic dysfunction in TLE. The present study agrees with the previous findings of abnormal HR regulation in patients with partial epilepsy and suggests that the degree of abnormality may not be related solely to the severity of TLE. Based on these results, it also seems that in addition to the conventional measures of HRV, new dynamic measures not related to means and variance are useful in detecting altered HR behavior in patients with TLE.

In cardiovascular reflex tests, the patients with partial epilepsy had diminished BP responses to isometric work, whereas patients with well controlled TLE had decreased values of the 30:15 ratio compared to the control subjects. Refractory TLE, however, was associated with decreased values of SD of RR intervals and the 30:15 ratio compared to the control subjects. Although statistical significance was not reached when these different subgroups of patients were compared to each other, a uniform trend towards lower values of all parameters of cardiovascular reflex tests were detected in patients with refractory TLE, compared to the patients with well controlled TLE. However, the most significant finding was that both refractory and well controlled TLE seem to be associated with altered cardiovascular reflexes.

It is also noteworthy that clinically significant changes in cardiovascular reflexes were detected in two patients with well controlled and three patients with refractory TLE. Interestingly, four of these five patients were male. This raises the question whether epilepsy per se may be associated with altered function of the ANS, and whether male gender may predispose to the observed changes.

In the analysis of HRV, all parameters of the traditional and frequency domain measures were lower in patients with TLE compared to the control subjects. In addition, the slope of the power law and the values of dynamic measurements were decreased in TLE patients compared to the control subjects. Patients with refractory TLE had a lower value of ApEn from the dynamic measures compared to the patients with well controlled TLE, whereas the long term correlation value α_2 of the fractal correlation properties was decreased in patients with well controlled TLE compared to that of refractory TLE patients. These broad changes of nearly all parameters of HRV together with the above mentioned altered values of cardiovascular reflex test suggest multidimensional affection of the ANS for TLE in particular.

The prognostic value of the changes in autonomic cardiovascular regulation in TLE is unknown. Cardiovascular reflex tests and traditional spectral measurements of the analysis of HRV have proved useful in determining autonomic regulatory dysfunction in various clinical conditions (Huikuri 1995c). Similar to our findings in TLE patients, altered autonomic cardiovascular function using cardiovascular reflex test and analysis of HRV has also been described in various cardiac diseases. Several studies have shown that reduced HRV is an independent risk factor for arrhythmic sudden death post myocardial infarction (Oppenheimer 1993, Bigger *et al.* 1996, Huikuri *et al.* 1996, Mäkikallio *et al.* 1997). A study on a large number of elderly people showed that the slope of the power-law relationship of HRV most strongly predicts cardiovascular mortality in a general population of elderly subjects (Huikuri *et al.* 1997). The slope of the power law is also especially deep in patients with denervated transplanted heart, suggesting abnormal

postganglionic adrenergic innervation of the heart (Bigger *et al.* 1996). Therefore, it is possible that changes in these parameters may also predict the cardiovascular risk in patients with TLE. Furthermore, the steep power law relation slopes refers to the pathology of the sympathetic cardiac innervation.

The physiological and clinical applicability of fractal and complexity measures of HR dynamics are not yet completely understood, but they are suggested to reveal abnormal patterns of RR interval behavior that are not easily detected by commonly used moment statistics of HRV (Mäkikallio *et al.* 1996). Reduced ApEn indicates larger predictability in HR behavior and it has previously been described to correlate with various pathological conditions, e.g. risk of the sudden infant death syndrome (Pincus 1991, Pincus & Viscarello 1992, Fleisher *et al.* 1993, Pincus & Goldberger 1994, Mäkikallio *et al.* 1996, Rosenstock *et al.* 1999). It is possible, therefore, that cardiovascular autonomic dysfunction, in the form of decreased HR responses to certain stimuli and tonic oscillations of HRV, could be a prognostically unfavorable phenomenon in TLE as well. Reduced ApEn has also been found to be associated with the onset of paroxysmal atrial fibrillation in subjects without any structural heart disease (Vikman *et al.* 1999) and infusion of norepinephrine (Tulppo *et al.* 1999) possibly reflecting concomitant, accentuated sympathetic and vagal outflow to the sinus node. The mean values of ApEn and the slope of the power law relationship of HRV, did not correlate with the traditional spectral measures of HRV, showing that these new indices may be more sensitive than conventional methods in detecting altered cardiovascular regulation in patients with TLE. Reduced ApEn in patients with refractory TLE compared to the patients with well controlled TLE and the control subjects may reflect the sympathetic imbalance due to repetitive seizures in these patients and could be prognostically unfavorable phenomenon.

The pathophysiological basis of the cardiovascular autonomic dysfunction in TLE is not completely understood. The insular cortex is considered the most important cortical area controlling cardiovascular regulation, and it has extensive connections with other cardiovascular control centers (Cechetti 1990, Oppenheimer 1993, Cechetti 2000). In TLE, the epileptic focus close to these frontal and temporal regulatory areas may interfere with their function. Oppenheimer *et al.* have demonstrated in humans that stimulation of the left insular cortex produces bradycardia, and stimulation of the right insular cortex produces tachycardia (Oppenheimer *et al.* 1992). Moreover, potentially life threatening vagotonic cardiovascular dysfunction can be associated with unilateral mesiotemporal epileptogenic discharges (Schraeder & Lathers 1989). Recently, Druschky *et al.* showed an impaired post-ganglionic cardiac sympathetic innervation and autonomic imbalance towards increased parasympathetic activity in cardiovascular reflex test in patients with TLE (Druschky *et al.* 2001).

Interestingly, in the present study, changes in cardiovascular regulation were seen both in refractory and in well controlled partial epilepsy, especially TLE, although the changes seem to be more evident in patients with refractory epilepsy. However, as the duration of epilepsy was longer in patients with refractory epilepsy, it can not be excluded that the duration of epilepsy may affect these result as well. Moreover, the slope of the power law was steeper in patients with TLE compared to the control subjects, thus reflecting impaired postganglionic sympathetic innervation of the heart in this study as well.

Therefore, according to the present results, TLE itself may be implicated, but long-lasting antiepileptic medication may also modify the ANS function.

6.3.4 The effects of different AEDs

It is difficult to distinguish the effects of AEDs on the ANS function from the effects of epilepsy itself. In the present study abnormal cardiovascular reflexes appeared to be associated with CBZ medication, but statistical significance was reached only when compared to the control subjects. However, on the contrary to some earlier studies (Quint *et al.* 1990, Devinsky *et al.* 1994, Tomson *et al.* 1998), an analysis of HRV did not show alteration in relation to any specific drug regimen. This does not exclude the possibility that AEDs could have effects on cardiovascular regulatory function. Many AEDs taken by the patients in the present study act by blocking sodium channels like many antiarrhythmic agents, e.g. flecainide, that are associated with increased arrhythmogenic mortality (The Cardiac Arrhythmias Suppression Trial 1989, The Cardiac Arrhythmias Suppression Trial II Investigators 1992). Therefore, AEDs may have effects on cardiac conduction system as well as on centrally mediated cardiovascular control system function and contribute to the observed changes. Moreover, CBZ is mainly used in the treatment of patients with TLE. Both CBZ medication and TLE may contribute to the observed abnormal cardiovascular reflexes.

However, the effects of AEDs on cardiovascular regulation are still poorly outlined and further studies are needed to establish the effects of CBZ and other AEDs on the ANS function. The present study was not designed to assess the effects of the AEDs on the function of the ANS and the results can not give unambiguous data to support the view that CBZ has a more potent effect on the cardiac regulatory system than the other commonly used AEDs.

6.4 Cardiovascular reflexes and heart rate variation

The results of the standard cardiovascular reflex tests agree well with the traditional measures of the ambulatory ECG recordings, both demonstrating diminished values of various parameters in different subgroup of epilepsy patients compared to those of the control subjects. The dynamic measures of HRV did not correlate with the findings of the standard cardiovascular reflex tests. Dynamic measures and fractal analysis of HRV have been developed to quantify complex HR dynamics and they are suggested to show abnormal patterns of RR interval not easily detected by commonly used statistics of HRV (Mäkikallio *et al.* 1996). Whereas the conventional methods typically detect quantitative properties, the dynamic measures if HRV detect rather qualitative properties of the HR series (Myllylä *et al.* 2002)

HRV can easily be analyzed from 24-hour ECG-recordings. There are numerous indexes to describe RR interval fluctuation during a 24-hour period (Myllylä *et al.* 2002). The advantages of this method are good reproducibility and the information concerning the LF bands of the spectral HRV gathered over longer time periods than the standard cardiovascular reflex tests can be provided (Kleiger *et al.* 1987, Huikuri *et al.* 1990, Öri *et al.* 1992, Myllylä *et al.* 2002). However, because of the great inter-individual variation in the measures of HRV used in this study, these parameters can only be used to assess autonomic dysfunction at a group level, as is often the case with the standard cardiovascular reflex tests as well (Bannister & Mathias 1999).

In the present study, autonomic dysfunction was detected using both cardiovascular reflex tests and analysis of HRV. These two methods have not been previously used in the assessment of autonomic cardiovascular regulation in the same patients with TLE. Although cardiovascular reflex tests are methodologically standardized and feasible, they may not be as sensitive as an analysis of HRV in detecting autonomic disturbances in patients with TLE. In addition, with dynamic measures, tonic, long-term oscillations of HRV can be revealed. In various other conditions, especially, the dynamic measures of HRV has been associated with an increased risk of sudden cardiac fatalities (Bigger *et al.* 1996, Huikuri *et al.* 1996, Mäkikallio *et al.* 1996, Mäkikallio *et al.* 1997). The problems concerning the method of the analysis of HRV are great intra- and interindividual variation of the measured values and its susceptibility to artifacts (Myllylä *et al.* 2002).

Despite the statistical data suggesting the predictive power of the various HRV indices especially in heart diseases, none are widely used in clinical practice to guide preventive therapy for individual patients because no trial has adequately linked the reliability of any of these variables of clinical outcome with intervention (Myllylä *et al.* 2002).

6.5 Hippocampal sclerosis and cardiovascular regulation

In the present study, diminished HRV was observed both in patients with or without hippocampal sclerosis. The measures of HRV tended to be smaller in patients with than without hippocampal sclerosis. Overall, the number of patients with hippocampal sclerosis was small. However, the present data suggests that there is no clinically significant difference in the presence of cardioregulatory autonomic dysfunction between TLE patients with or without hippocampal sclerosis. Therefore, epilepsy related functional rather than structural changes may be important in relation to alterations in cardioregulatory functions.

Focal brain lesions are frequently associated with disturbances of the cardioregulatory system (Appenzeller & Goss 1971, Senaratne *et al.* 1984, Ørskov *et al.* 1987, Pentland & Ewing 1987, Turkka *et al.* 1987, Oppenheimer *et al.* 1990, Korpelainen *et al.* 1994, Freitas *et al.* 1996, Korpelainen *et al.* 1996a, Korpelainen *et al.* 1996b). The cardioregulatory system can be described as a continuously functioning network widely distributed in the temporal lobes with various ascending and descending connections to other parts of the brain (Cechetti 1990, Oppenheimer 1993, Cechetti 2000). The clinical

and experimental data indicate the crucial role of the insula and limbic structures such as amygdala in cerebrogenic cardiovascular disturbances and sudden death (Cheung *et al.* 2000). For example, electrical stimulation of the insula and amygdala with its adjacent areas produces changes in HR, BP, respiration and increased norepinephrine secretion in various mammals including humans (Oppenheimer *et al.* 1990). In fact, various changes of HR and cardiovascular regulation has been demonstrated in patients with TLE (Schraeder & Lathers 1989, Oppenheimer *et al.* 1992, Druscky *et al.* 2001), as also shown in the present study.

Therefore, it is possible that functional imbalance of the ANS in the form of changing biochemical neuromodulation may contribute to cardioregulatory dysfunction in patients with TLE. The presents results agree with this hypothesis, suggesting that dysfunction of the cardioregulatory system is rather associated with functional than structural changes of the inner temporal lobe in patients with TLE.

6.6 Magnetic resonance imaging

In the present study hippocampal sclerosis was found in eight patients. The volumes of the hippocampus and the amygdala were smaller in patients with hippocampal sclerosis compared to the patients without hippocampal sclerosis, but the difference did not reach statistical significance. Slightly decreased hippocampal and amygdaloid volumes were detected with a long duration of TLE.

Based on the results of this study, the volumes of the hippocampi and amygdalas may decrease with the duration of epilepsy. The etiology and pathogenesis of structural damage in the medial temporal lobe of patients with epilepsy has been a matter of controversy for years. It is known that structural damage in the hippocampus precedes the appearance of TLE in many patients but not all cases with hippocampal sclerosis have a history of initial insult. On the other hand, whereas some studies have suggested an association between atrophy of the mesial temporal structures and duration of epilepsy, the others have failed to show this association. (Mathern *et al.* 2002, Kälviäinen & Salmenperä 2002)

Today it has been concluded that hippocampal sclerosis is probably both the cause and the effect of seizures (Mathern *et al.* 2002, Kälviäinen & Salmenperä 2002).

7 Conclusions

1. Epilepsy is associated with alterations in cardiovascular autonomic regulation. The patients did not have any clinical symptoms related to ANS dysfunction, but in cardiovascular reflex tests, cardiovascular dysregulation was detected. Patients with partial as well as idiopathic generalized epilepsies had changes in cardiovascular reflexes. At the group level, the cardiovascular reflexes of patients with untreated, newly diagnosed epilepsy were unaltered. The role of CBZ in contributing to these changes remains controversial.
2. TLE is associated with cardiovascular dysregulation. Patients with TLE did not complain of any symptoms of dysfunction of the ANS but altered cardiovascular regulation was detected with cardiovascular reflex tests and analysis of HRV. The dynamic measures of HRV were studied for the first time in patients with TLE. Spectral as well as dynamic measures of HRV showed altered pattern of oscillation of HRV in TLE patients. Clinically significant changes in cardiovascular reflex tests were detected in two patients with well controlled TLE and in three patients with refractory TLE, one of whom had hippocampal sclerosis as well.
3. Altered HRV is present both in patients with refractory and in patients with well controlled TLE. Although the results suggested that these changes are more prominent with severe form of TLE, it seems that TLE itself rather than its severity is important with regard to the observed changes in cardiovascular regulation in patients with TLE. Therefore, both patients with well controlled as well as with refractory TLE can be at risk for sudden cardiac fatalities. Whether the high number of different risk factors in an individual patient with TLE may additionally predispose to fatal dysfunction of the ANS remains unsolved.
4. The results of the present study did not support an association of structural changes in temporal lobes with particularly altered pattern of HRV. Diminished values of HRV were detected both in patients with and without hippocampal sclerosis. However, the number of patients with hippocampal sclerosis was small, and further studies in larger patient populations are needed to explore the hypothesis that functional imbalance of the ANS in the form of changing biochemical

neuromodulation may contribute to cardioregulatory dysfunction in patients with TLE.

5. Both the cardiovascular reflex tests and analysis of HRV from ambulatory ECG appear to be useful in the assessment of ANS function in patients with TLE. However, their predictive value with regard to increasing the risk of sudden cardiac fatalities in patients with epilepsy remains to be established.

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