

Research Article

Electroencephalography as a Tool for Assessment of Brain Ischemic Alterations after Open Heart Operations

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Cardiac surgery is commonly associated with brain ischemia. Few studies addressed brain electric activity changes after on-pump operations. Eyes closed EEG was performed in 22 patients (mean age: 45.2 ± 11.2) before and two weeks after valve replacement. Spouses of patients were invited to participate as controls. Generalized increase of beta power most prominent in beta-1 band was an unambiguous pathological sign of postoperative cortex dysfunction, probably, manifesting due to gamma-activity slowing (“beta buzz” symptom). Generalized postoperative increase of delta-1 mean frequency along with increase of slow-wave activity in right posterior region may be hypothesized to be a consequence of intraoperative ischemia as well. At the same time, significant changes of alpha activity were observed in both patient and control groups, and, therefore, may be considered as physiological. Unexpectedly, controls showed prominent increase of electric activity in left temporal region whereas patients were deficient in left hemisphere activity in comparison with controls at postoperative followup. Further research is needed in order to determine the true neurological meaning of the EEG findings after on-pump operations.

1. Introduction

Cardiac surgery is commonly associated with perioperative brain ischemia. Neuroimaging studies consistently demonstrated acute brain edema and global decrease of brain metabolism during first three days after on-pump surgery [1–4]. In addition, 20–45% of on-pump patients demonstrated multiple small ischemic lesions postoperatively [4–8]. Only 20% of patients with neuroimaging ischemic lesions showed clinical signs of stroke or acute encephalopathy. Nevertheless, the majority of on-pump patients reported memory decrease several months or even several years after surgery [9, 10]. Neuropsychological studies consistently confirmed mild cognitive decline in the majority of cardiac surgery patients at discharge and in 7–69% of patients at 1–3 months followup after surgery [11]. Hence, mild brain ischemic injury is common after on-pump surgery appearing as postoperative cognitive dysfunction. Overall, total volume of brain ischemic alterations correlated with

clinical symptoms in the majority of neuroimaging studies [7, 8, 12, 13].

Many researchers pointed to the embolic genesis of the postoperative brain infarcts due to characteristic distribution of the latter ones [12, 14]. Significant associations between microembolic load and severity of postoperative brain injury were consistently shown [2, 15, 16]. In our relatively young patient cohort we found the threshold association between microembolic load and postoperative delirium, that is, patients with delirium were characterized by more than 900 microembolic signals during on-pump period [17]. Postoperative cognitive dysfunction was shown to be associated with intraoperative cerebral microembolic load in a range of studies as well [18–20]. Important, Stygall and colleagues [21] determined the association between cognitive decline at 5 years after CABG and the number of intraoperative microemboli in their study. Hence, cerebral microemboli appear to be a primary cause of brain ischemia in the majority of patients undergoing on-pump operations.

Microemboli are observed during on-pump procedures in nearly all patients [20, 22]. The number of microemboli considerably varies in different cases being the largest in open heart operations. In the study of Abu-Omar and colleagues [23], open heart procedures were associated with a 22-fold increase in microemboli in comparison with off-pump group. Several studies showed a 2–5-fold increase in microemboli during open heart operations in comparison with on-pump coronary surgery [20, 23–25]. It is not unexpected that prevalence of acute postoperative encephalopathy and cognitive dysfunction was reported to be higher after valve operations in comparison with coronary surgery [20, 26].

The inventor of electroencephalography (EEG), Hans Berger, hypothesized brain electric oscillations to be directly associated with cognitive activity [27]. However, until computer processing of EEG data became available, this suggestion was rejected by the majority of clinical neurologists and even scientists. Moreover, such striking EEG phenomenon as alpha-rhythm was widely interpreted as a “resting state” activity resulting from inhibitory thalamic effects, and slow-wave oscillations were considered to be an indicator of pathological or somnogenic brain states. Recent computer EEG studies showed that only small proportion of cortical alpha activity related to corticothalamic interactions, and the majority of alpha-band oscillations originated due to functional interconnectivity of cortical regions [28, 29]. The direct associations between slow-wave oscillations and cognitive activity were shown in neurologically healthy individuals as well [28, 30]. At present, it is widely accepted by the psychophysiological community that slow-wave activity, alpha- and high-frequency (beta and gamma) oscillations in healthy awoken subjects are directly involved in cognitive processing [28, 30, 31].

Brain oscillations during “resting” state were consistently shown to highly correlate with intelligence and a range of cognitive functions [31–33]. Clearly, the situation of EEG registration is completely unusual for the majority of patients and healthy subjects, and therefore induces intensive cognitive processing including internal representations and memorizing of a new environment of a neurophysiological lab, imaging of a personal localization, and associations of the present experience and past memories. Magnetic resonance functional neuroimaging demonstrated prominent activation of a range of brain structures (medial prefrontal cortex, posterior cingulate, inferior parietal cortex, precuneus, and medial temporal cortex) during awoken eyes closed state, which was conventionally called “resting” condition [34–36]. Hence, contemporary spectral EEG studies evidence that electric brain oscillations during “resting” state predominantly relate to cortex cognitive processing. Therefore, computer EEG is a perspective tool for assessment of mild postoperative ischemic brain alterations appearing as cognitive dysfunction.

Studies using intraoperative computer EEG monitoring evidence that brain electric activity demonstrates moderate sensitivity (0.55) and high specificity (1.0) in detecting brain ischemic alterations [37]. Decrease in EEG amplitude and/or EEG slowing manifest when mean cerebral blood flow

falls below 22 ml/100 g/min. Initial decrease in fast activities (alpha and beta) is followed by appearance of delta rhythms. A further decrease in perfusion leads to flattening of the EEG activity [37]. Nevertheless, flattening of brain electric activity is typical for brain cooling during bypass and for general anesthetic effects [38]. Although, effects of brain ischemia and general anesthesia on brain electric activity are somewhat similar, intraoperative EEG characteristics appear to be predictive for postoperative cognitive dysfunction. Gugino and colleagues [39] found significant associations between intraoperative characteristics of brain electric activity and postoperative decrement of performance on two or more neuropsychological tests in 2–3 months after on-pump operations.

A handful of studies evaluated brain electric activity in patients after cardiac operations. Evoked auditory cognitive potential (P300) was consistently shown to be deteriorated during first weeks after valve and on-pump coronary operations [40–43]. Importantly, several studies found significant associations between severity of cardiac operations and postoperative impairment of evoked brain electric activity [41–43]. For instance, Grimm and colleagues [43] observed impairment of P300 after mitral valve replacement but not after valve repair. Zimpfer and colleagues [42] found prolongation of P300 in four months after aortic valve replacement but not after CABG. Kilo et al. [41] reported impairment of P300 after on-pump but not after off-pump CABG. The group means differed significantly at followups in all cited studies. Overall, the studies of evoked cognitive potentials showed that the operations with larger embolic load (valve replacement versus valve repair or CABG; on-pump CABG versus off-pump CABG) were associated with greater postoperative impairment of brain electric activity.

Characteristics of spontaneous (resting state) brain electric activity were demonstrated to change after cardiac operations as well [44–47]. Zeitlhofer and colleagues [44] found slight delta-theta relative power increase, alpha decrease and beta increase in 10 days after open heart surgery. In contrast, Hauser et al. [45] reported significant decrease of beta along with alpha-2 power in children after open heart surgery. Vanninen and colleagues [47] found slowing of background activity and increase of relative slow-wave activity at bipolar central and posterior derivations at three months after CABG. EEG slowing did not correlate with the occurrence of new cerebral lesions in the postoperative MRI scans or with deterioration in neuropsychological test performance in that study. Nevertheless, Toner and colleagues [46] reported significant decrease of relative delta and theta power at both 7-day and 2-month followups after CABG. Significant association between postoperative EEG slowing and neuropsychological deficits was found in the latter study. It should be noted that the discrepancies between findings in the cited reports may be partially attributed to the use of relative power parameters, which are less reliable EEG measures in comparison with absolute power [31]. Absence of repeated evaluations of healthy controls is a shortcoming of both studies as well.

Using EEG for repeated evaluations of neurological patients is problematic due to obligatory changes of brain

electric activity at followups in healthy subjects. This electrophysiological phenomenon is widely known for evoked potentials [48, 49] and was less investigated for “resting” brain activity. Corsi-Cabrera and colleagues [50] reported significant increase of theta power and decrease of beta-2 power at eyes closed condition, and decrease of alpha and beta at eyes open condition at 1-month followup in comparison with the first assessment in healthy women. Angelakis et al. [51] showed significant increase of alpha peak frequency at followup in healthy subjects. In our study of healthy subjects [52], presented here as a control group, we observed significant decrease of alpha and theta-2 power along with changes of alpha-1 and alpha-2 mean frequencies in right hemisphere at 2-week followup. In addition, increase of delta-2, theta and beta power was prominent in left temporal region in the majority of subjects. Slowing of delta-1 mean frequency in left hemisphere and slowing of theta-2 frequency in temporal region were also characteristic for followup EEG recordings. Hence, physiological changes of brain electric activity at repeated evaluations are prominent, and this fact should be correctly treated during clinical longitudinal studies using EEG.

The primary aim of the present study was to test the possibility of using the computer EEG as a tool for detecting and evaluating mild neurological alterations in patients after open heart operations. Here we present the data of the repeated EEG assessments of cardiac surgery patients in comparison with healthy controls. In addition, patients were repeatedly evaluated by a battery of neuropsychological tests, and the interrelationships between postoperative brain electric activity and cognitive changes are currently being analyzed and are going to be presented elsewhere. As correlations between brain electric activity and separate cognitive domains are region specific [32, 33], we investigated both global and regional postoperative dynamics of brain electric activity. Post hoc analyses at separate leads were undertaken as well, because this approach consistently showed similar correlations between performance on cognitive tests and brain electrical oscillations [32, 33]. We studied eight frequency bands instead of the usual four ones (delta, theta, alpha, and beta), as the narrow bands demonstrated more reliable neurophysiological correlates in a range of studies [32, 53, 54]. Both eight bands’ power and mean frequency parameters were analysed as mean frequency was consistently shown to be a highly informative measure in investigating cognitive versus EEG associations [32, 33]. In addition, we tested associations between postoperative brain electric activity changes and the presence of risk factors of excessive intraoperative cerebral microembolic load.

2. Materials and Methods

2.1. Subjects. A total of 25 patients were included into the study; however, followup EEG recordings were completed only in 22 subjects. Inclusion criteria were age 16–59 years old and preoperative cardiac ejection fraction >40. Exclusion criteria were emergency and reoperative surgical procedures; previous cerebrovascular accident or other neuropsychiatric disorder; serious concomitant noncardiac disease. Ten

spouses of patients were invited as controls; however, only eight of them returned for a followup. The preoperative and intraoperative characteristics of patients and demographic characteristics of controls are presented in Table 1.

2.2. Study Design. The present study protocols were reviewed and approved by the academic council of Bakulev’s cardiovascular surgery center. The study design was explained to patients, and each patient gave informed consent to participate. Patients underwent clinical, EEG, and neuropsychological evaluation 2-3 days before surgery. Clinical examination included M-mode two-dimensional echocardiography for measuring a left ventricular end systolic dimension (absolute value was not normalized), because an enlarged left ventricular was associated with a high risk of elevated intraoperative cerebral microembolism in our previous study [55]. Mini-Mental State Examination was applied to evaluate overall cognitive status. In addition, subjects performed a set of cognitive tests (the data will be published elsewhere). The postoperative assessment was performed in 10–15 days after surgery. Controls were reevaluated with a 2-week interval as well.

2.3. Anesthesia, CPB, and Surgical Management. The protocols of anesthesia and surgical techniques were standardized. Diazepam and morphine served as premedication. Anesthesia was induced and maintained with propofol, fentanyl, and pancuronium. The perfusion apparatus consisted of the Stöckert S3 roller pump (Germany), DIDECO-703 membrane oxygenator (Italy), and a 40 μm arterial filter. Nonpulsatile pump flow rates were maintained between 2.4 and 2.6 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and mean perfusion pressure at 60 mm Hg. The operations were accomplished during moderate hypothermia (28°C). All patients underwent median sternotomy, the aorta was cross-clamped and the heart was arrested with antegrade cold pharmacological cardioplegia by solution of custodiol. Topical ice saline was used as an adjuvant to myocardial protection. Aortic valve replacement was performed in 9 patients. Mitral valve was replaced in 10 patients. And 3 patients underwent combined valve surgery. Overall, the patients uneventfully underwent operations on aortic and/or mitral valve. Three patients demonstrated transitory mild psychotic symptoms (visual hallucinations and disorientation) during first postoperative day.

2.4. EEG Recordings and Analysis. Eyes closed resting EEG data were collected from the 21 monopolar electrode sites of the international 10/20 system (Fp1/Fp2, F3/F4, C3/C4, P3/P4, O1/O2, F7/F8, T3/T4, T5/T6, Fpz, Fz, Cz, Pz, Oz), referred to linked earlobes. EEG signal was amplified using EEG machine (Neuron-Spectr 4/EP, Neurosoft, Russia) with bandpass filter settings 0.5 and 35 Hz. All signals were digitized online at a sampling rate of 200 Hz. Electrode impedances were below 5 K Ω . Each recording comprised 7–10 min.

The resulting time series were inspected visually for body movements, eye blinks, eye movements, EMG, ECG, rheogram, and loose electrodes artifacts. Intervals identified

TABLE 1: Subject characteristics and operative data.

	Open heart surgery	Controls	<i>P</i>
Number of subjects	22	8	
Male/female sex (<i>n</i>)	11/11	1/7	NS
Age (years)	45.2 ± 11.2	39.4 ± 16.6	NS
Education (years)	14.5 ± 2.8	15.4 ± 3.4	NS
MMSE at first assessment (score)	27.3 ± 2.6	27.6 ± 3.3	NS
MMSE at followup (score)	27.0 ± 3.0	28.1 ± 3.7	NS
History of hypertension (<i>n</i>)	6	0	NS
History of diabetes (<i>n</i>)	1	0	NS
History of atrium fibrillation (<i>n</i>)	7	0	NS
NYHA class III and IV (<i>n</i>)	8	0	0.046
Ejection fraction (%)	62.3 ± 7.0		
End systolic size of left ventricular (mm)	35.6 ± 0.8		
Mitral valve replacement (<i>n</i>)	10		
Aortic valve replacement (<i>n</i>)	9		
Aortic and mitral valve replacement (<i>n</i>)	3		
Cardiopulmonary bypass time (minute)	115.6 ± 49.5		
Aortic cross-clamp time (minute)	73.9 ± 34.5		
Postoperative delirium (<i>n</i>)	3		

Data given as means and SD, unless otherwise indicated.

Abbreviations: *n*: number of patients; NS: not significant; NYHA: New York Heart Association.

as disturbed by artifacts were excluded from the spectral analysis. Finally, 4 sec with 50% overlap epochs were obtained from artifact-free EEG tracings and submitted to a fast Fourier transform. For each of the 21 monopolar derivations, absolute power and mean frequency were computed for the delta1 (1–2 Hz), delta2 (2–4 Hz), theta1 (4–6 Hz), theta2 (6–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz) frequency bands.

2.5. Statistical Analysis. Statistical analysis was performed using SPSS software for windows (SPSS 17.0, Chicago, IL, USA). Repeated-measures analyses of variance (ANOVAs) were used to analyze EEG power and mean frequency data at 12 leads with regions, that is, *laterality* (central (F3/F4, C3/C4, P3/P4), temporal (F7/F8, T3/T4, T5/T6)), *sagittality* (anterior (F3/F4, F7/F8), medial (C3/C4, T3/T4), posterior (P3/P4, T5/T6)), *hemisphere* (left (F3, C3, P3, F7, T3, T5), right (F4, C4, P4, F8, T4, T6)), and time (preoperative versus postoperative) as within-subject factors. First, repeated-measures ANOVAs included only EEG variables of patients, and time effects (global changes) and interaction of time with regions (regional changes) were tested. Second, the same ANOVAs were conducted using the data of patients and controls with a group as a between-subject factor. The time * group and region * time * group interactions were tested. When significant region * time or region * time * group interactions were found, ANOVAs were conducted using only the data of the region of interest. Finally, post-hoc analyses of dynamics of EEG variables at separate leads were conducted to test time * group interaction. As a small proportion of EEG variables tended to be nonparametric, we preferred to apply Wilcoxon test to explore time effects at separate leads in patient group.

In order to test effects of cardiopulmonary bypass duration on postoperative dynamics of brain electric activity, the patient sample was split into two groups according to the median of on-pump time: CPB <100 minutes and CPB >100 minutes. Repeated-measures ANOVAs were also used to analyze differences in dynamics of EEG power and mean frequency in two patient subgroups. The similar approach was used to explore effects of left ventricular end systolic size (LV) on postoperative brain electric activity. The patients were divided into two groups according to the median of LV: LV < 35.5 mm and LV > 35.5 mm. Then repeated-measures ANOVAs were conducted with regions and time as within-subject factor and group according to LV size as a between-subject factor. Post-hoc analyses at separate leads were undertaken as well.

3. Results

3.1. Characteristics of Electrical Brain Activity before Surgery. Preoperatively, patients differed significantly from controls by *lower beta-1 power* in right hemisphere (hemisphere * group interaction: $F = 6.31, P = .018$) with the similar trend for delta-2, theta-2, alpha-1, and alpha2 activity ($F_s > 3.5, P_s < .10$, resp.). Group differences in total alpha-2 and beta-1 mean frequencies reached significance as well ($F_s = 4.40$ and $6.43, P_s = .045$ and $.017$, resp.) with *higher alpha-2* and *lower beta-1 mean frequencies* in the patient group in all brain regions.

3.2. Global Changes of Brain Activity after Open Heart Operations. Global changes of brain electric activity after open heart operations are summarized in Table 2. After surgery

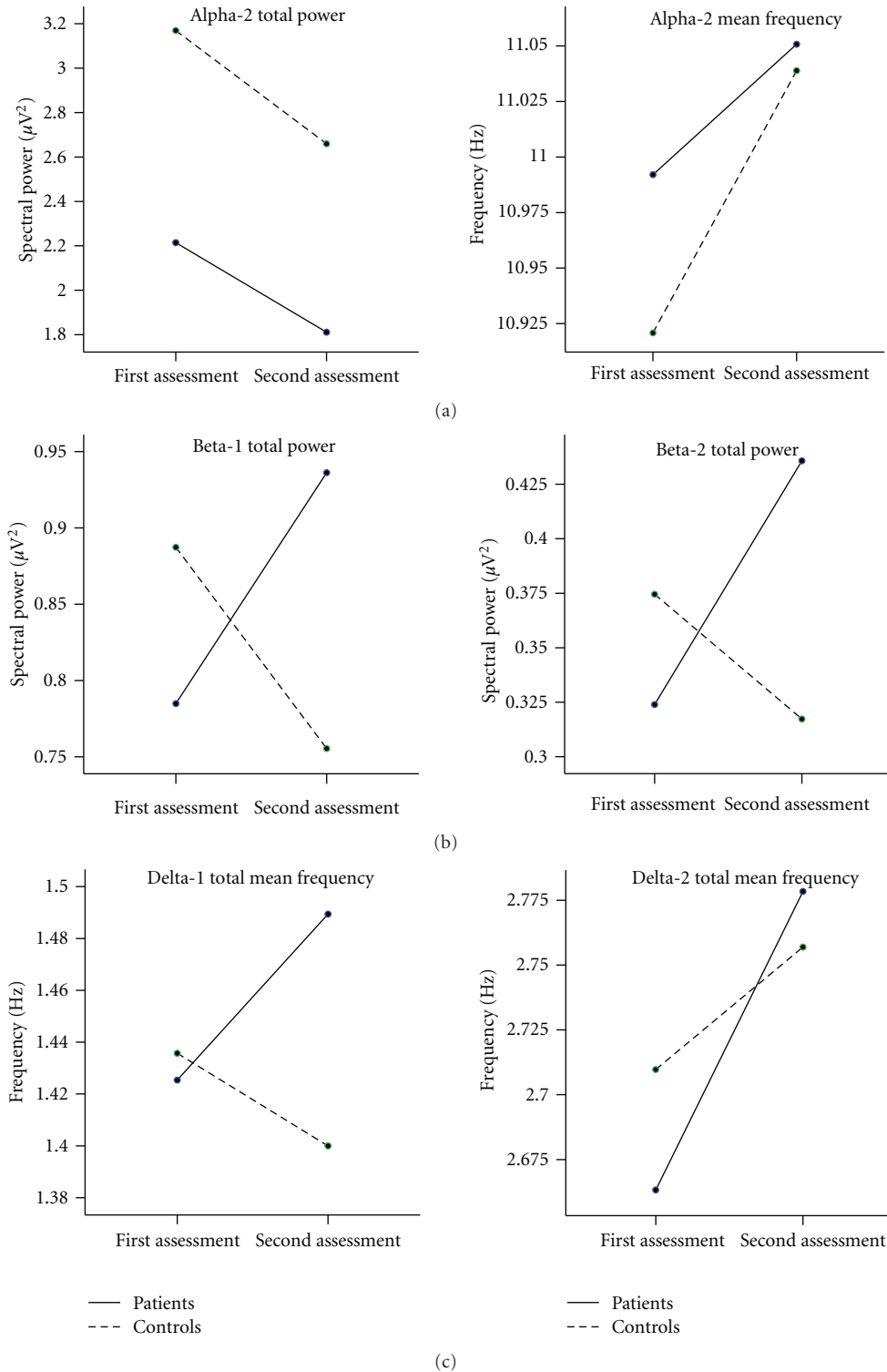


FIGURE 1: Global changes of alpha (a), beta (b), and delta (c) activity in patients after open heart operations and controls.

patients demonstrated significant decrease of alpha-2 power in all brain regions ($F = 5.28, P = .032$). Healthy controls showed significant decrease of alpha-2 power in right hemisphere, and therefore groups did not differ on global dynamics of alpha-2 power ($F = 0.037, P = .85$) (Figure 1(a)).

Nevertheless, groups differed on regional dynamics of alpha-2 power due to somewhat larger decrease of alpha-2 power in right hemisphere in healthy controls and more prominent changes of this EEG variable in left hemisphere in patient group ($F = 6.90, P = .014$). It should be noted, that global

alpha-2 mean frequency increased in both groups at followup ($F = 4.25, P = .049$; Figure 1(a)).

As opposite to controls, patients demonstrated global increase of beta-1 and beta-2 power ($F_s = 7.28$ and $5.42, P_s = .013$ and $.030$). Accordingly, patients differed significantly from controls on dynamics of beta-1 total power ($F = 6.11, P = .020$; Figure 1(b)) with the similar trend for beta-2 total power ($F = 3.41, P = .076$). Group effects were significant at C3, C4, Cz, P3, P4, Pz, O1, O2, F8, T4, and T6 ($F_s > 4.2, P_s < .05$) for changes of beta-1 power, and tended to be significant at Fpz, F3, C3, C4, Cz, P4, O1, T4, and T5 ($F_s > 3.0, P_s < .10$) for beta-2 power. It should be noted that maximal postoperative increase of beta-2 power was found at left posterior temporal and occipital region (leads T5 and O1, $z_s > 2.5, P_s < .01$) along with concomitant increase of beta-2 mean frequency at T5 ($z = 2.05, P = .04$). No significant postoperative changes or group effects on global or regional dynamics of beta-1 or beta-2 mean frequencies were found.

Delta-1 mean frequency showed postoperative increase in all brain regions in open heart patients ($F = 15.8, P = .001$), and, accordingly, patients differed from controls on dynamics of total delta-1 mean frequency ($F = 10.2, P = .004$; Figure 1(c)). Postoperative changes of delta-1 mean frequency at Fp2, C3, C4, P4, Pz, O1, O2, F7, T3, T5, F8, T4, and T6 reached significance ($z_s < -2.00, P_s < .05$). Group effects were significant at C3, C4, P3, Pz, O1, O2, Oz, F7, and T3 ($F_s > 4.3, P_s < .05$). Maximal increase of delta-1 mean frequency was registered in left (T3) and right (F8) temporal derivations ($P_s < .005$).

In addition, patients showed significant increase of delta-2 mean frequency in all brain regions ($F = 16.2, P = .001$). However, no group effects on dynamics of delta-2 mean frequency was found ($F = 1.32, P = .26$) as healthy controls demonstrated the similar global increase of this EEG parameter (Figure 1(c)).

3.3. Right Hemisphere Electrical Activity after Open Heart Surgery. As opposite to healthy controls, patients showed no regional changes of delta-1, delta-2, theta-1, theta-2, or alpha-1 power. Nevertheless, patients significantly differed from controls on dynamics of delta-1, delta-2, theta-2, and alpha-1 power in right hemisphere ($F_s > 5.4, P_s < .03$) due to significant decrease of brain activity power in right hemisphere in healthy subjects (Figure 2(a)). Analyses at separate leads showed group effects at T6 for delta-1; at C4, F8 and T6 for delta-2; at P4 and T6 for theta-2; at T4 for alpha-1 and alpha-2 ($F_s > 4.5, P_s < 0.05$).

Dynamics of theta-1 power was similar in left and right hemispheres in both groups ($F = 0.51, P = .48$). Nevertheless, groups differed on changes of theta-1 power in central region of right hemisphere ($F = 5.11, P = .032$; Figure 2(b)) due to postoperative increase of theta-1 power in the patient group. At the same time, patients and controls demonstrated similar increase of theta-1 power at right temporal derivations. Increase of theta-1 power at T4 and T6 was significant at postoperative followup in the patient group ($z_s = -2.90$ and $-2.71, P_s = .004$ and $.007, \text{ resp.}$). It should be noted,

that delta-2 and theta-2 power increased at P4, T4, and T6 leads ($z_s < -1.7, P_s < .08$) in patients but not in controls at followup. No concomitant regional changes or group effects on theta-1 and theta-2 mean frequencies were found. Nevertheless, analyses at separate leads showed significant slowing of theta-2 mean frequency at C4 and T6 in the patient group ($z_s < -2.00, P_s < .05$) after surgery.

In addition, patients showed significant slowing of alpha-1 mean frequency at O2 ($z = -2.89, P = .004$). However, this phenomenon was registered in healthy subjects as well, and analyses including both groups showed significant slowing of alpha-1 activity at O1, O2, and Oz at followup ($F_s > 7.0, P_s \leq .01$).

3.4. Left Hemisphere Electrical Activity after Open Heart Surgery. After surgery, patients differed from controls on dynamics of delta-2, theta-1, and theta-2 power in central and temporal regions of left hemisphere ($F_s > 4.3, P_s < .05$) (Figure 3(a)). In central region power of slow-wave activity decreased in healthy controls and did not change in patients at followup. In temporal region, controls demonstrated increase of slow-wave activity power whereas patients did not show any changes. Analyses at separate leads showed group differences on dynamics of delta-1 ($F = 4.07, P = .05$) and delta-2 ($F = 4.31, P = .048$) power at left temporal derivation (T3). In addition, groups differed on dynamics of theta-2 mean frequency in central and temporal region of left hemisphere ($F = 5.30, P = .030$). No group effects at separate leads analyses were found.

3.5. Cardiopulmonary Bypass Length and Left Ventricular Size Effects on Brain Activity. Patients with prolonged CPB were characterized by increase of alpha-1 power in central region whereas patients with shorter CPB length showed decrease of alpha-1 activity in central derivations ($F = 8.94, P = .007$) (Figure 4(a)). Group differences reached significance only at P3 ($F = 5.73, P = .027$) with the similar trend for P4 and Pz ($F_s = 3.63$ and $3.92, P_s = .071$ and $.062, \text{ resp.}$).

Patients with enlarged left ventricular size showed increase of beta-1 mean frequency in right hemisphere whereas patients with smaller left ventricular were characterized by decrease of this EEG parameter ($F = 4.43, P = .048$) (Figure 4(b)). Group differences in dynamics of beta-1 mean frequency at C4 and P4 showed a trend to be significant ($F = 3.28$ and $3.21, P_s = .085$ and $.088, \text{ resp.}$).

4. Discussion

In the present study we observed both physiological and pathological phenomena of brain electric activity dynamics after open heart operations. Indeed, some prominent postoperative EEG changes in our patient cohort did not differ from dynamics of brain electric activity in healthy controls. At the same time, a range of EEG parameters abnormally altered after cardiac operations, and the latter were highly probable signs of perioperative brain ischemia.

TABLE 2: Global changes of BEA after open heart operation*.

	Patient group dynamics**	Group effect***	Local dynamics**	Local group effects***
Total alpha-2 power decrease	$F = 5.28,$ $P = .032$	NS	F3, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, Oz, T5	T4 (larger decrease in controls)
Total beta-1 power increase	$F = 7.28,$ $P = .013$	$F = 6.11,$ $P = .020$	C3, C4, Cz, P3, P4, Pz, O1, O2, T3, T5, F8, T4, T6	C3, C4, Cz, P3, P4, Pz, O1, O2, F8, T4, T6
Total beta-2 power increase	$F = 5.42,$ $P = .030$	$F = 3.41,$ $P = .076$	C3, P3, P4, Pz, O1, O2, T3, T5, F8, T6	Fpz, F3, C3, C4, Cz, P4, T4
Total delta-1 mean frequency increase	$F = 15.8,$ $P = .001$	$F = 10.2,$ $P = .004$	Fp2, C3, C4, P4, Pz, O1, O2, F7, T3, T5, F8, T4, T6	C3, C4, P3, Pz, O1, O2, Oz, F7, T3
Total delta-2 mean frequency increase	$F = 16.2,$ $P = .001$	NS	Fp2, Fpz, F3, F4, C3, C4, Cz, P4, O2, Oz, F7, T5, F8, T4, T6	Fp2, Fpz, Cz, T4
Total alpha-2 mean frequency increase	$F = 4.25,$ $P = .049$	NS	P3, Pz, T3	NS

* Findings at $P < .1$ are presented.

** Repeated measures ANOVAs or Wilcoxon tests included only patients.

*** Repeated measures ANOVAs included patients and normal controls.

TABLE 3: Hemisphere effects on electric activity after open heart operations*.

	Patient group dynamics**	Group effect***	Local dynamics**	Local group effects***
<i>Right hemisphere</i>				
Delta-1 power did not change versus decrease in controls	NS	$F = 6.67,$ $P = .016$	NS	C4, T4, T6 (decrease in controls)
Delta-2 power did not change versus decrease in controls	$F = 3.62,$ $P = .071$	$F = 5.95,$ $P = .022$	P4, T4 (increase)	C4, F8, T4, T6 (decrease in controls)
Theta-2 power did not change versus decrease in controls	NS	$F = 5.49,$ $P = .027$	P4, T4, T6 (increase)	Fp2, C4, P4, T6 (decrease in controls)
Alpha-1 power did not change versus decrease in controls	NS	$F = 5.83,$ $P = .023$	F8, T4 (increase)	T4 (decrease in controls)
Theta-1 power increase in central region	NS	$F = 5.11,$ $P = .032$	P4, O2, T4, T6 (increase)	P4 (decrease in controls)
<i>Left hemisphere****</i>				
Delta-2 power increase in central region and no change in temporal region versus opposite dynamics in controls	NS	$F = 4.42,$ $P = .045$	NS	T3 (increase in controls)
Theta-1 power did not change versus significant changes in controls	NS	$F = 4.33,$ $P = .042$	NS	NS
Theta-2 power did not change versus significant changes in controls	NS	$F = 4.83,$ $P = .037$	NS	NS
Alpha-2 power decrease	NS	$F = 6.90,$ $P = .014$	F3, C3, P3, O1, T5	NS
Theta-2 mean frequency decrease in central region	NS	$F = 5.30,$ $P = .030$	NS	NS

* Findings at $P < .1$ are presented.

** Repeated measures ANOVAs or Wilcoxon tests included only patients.

*** Repeated measures ANOVAs included patients and normal controls.

**** Statistics on interaction of time *central/temporal region *group factors in left hemisphere is presented.

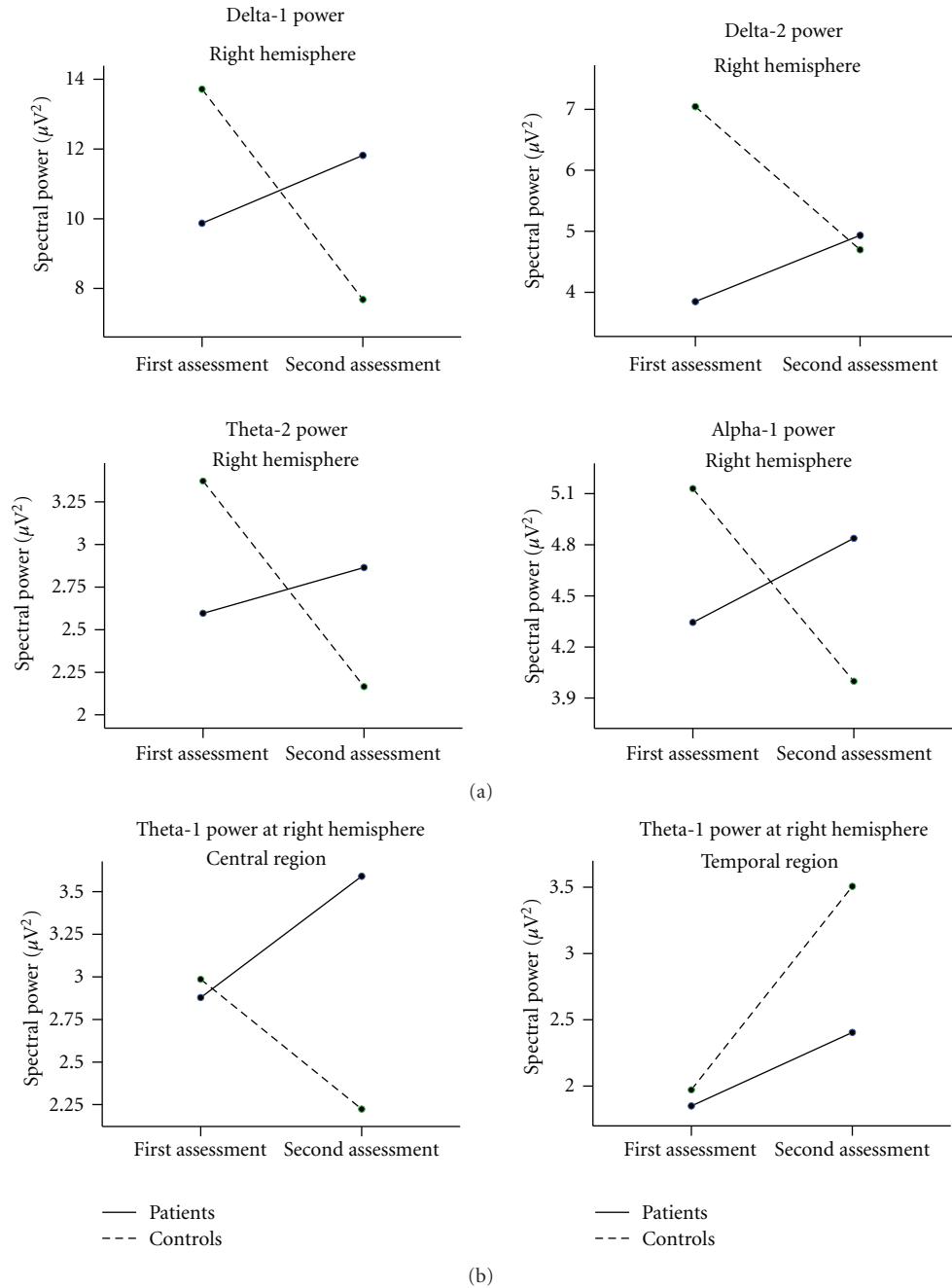


FIGURE 2: Group differences in dynamics of delta-1, delta-2, theta-2, and alpha-1 power in right hemisphere (a); group effects on dynamics of theta-1 power in central and temporal regions of right hemisphere (b).

4.1. Postoperative Beta Activity. Postoperative increase of beta power especially prominent in beta-1 band was a certain pathological phenomenon in our patient cohort. The similar postoperative increase of beta activity was previously reported after open heart operations [44] and on-pump coronary surgery [46]. Interestingly, increase of beta activity was reported in acute alcohol and heroin withdrawal, that is, conditions with pronounced neurochemical imbalances [48, 49]. Moreover, a “beta buzz” phenomenon with strong

increase in EEG beta power was reported after administration of benzodiazepines and other GABA agonists [27, 56].

Porjesz and colleagues [27] explained the functional meaning of a “beta buzz” as a “slow gamma” activity. Normally, only excitatory neurons oscillate at beta frequency whereas inhibitory interneurons simultaneously oscillate at subharmonic gamma rate. GABA agonists synchronize excitatory and inhibitory neurons oscillations at beta frequency. In a range of studies (including our previous study

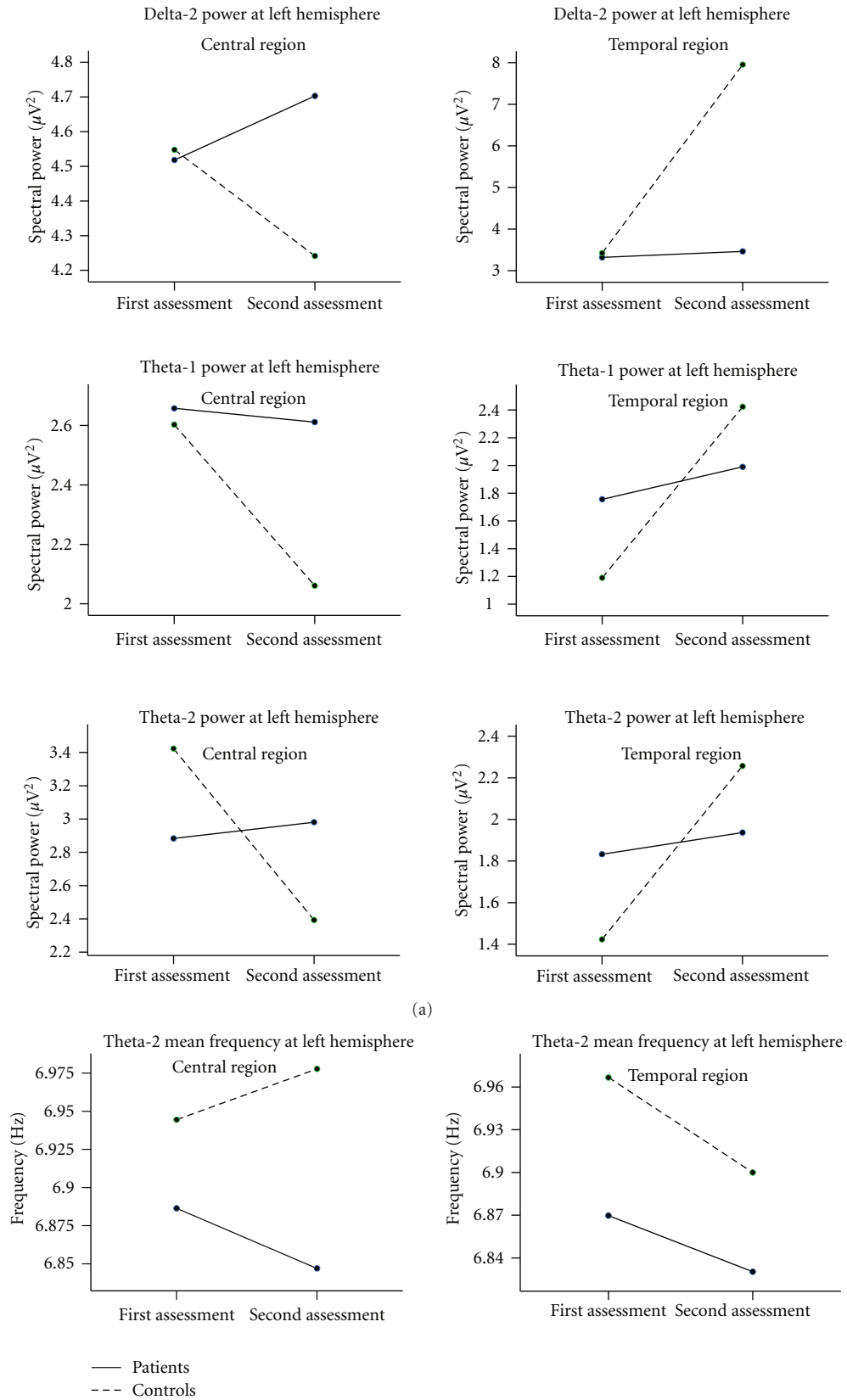


FIGURE 3: Group differences in dynamics of delta-2, theta-1, and theta-2 power (a); theta-2 mean frequency (b) in central and temporal regions of left hemisphere.

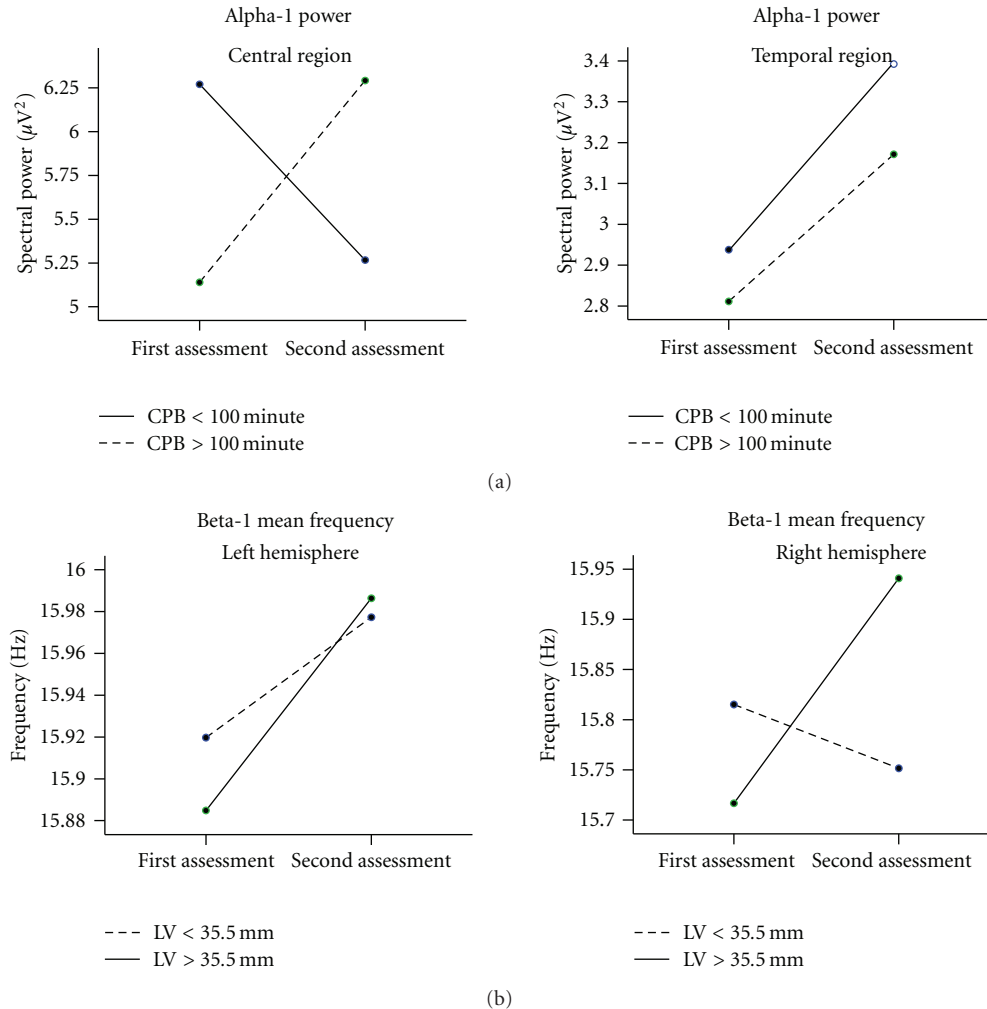


FIGURE 4: Effects of cardiopulmonary bypass length (a) and left ventricular size (b) on postoperative dynamics of brain electric activity.

of heroin addicts), strong association between beta power increase and slowing of psychomotor speed was observed [57–59]. Importantly, slowing of psychomotor speed is a very common postoperative deficit [11]. At the same time, postoperative increase of beta activity [46] and psychomotor slowing [11] were shown to be transitory, and this dynamics gives grounds to associate a postoperative “beta buzz” with global cortex edema and metabolism decrease reported by neuroimaging studies. Additional increase of beta-1 mean frequency in right hemisphere in patients with high risk of excessive embolism is logical, as previously we found asymmetrical distribution of emboli to right hemisphere in a similar cohort of patients [20]. The latter phenomenon may result from perfusion techniques.

4.2. Postoperative Alpha Activity. In agreement with almost all previous studies [44–47], we found prominent changes of alpha activity, especially, in fast (alpha-2) band. For instance, Hauser and colleagues [45] reported alpha-2 power decrease at 6-, 11-, and 44-day followups after open heart operations in children. Slowing of alpha-rhythm (alpha activity in

occipital region) at followup was consistently reported in previous studies of postoperative EEG changes as well [44, 47]. Nevertheless, healthy subjects in our study demonstrated the similar decrease of alpha-2 activity at second assessment [52]. In addition, both patient and control groups showed analogous widespread alpha-2 mean frequency and localized alpha-1 mean frequency changes. Importantly, two more studies reported significant decrease of alpha activity and increase of peak alpha frequency in healthy subjects during repeated EEG evaluations [51, 60]. Thus, decrement of alpha activity along with alpha mean frequency shifts at repeated EEG is regularly observed in both healthy subjects and cardiac surgery patients. Therefore, alpha activity changes in our patient cohort appear to represent at least partially a physiological phenomenon.

It is widely known, that alpha rhythm is a dominating activity in adult subjects during eyes closed “resting” condition. In healthy young subjects, alpha-2 activity (10–12 Hz) dominates at occipital derivations, and the source of alpha-2 oscillations is lateralized to right hemisphere [61]. Previously, alpha rhythm was commonly considered

as an idling rhythm of visual cortex as it was blocked by eyes opening. However, this view is contradicted by the stimulus-related enhancement of alpha activity, which was consistently shown in a range of studies. For instance, alpha rhythm maximally synchronizes at rhythmic light stimulation, and in healthy subjects occipital cortex responds with 10–12 Hz wave forms [62, 63]. Intensive contemplating of complex pictures induces prominent increase of interhemispheric coherence of alpha-oscillations at occipital and posterior temporal derivations, and memorizing of the same pictures does not affect alpha activity coherence in comparison with “resting” background [53]. Enhancement of synchronization of alpha activity after simple auditory stimuli (tones) was consistently shown in a range of studies as well [28, 64, 65]. Overall, the cited studies evidenced that alpha activity is an intrinsic component of cortex cognitive processing rather than an “idling” cortex phenomenon. Not surprisingly, spectral characteristics of alpha-rhythm and overall spontaneous alpha-activity were consistently shown to highly correlate with a range of cognitive abilities [51, 66, 67].

Laufs and colleagues [68] showed positive correlations between alpha-oscillations and activation of cingulate and occipital cortex at fMRI scans during “resting” eyes closed condition. Sadaghiani et al. [36] found similar positive associations between global alpha-2 activity power at eyes closed resting state and activity at a network comprising dorsal anterior cingulate cortex, anterior insula, anterior prefrontal cortex, and thalamus. The latter brain structures are commonly designated as a “default-mode” network, which maximally activates during “resting” state. We could not identify MRI studies, which repeatedly evaluated a default-mode network functioning in healthy subjects. We just may hypothesize that activity of the former decreased at followup in our patients and healthy subjects, and therefore alpha-2 activity power decreased as well. As it was cited earlier, alpha oscillations are an intrinsic component of cognitive evoked potentials, and decrease of amplitude of the latter is a widely known phenomenon [48, 49]. Therefore, at least partially, alpha power decrease in our patient cohort appear to be physiological. Perhaps, only the elevation of alpha-1 power in central derivations in patients after prolonged bypass may be hypothesized to be pathological; however, further research is needed to determine the significance of the latter finding. We hope to elucidate the nature of alpha activity reduction in our patient cohort after analyses of interrelationships between postoperative EEG data and performance on cognitive tests.

4.3. Postoperative Delta and Theta Activity. Both patient and control groups demonstrated significant changes of slow-wave activity at followup assessment. Important, that healthy controls showed increase of delta-2, theta-1, and theta-2 power in left temporal region (T3) at followup. Patients did not demonstrate comparable dynamics of regional slow-wave activity in left hemisphere, and absence of the latter physiological EEG changes may be suggested to be a deficient neurological sign. As left hemisphere and posterior brain

cortex were consistently shown to be highly vulnerable to ischemia during cardiac operations [7, 19, 69–72], we discuss the left temporal region deficit in our patient cohort in detail.

A range of experimental studies consistently demonstrated that delta/theta activity is an intrinsic component of information processing in normal human brain [30, 73–75]. At present, it is widely accepted that theta activity synchronizes during mnemonic processes in humans [73, 75]. For instance, Kirk and Mackay [75] showed that theta activity synchronized left temporally during digit span task and right temporally during spatial memory task. Complex calculations and concept formation were shown to be associated with prominent synchronization of delta activity over frontal and temporal regions as well [30, 75]. Although visual and auditory stimuli usually evoke a broadband response, delta-theta oscillations tend to demonstrate larger synchronization during processing of auditory information as opposed to alpha activity, which predominates during visual tasks over posterior brain regions [53, 76]. During eyes closed “resting” condition the source of delta and theta activity localizes anterior and somewhat leftward from midline, that is, closer to auditory cortex in comparison with alpha activity [61]. Importantly, Corsi-Cabrera and colleagues [50] showed significant increase of theta power at followup in their study of healthy women.

The cited above neurophysiological studies give grounds to hypothesize that electric brain activity in healthy subjects shifted from “visualizing” regimen during primary assessment to “internal speech” regimen, and therefore slow-wave activity at left temporal region increased along with concomitant alpha activity decrease. Patients did not demonstrate this physiological shift of electric brain activity probably due to ischemic alterations in left temporal cortex. At least two neuroimaging studies showed localized postoperative dysfunction of left temporal cortex in patients after on-pump coronary surgery [19, 72]. Moreover, verbal memory decline is the most common postoperative cognitive deficit in cardiac surgery patients [11, 19]. Interestingly, Zeitlhofer and colleagues [44] reported a trend for more pronounced EEG changes in left hemisphere after open heart surgery.

In addition, we observed significant postoperative increase of delta-1 and delta-2 mean frequencies in all brain regions without concomitant generalized changes of delta power. However, only dynamics of delta-1 mean frequency differed between patients and controls. A trend for region-specific postoperative elevation of delta-2 power was observed. Analyses at separate leads showed significant increase of delta-2 and theta activity in posterior derivations of right hemisphere after open heart operations. The latter EEG changes in the patient group differed significantly from controls, which showed the most prominent decrease of delta and theta-2 activity in this region. It should be noted that Vanninen and colleagues [47] found similar postoperative increase of delta activity in right posterior region (bipolar derivation T6-O2), along with increase of theta activity in bilateral central derivations. Moreover, overall mean frequency significantly slowed in right hemisphere in their study.

Slow-wave activity was traditionally associated with compromised brain states, and therefore was considered as an unambiguous pathological sign [37, 77]. Thatcher and colleagues [31] found opposite association between increase of delta amplitude and the severity of white matter alterations in patients after brain injury. It may be hypothesized, that generalized shift of delta-1 mean frequency and elevation of slow-wave activity in posterior right region were pathological in our patient cohort. Further research is needed in order to identify the mechanisms of slow-wave activity changes after cardiac operations.

4.4. Limitations of the Study. The small number of patient and control subjects makes the present results preliminary. A somewhat imbalanced gender distribution between patient and control groups may be a source of result bias in the present study, as gender was recently shown to affect brain electric activity characteristics. Preoperative abnormalities of brain electric activity in patients in comparison with healthy controls is the other limitation of this study. It should be noted that premorbid cognitive and electrophysiological dysfunction is a common problem for studies investigating patients with chronic diseases as good general health is an important contributor to normal brain functioning. Absence of direct measurements of intraoperative cerebral microembolism is an important limitation as well, and further research is needed in order to determine effects of intraoperative emboli on postoperative brain electrophysiology.

5. Conclusions

Both pathological and physiological changes of brain electric activity were observed after open heart operations. Generalized postoperative increase of beta power most prominent in beta-1 band was an unambiguous pathological sign of postoperative cortex dysfunction, probably, manifesting due to gamma-activity slowing (“beta buzz” symptom). Generalized increase of delta-1 mean frequency along with increase of slow-wave activity in right posterior region may be hypothesized to be a consequence of intraoperative ischemia as well. At the same time, significant changes of alpha activity were observed in both patient and control groups, and, therefore, may be considered as physiological. Unexpectedly, controls showed prominent increase of electric activity in left temporal region whereas patients were deficient in left hemisphere activity in comparison with controls at postoperative followup. Further research is needed in order to determine the true neurological meaning of the EEG findings after on-pump operations.

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