Heart-type fatty acid-binding protein as a predictor of cardiac ischemia in intractable seizures in children

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Abstract

Background:

Children with intractable epilepsy have chronic dysfunction of the autonomic nervous system causing myocardial ischemia. Heart-type fatty acid-binding protein (H-FABP) is a sensitive biomarker for myocardial ischemia.

Aims:

We aimed to evaluate serum levels of H-FABP during seizures compared to their interictal levels and healthy controls and changes in heart rate (HR) and HR variability (HRV) in epileptic children with intractable seizures.

Materials and Methods:

We included 30 epileptic seizures in 25 children with intractable epilepsy and 30 matched controls. They were subjected to video-electroencephalography monitoring simultaneously with Holter electrocardiogram and measurement of H-FABP.

Results:

Mean serum levels of H-FABP were increased significantly in patients either in the ictal or interictal periods compared to that in the controls ($P < 0.001$ and $P < 0.01$, respectively). There is no significant difference in serum levels of the H-FABP in the ictal and interictal periods. The basal time domain measures of HRV were significantly lower in the patient group compared to the control group.

Conclusion:
H-FABP might suggest a degree of myocardial ischemia in intractable epilepsy. HRV is impaired in patients with refractory seizures.

**Key words:** Heart-type fatty acid-binding protein, myocardial ischemia, refractory seizures

**Introduction**

Heart-type fatty acid-binding protein (H-FABP) is a small cytoplasmic protein (15 kDa) released from cardiac myocytes following an ischemic episode. H-FABP is a sensitive and an early biomarker for myocardial infarction. H-FABP is twenty times more specific to the cardiac muscle than myoglobin. The pharmacokinetic properties of H-FABP have led to an interest in its use as an early diagnostic tool for myocardial infarction. It has been shown that epilepsy and seizures can have a profound effect on cardiac functions. The phenomenon of sudden unexpected death in epilepsy is closely linked to the ictal cardiac changes. Tachycardia and development of tachyarrhythmia during seizures are one of the possible causes of sudden unexpected death in epilepsy. During electroencephalography (EEG) recording in seizures notably intractable ones, the synchronous electrocardiogram (ECG) monitoring, and other autonomic parameters help in the evolution of a potentially fatal condition, which is sudden unexpected death in epilepsy. The aim of this study was to evaluate the serum levels of H-FABP as a marker of cardiac ischemia during seizures compared to their interictal serum levels and healthy controls and to evaluate changes in heart rate (HR) and HR variability (HRV) in epileptic children with intractable seizures.

**Materials and Methods**

The study was conducted on 25 children with intractable epilepsy enrolled from pediatric neurology outpatient clinic, Al Hada and Taif Military Hospitals, Saudi Arabia. There were 16 males and 9 females. Their ages ranged from 3 to 14 years with a mean of 7.3 ± 3.6 years. Patients with intractable epilepsy who had one or more seizure episodes per week were selected to augment the chance of capturing an ictal episode. The study was conducted in the period from February 2014 to July 2015 after informed consent from the participants. The study protocol was reviewed and approved by an independent research board before the study was conducted.

The study protocol conforms to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments.

**Exclusion criteria**

Exclusion criteria include

- Known cardiac lesion
- Any systemic disease affecting cardiovascular system or autonomic vascular system
- Any regular medication apart from antiepileptic drugs
- Recent acute illness.

Thirty seizure attacks in 25 patients were included. (Two attacks of seizures were recorded in five patients.) Thirty apparently healthy children of matched age and sex served as a control group. They were 18 males and 12 females. Their ages ranged from 4 to 15 years with a mean of 6.8 ± 3.7 years.

**Complete history taking and thorough clinical examination**

For all patients and controls with special emphasis on history or clinical evidence of cardiac disease, chronic illness or history of chronic medications.

**Detailed neurological sheet**

For all patients with stress on age, age of onset of disease, duration of illness, type and frequency of seizure, type of antiepileptic drugs and seizure severity according to Chalfont seizure severity scale.[10]

**Video-electroencephalography monitoring and Holter electrocardiogram**

All patients and controls were hospitalized and admitted in the epilepsy monitoring unit for 48 h video-EEG recording. All patients developed seizures within 1–2 days without the need for withdrawal of antiepileptic medications. Each patient was subjected to video-EEG recording to capture an ictal episode synchronously with Holter ECG for 6 h. Video-EEG and Holter ECG monitoring were continued later for a complete 24 h. All controls showed no seizure activity and were subjected to 24 h Holter ECG monitoring without synchronization.

Seizure semiology as well as onset and termination of the epileptic seizure depends on clinical observation and simultaneously with video-EEG records. The video-EEG set (Galileo, Nizar 40 multichannel EBN-Uro, Italy) was placed in a special room confined for EEG monitoring. The Holter ECG set, (cardio light FMC, A. Med set, Medizintechnik, Hamburg, Germany) was a portable six leads three channels ECG that was connected to the patient at the same time of EEG set. Recordings were synchronized at the onset.[11]

**Measurement of heart-type fatty acid-binding protein**

One venous blood sample was taken from each control subject, and two venous blood samples were taken from each patient enrolled in the study under aseptic technique.

The first blood sample was taken within half an hour of an epileptic fit (ictal). The second blood sample was taken when patients are free of fits for at least 12–24 h (interictal). Each sample filled about 3 ml plain tube. The first sample was ictal, taken within half an hour of a seizure episode. The second sample was interictal, taken when a patient has seizure free period for at least 24 h. Enzyme-linked immunosorbent assay is used to measure H-FABP by.[12]
The Holter ECG was retrospectively analyzed as follows: The mean values of HR were analyzed in the following periods: Basal, preictal hour, in the ictal period, as well as in the first and second postictal hour. Further analysis included the mean values of the first and second 5 min periictally. Basal values of HR were evaluated during recording after elimination of the ictal period, preictal hour, and two postictal hours. When there is at least a 10% increase over the basal HR, ictal tachycardia was recorded. When there is at least a 10% decrease over the basal HR, ictal bradycardia was recorded.[11] Other variables that can be retrieved from ECG analysis included periictal arrhythmias: Premature atrial contraction, premature ventricular contraction, and ST segment changes. We measured corrected (QTc) interval according to the formula: QTc = QT measured/squared root of RR interval. The mean value of the basal QTc was evaluated during recording after elimination of the ictal period, preictal hour, and two postictal hours. HRV, time domain measures were analyzed as basal levels in the preictal hour, first and second postictal hours.[13] HRV measures included standard deviation of all normal RR intervals in the entire 24 h ECG recording (SDNN) (ms), standard deviation of the averaged normal sinus RR intervals for all 5 min segments of the entire recording (SDNNI) (ms), root mean square of successive RR intervals difference (the square root of the mean of the sum of the squares of difference between adjacent normal RR intervals over the entire recording) (rMSSD) and percentage of difference between adjacent normal RR intervals that are >50 ms computed over the entire 24 h recording (PNN50) (%).[14]

**Statistical analysis**

Qualitative data are presented as numbers and percentages whereas quantitative data are presented as means ± standard deviation with ranges. Student's t-test was used to test differences in means while Mann–Whitney U-test was used for nonparametric statistics. Pearson's correlation coefficient was used to test the correlation of various variables within the case group. The significance level was set at $P < 0.05$.

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**Results**

This study was conducted on 25 epileptic patients with intractable seizures. Thirty epileptic seizures were included in the study. Epileptic seizures were focal in 6 patients (20%), generalized in 12 patients (40%) and focal with secondary generalization in 12 patients (40%). Fifteen patients (83.3%) were complex partial seizures. EEG analysis in focal seizures showed temporal epileptogenic activity in 5 (27.8%) epileptic seizures while 13 (72.2%) showed extratemporal origin. All patients showed symptomatic etiology in the form of hypoxic ischemic encephalopathy in 14 (60%) patients, postinfectious sequelae in 6 (24%) patients, cerebrovascular accidents in 3 (12%) patients, and neurodegenerative brain disease in 1 (4%) patient. Duration of illness ranged from 2.5 to 11 years with a mean of 6.8 ± 3.2 years. Duration of seizure ranged from 20 to 180 s with a mean of 75 ± 22.4 s. Chalfont seizure severity score ranged from 11 to 55 with a mean of 33.4 ± 12.5. All seizures recorded by video-EEG were the same as described in the history. Different regimens of antiepileptic drugs were used in our patients: 8 (32%) patients were on 2 drugs, 13 (52%) patients were on triple therapy, and 4 (16%) patients were on 4 drugs. Old and
new antiepileptic drugs were used including valproic acid, carbamazepine, clonazepam, phenytoin, phenobarbitone, lamotrigine, topiramate, levetiracetam, and oxcarbazepine [Table 1].

Table 1
Demographic characteristics of studied groups

<table>
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<tr>
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<th>Patients (n=68)</th>
<th>Controls (n=68)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
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<td>6.8±3.7</td>
</tr>
<tr>
<td>Sex (%)</td>
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<td></td>
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<tr>
<td>Male</td>
<td>40 (60)</td>
<td>18</td>
</tr>
<tr>
<td>Female</td>
<td>28 (40)</td>
<td>50</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>9 (50)</td>
<td>12</td>
</tr>
<tr>
<td>Status (%)</td>
<td>6.8±3.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Hypoxic ischemic</td>
<td>5 (60)</td>
<td></td>
</tr>
<tr>
<td>encephalopathy</td>
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</tr>
</tbody>
</table>

Heart-type fatty acid-binding protein findings

Mean serum levels of H-FABP (pg/ml) were increased significantly in the patients' group, even if they are asymptomatic, either in the ictal (1697.2 ± 1311.6) or interictal periods (1127 ± 613.6) compared to their values in the control group (523.4 ± 73.8) (t = 3.7 and 3.5, respectively) (P < 0.01 and P < 0.05, respectively). No significant difference in the serum levels of the H-FABP in the ictal and interictal periods [Figure 1]. We found no significant correlation between the ictal levels of H-FABP and the duration of the illness, duration of seizures, and Chalfont seizure severity score.

Figure 1
Mean serum levels of heart-type fatty acid-binding protein (pg/ml) in patient (ictal - interictal) and control groups

Heart rate and heart rate variability findings

All epileptic seizures showed ictal tachycardia whereas ictal bradycardia was recorded in only one epileptic seizure. We recorded premature atrial contractions in 4 out of 30 (13.3%) and premature ventricular contractions in 10 out of 30 (33.3%) cases of epileptic seizures. Premature atrial contractions and premature ventricular contractions occurred in the first postictal hour. The mean values of the basal HR were significantly lower in the patient group (82.6 ± 10.9) compared to the control group (96.8 ± 10.2) t = 3.9. Among patients, the mean ictal HR was significantly increased compared to the values of the basal and the first preictal hour (Z = 3.8 and 2.3, respectively). In addition, this significant increase was seen in the first preictal 5 min and the second preictal 5 min (Z = 4.6 and 3.3, respectively). In the first postictal hour, as well as in the second postictal hour, the mean HR values showed a significant decrease compared to its ictal values but did not reach the basal values (Z = 2.2 and 3.5, respectively). The ictal HR was significantly higher than the basal level, first preictal 5 min, second preictal 5 min, first preictal hour, first postictal 5 min, second
postictal 5 min, first postictal hour, and the second postictal hour (Z = 3.8, 4.6, 3.3, 2.3, 2, 3.2, 2.2, and 3.5, respectively) [Table 2].

Table 2
Relations of basal, preictal and postictal heart rate in patients and controls

The mean ictal HR showed no significant correlation with the duration of the illness (r = −0.2), the duration of seizures (r = −0.3), and Chalfont seizure severity score (r = −0.3). The mean values of basal QTc showed no significant difference between the patient and control groups (429.3 ± 6.1 and 428.8 ± 3.2 ms, respectively). Of 25 patients, 3 (12%) showed a prolonged QTc interval (≥440 ms). The basal time domain measures of HRV were significantly lower in the patient group when compared to the control group. They included SDNN, SDANN, SDNNI, PNN50, and rMSSD with t-values of 6.2, 5.3, 4.8, 7.8, and 6.1, respectively. In the preictal 1st h, SDNN, SDANN, PNN50, and rMSSD were significantly lower in the patient group when compared to their basal values (t = 4.8, 3.1, 2.1, 7.8, and 5.6, respectively. In the first postictal hour, SDNN, SDANN, SDNNI, and PNN50 were significantly lower in the patient group when compared to their basal values (t = 5.8, 6.2, 5.3, 12.1, and 3.2, respectively) and the preictal values (t = 5.6, 7.9, 4.8, 11.2, and 0.6, respectively). During the second postictal hour, all values of HRV were significantly lower in the patient group when compared to their basal and the preictal 1st h values. Among the patient group, all values of HRV showed no significant difference in the first and second postictal hour [Table 3].

Table 3
Parameters of heart rate variability in studied groups

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Discussion

In patients with intractable epilepsy and multiple seizures, there is an evidence for a chronic dysfunction of the autonomic nervous system causing myocardial ischemia. The periictal changes can lead to short-term alteration of cardiac functions in patients with seizures.[15] Early recognition of short- and long-term cardiac effects will
become useful in predicting seizures and in guiding more individualized management protocols in the future.\cite{16,17} Recently, diminished HRV has been associated with high-risk arrhythmias and sudden unexpected death in epilepsy.\cite{15} Therefore, our study focused on estimation of serum levels of H-FABP and evaluating changes in HR and HRV in children with refractory epilepsy.

**Heart-type fatty acid-binding protein changes**

The diagnosis of myocardial infarction was based upon cardiac troponin measurement and current guidelines recommend measurement 10–12 h after onset of symptoms to allow for the suboptimal early sensitivity of troponin.\cite{18} Patients with uncomplicated seizures do not seem to have the postictal troponin elevation, but signs of ischemia on ECG and elevated cardiac enzymes in epileptic patients suggest secondary cardiac damage.\cite{19,20} Alehan et al. could show the presence of elevated brain-natriuretic peptide and creatine kinase in patients with seizures, the first evidence of subtle cardiac dysfunction in epilepsy patients.\cite{21} However, previous studies failed to show significant increase in the serum levels of cardiac troponin as a marker of myocardial ischemia following seizures.\cite{19,21,22,23} On the other hand, earlier studies using other markers reported a significant increase in brain-natriuretic peptide in the first postictal hour. This was attributed to transient cardiac ischemia. These data support the hypothesis that overt myocardial necrosis does not occur during convulsive seizures. However, seizure-related myocardial ischemia without injury cannot be excluded that might induce fatal arrhythmias. As a result, there has been an interest in developing another early marker of myocardial necrosis.\cite{23,24} Recent studies reported that H-FABP was more sensitive and specific than other cardiac markers in the early diagnosis of the acute coronary syndrome.\cite{25,26} In our patients, H-FABP showed significantly increased levels during seizures and in between seizures when compared to the control group. The ictal serum levels of H-FABP were higher than their interictal levels, but the difference was statistically not significant. This may reflect a degree of cardiac ischemia in our patients. H-FABP in the ictal and interictal periods showed no significant correlation with duration of illness, duration of seizures or Chalfont seizure severity score. Similar findings were reported by other authors.\cite{27}

**Heart rate and heart rate variability changes**

Subtle cardiac rhythm changes in the preictal and ictal periods are potential biomarkers and are used in algorithms to anticipate and detect seizures.\cite{28} Ictal tachycardia was the most prominent event during an epileptic seizure in our patients (100% of seizures). Previous studies reported a similar finding even in adults.\cite{8,29} Tachycardia can precede, coincide, or follow ictal discharges.\cite{8,30} In our study, HR changes preceded electrical discharge and clinical seizure by a few minutes; hence, preictal HR changes can be used to predict seizure occurrence before its clinical presentation. The significant tachycardia compared to basal HR values was persistent for 2 h after seizures. This was in concordance with other studies that evaluated periictal HR changes at variable periods from an ictal event.\cite{31,32} Ictal tachycardia leading to malignant ventricular tachycardia and ventricular fibrillation has been illustrated to be the cause of sudden unexpected death in epilepsy in a patient with temporal lobe epilepsy.\cite{7} Basal HR values were significantly lower in the patient group when compared to their values in the control group. It seems that a sustained...
disturbance of autonomic control of HR is a probable explanation of our results. Our patients showed a lower incidence rate of ictal bradycardia. It was reported in only one epileptic seizure out of 30 (3.3%) cases. Similar findings were recorded by other authors.[8,27,30] Bradycardia and bradyarrhythmia are much less frequent and are seen in seizures of various origins. Factors predisposing patients to ictal bradyarrhythmia remain difficult to define.[8,31] It has been reported in patients with refractory partial seizures and could be a contributing factor in sudden unexpected death in epilepsy.[33] In our study, basal levels of HRV was significantly reduced in cases when compared to the control group. Our findings were supported by the results of the previous studies.[13,27,31] The cardiac effects of epilepsy are widespread and range from subtle changes in HRV to ictal sinus arrest. HRV reflects the beat-to-beat alterations in the HR and is mainly modulated by the parasympathetic and sympathetic activity.[16] HRV can be used as a tool to show information on the functional state of the autonomic nervous system.[34] It was found to be lower with refractory epilepsy, possibly resulting from parasympathetic or vagal reduction. This can make patients more susceptible to tachycardia and fibrillation and possibly sudden unexpected death in epilepsy.[35]

Regarding mean values of basal HRV during seizures in our patients, there was a progressive reduction in all studied parameters of HRV from the preictal to the postictal phase. The reduction in HRV in the pre- and post-ictal phases might contribute to the susceptibility of higher cardiac control centers causing an increase in the excitability of ventricular conduction system leading to cardiac arrhythmia. This may be another contributing factor in sudden unexpected death in epilepsy.[36] It is possible that malignant dysrhythmia was triggered by the prolonged/repeated ictal activity.[37] The abnormalities in QTc in epileptic patients are risk factors for the development of fatal ventricular arrhythmia and sudden cardiac death.[38] Prolonged QT interval leads to early after depolarization that triggers a tachyarrhythmia. Shortening of the QT interval is an indicator of abnormal cardiac repolarization. Malignant tachyarrhythmia is facilitated by abnormal cardiac repolarization. Short QT interval is an established risk factor for supraventricular arrhythmia and sudden cardiac death.[39] In our study, we found prolonged QT interval in only 12% of our patients. However, the mean values of basal QTc showed no significant difference between the patient and control groups. This was in agreement of Tomoum et al., who reported similar findings.[27] Contradictory results reported that QTc values were increased in epileptic patients compared to that in the control group.[40] Furthermore, other researchers found a statistically significant prolongation of QTc in association with epileptic discharges in EEG.[41] We did not find a specific pattern of ECG changes in our patients. Premature atrial contractions were recorded in four patients and premature ventricular contractions were recorded in ten patients. No other changes were recorded in our patients. Conduction disorders are common during seizures in intractable epilepsy. Nei et al. could demonstrate the presence of arrhythmia or conduction disorders in seizures, particularly if these are prolonged or generalized. They include atrial fibrillation, supraventricular tachycardia, and atrial and ventricular premature depolarization. ECG changes, including T-wave inversion and ST-depression, were more frequent and potentially more dangerous in patients with generalized seizures.[42] Although sudden unexpected death in epilepsy was not reported in our patients, we propose possible underlying cardiac mechanisms. Identification of high-risk patients susceptible for sudden cardiac death due to cardiac ischemia amenable for early intervention is not yet established. The younger the age
of the patient and the more the number of antiepileptic drug used, the higher the risk of sudden unexpected death in epilepsy.[43] We recommend estimation of serum levels of H-FABP in those groups of high-risk patients. There are several limitations; we did not include detailed information regarding certain possible risk factors for sudden unexpected death in epilepsy such as abnormalities in ECG, etiology of seizure and antiepileptic drug doses and serum levels.

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**Conclusion**

Acute changes in cardiac function during seizures include tachycardia, bradycardia, and more subtle conduction disorders. HRV is impaired in patients with long-lasting epilepsy and refractory seizures suggesting a decreased vagal tone, which may be related to the drug therapy or epilepsy as such. Further studies are warranted to explore these changes and their possible relevance for sudden death in epilepsy. H-FABP might suggest a degree of myocardial ischemia in intractable epilepsy.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**Acknowledgments**

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**References**


Table 1

Demographic characteristics of studied groups

<table>
<thead>
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<th>Patients (n=25)</th>
<th>Controls (n=30)</th>
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<tbody>
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<td>6.8±3.7</td>
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<tr>
<td>Sex (%)</td>
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<tr>
<td>Male</td>
<td>16 (64)</td>
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<tr>
<td>Duration of illness</td>
<td>6.8±3.2</td>
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<td>Etiology (%)</td>
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<tr>
<td>Postinfectious sequale</td>
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<td>Neurodegenerative brain</td>
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<tr>
<td>disease</td>
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<tr>
<td>Type of seizure (%)</td>
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<tr>
<td>Focal</td>
<td>6 (20)</td>
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<tr>
<td>Generalized</td>
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<tr>
<td>Focal with secondary</td>
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<td>generalization</td>
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<td>Chalfont seizure severity score</td>
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<td>Duration of seizure (s)</td>
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<td>Antiepileptic drugs (%)</td>
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<td>Three drugs</td>
<td>13 (52)</td>
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<td>Four drugs</td>
<td>4 (16)</td>
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</table>

Data are expressed as n (%), range with (mean±SD). SD: Standard deviation
Figure 1

Mean serum levels of heart-type fatty acid-binding protein (pg/ml) in patient (ictal - interictal) and control groups
Table 2

Relations of basal, preictal and postictal heart rate in patients and controls

<table>
<thead>
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<th>HR (bpm)</th>
<th>Mean±SD</th>
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<th>Control</th>
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<tr>
<td>Basal</td>
<td>82.6±10.9***</td>
<td>96.8±10.2</td>
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<tr>
<td>First preictal 5 min</td>
<td>112.2±18.1*,**</td>
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<td></td>
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<tr>
<td>Second preictal 5 min</td>
<td>96.2±12.8**</td>
<td></td>
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<tr>
<td>First preictal hour</td>
<td>111.1±18.6****</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ictal</td>
<td>130.2±22.6*,**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First postictal 5 min</td>
<td>118.4±14.8*,**</td>
<td></td>
<td></td>
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<tr>
<td>Second postictal 5 min</td>
<td>100.2±14.6**</td>
<td></td>
<td></td>
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<tr>
<td>First postictal hour</td>
<td>112±12.2*,**</td>
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<tr>
<td>Second postictal hour</td>
<td>99.5±9.2**</td>
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*Significant difference compared to controls, **Significant difference compared to basal value. SD: Standard deviation, HR: Heart rate.
### Table 3

Parameters of heart rate variability in studied groups

<table>
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<th>HRV</th>
<th>Cases</th>
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<td>SDNN (ms)</td>
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<td>85.2±18.3</td>
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<td>SDANN (ms)</td>
<td>70.8±5.2</td>
<td>68.7±5.3</td>
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<td>SDNNI (ms)</td>
<td>44.4±9.1</td>
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<td>PNN50 (%)</td>
<td>12.7±3.5</td>
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<tr>
<td>rMSSD (ms)</td>
<td>32.4±6.4</td>
<td>30±7.1</td>
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</table>

*Significant difference compared to controls, †Significant difference compared to basal value. ‡Significant difference compared to the preictal 1st h. SDNN: Standard deviation of all normal RR intervals in the entire 24 h ECG recording (ms). SDANN: Standard deviation of the averaged normal sinus RR intervals for all 5 min segments of the entire recording (ms). SDNNI: Mean of the standard deviation of the all normal RR intervals for all 5 min segments of the entire recording. PNN50 (%): Percentage of difference between adjacent normal RR intervals that are >50 ms computed over the entire 24 h recording. rMSSD: Root mean square of successive RR intervals difference (the square root of the mean of the sum of the squares of difference between adjacent normal RR intervals over the entire recording). HRV: Heart rate variability, ECG: Electrocardiogram.