

Cortical lateralization and cardiac autonomic control. Insights from insular stroke and epilepsy

Victor Constantinescu^{*,1}, Olivier Detante², Daniela Matei³, Irina Constantinescu¹, Catalina Arsenescu-Georgescu⁴, Pascal Defaye⁵, Cristian Dinu Popescu¹, Dan Cuciureanu¹

¹Neurology Department, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania;

²Neurology Department, Stroke Unit, University Hospital of Grenoble, University Grenoble Alpes, France;

³Department of Biomedical Sciences, Faculty of Medical Bioengineering, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania;

⁴Cardiology Department, "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania;

⁵Cardiology Department, Arrhythmia Unit, University Hospital of Grenoble, University Grenoble Alpes, France

Abstract

Autonomic nervous system dysfunction is a common complication of stroke. Human studies and experimental data showed a hemispheric lateralization of autonomic activity concerning the forebrain and particularly the insular cortex. Insular cortex involvement is associated with more pronounced autonomic imbalance leading to life threatening arrhythmias and sudden death. We present two case reports of insular infarction in young patients without any cardiac comorbidity, illustrating a specific lateralized function of insula and its influence on the sympatho-vagal balance that implied differentiated therapeutic management after stroke. The right insular stroke was associated to sympathetic activation and left insular stroke was associated to parasympathetic predominance. The same lateralization of autonomic function with opposite effects on sympatho-vagal balance was also reported in two insular epilepsy cases, illustrating the fact that, beyond the controlling network, the cortical modulation of the autonomic nervous system is asymmetric. Identifying high risk patients prone to develop neurogenic cardiac complications, by better understanding of dysautonomia pathophysiology and consequent implementation of prophylactic and therapeutic interventions may significantly reduce mortality rate in stroke and epilepsy.

Keywords: *insular cortex, ischemic stroke, epilepsy, cardiac dysautonomia*

Introduction

Cardiovascular system presents cortical modulation. It is known that cardiovascular disease can generate stroke, such as atrial fibrillation or atheroma, but the fact that cerebrovascular disorders can alter

cardiovascular function is a recent discovery.

In the last decades, studies about neuro-cardiology proposed the concept of neurogenic cardiac disease, clinically and pathogenically different from the actual cardiac disease.

Previous studies showed subcortical structures playing a role in modulating autonomic nervous system activity, with a special focus on autonomic circuits at the spinal and brainstem level [1-3]. Using neuroimaging methods such as PET-scan and functional MRI, a complex cortical network formed by insular cortex, anterior cingulate cortex and amygdala was identified, which

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*Corresponding author: Victor Constantinescu; "Grigore T. Popa" University of Medicine and Pharmacy, 16 University Street, 700115, Iasi, Romania; Tel: 0232-240822 .

E-mail: victorcons@yahoo.com

seems to be involved in central control of autonomic nervous system [4].

Insula, a structure located in the lateral sulcus and with a complex role, is supposed to represent a transition between neo-cortex and limbic system. It presents connections with amygdala, gyrus cinguli, thalamus, entorhinal cortex and different areas from frontal, parietal and temporal lobe [5]. Its vascularization is provided by perforant segments from M2 (and occasionally from M1 or M3) of the middle cerebral artery (MCA). The multitude of vessels and their small caliber make insular strokes derive not from an individual insular vessel occlusion, but from segments of M1 or M2 of MCA. Therefore, insula is often involved in MCA ischemic stroke. However, strictly insular strokes represent a rare occurrence [6, 7].

In stroke patients, insular cortex lesions have been frequently associated with cardiac arrhythmia, abnormal arterial pressure variations during daytime and nighttime (non-dipper profile), myocardial or respiratory impairment during sleep, associated with high levels of catecholamine, troponin T and brain natriuretic peptide (BNP) [8-10].

Changes in autonomic nervous system activity have also been evidenced in epileptic patients, half of the sudden unexpected death in epilepsy (SUDEP) patients experiencing cardiac rhythm or repolarization abnormalities including sinus arrhythmia, atrial fibrillation and ST-segment elevation during the ictal or post-ictal period [11, 12]. These cardiac manifestations of seizures have been considered as possible causes of SUDEP. Some of these pre-ictal modifications of cardiac activity, determined by cardiovascular and cardiorespiratory reflexes under the influence of autonomic nervous system, could be used as markers of seizure onset [13] and could provide important information regarding seizure progression and outcome [14].

Cerebral imaging has not yet offered a clear correlation between certain cerebral structures involved in pathophysiology of seizures and cardiac activity changes.

Objectives

The aim of this research is to investigate the possible dysregulation of the autonomic nervous system in insular epilepsy and ischemic stroke patients. We also looked for correlations between cortical lateralization of autonomic control and autonomic changes on sympatho-vagal balance like sympathetic tonus predominance and non-dipper profile in continuous blood pressure monitoring, as these might predict patient's progress.

Cases report

We report four cases: two patients presenting ischemic stroke with insular damage and two patients with insular epilepsy. These cases suggest a lateralization of autonomic control. The study was approved by our institutional ethics committee (No 6878/2015) and all patients gave informed consent in accordance with ethical principles and the Helsinki Declaration.

Insular stroke patients

Two patients hospitalized in our Department of Neurology presented an ischemic stroke confirmed with CT-scanning to include insular damage. Both males, right-handed did not associate any cardiovascular history, diabetes or other known comorbidity. They were not under beta-blocker antiadrenergic medication or any other drugs that could interfere with autonomic nervous system activity. They were evaluated within the first two weeks after stroke. The previous medical evaluations (general practitioner) of these two patients registered normal heart rate (the average resting heart rate is considered for adults between 60 - 100 beats per minute [15]), normal blood pressure and routine blood tests (complete blood count, proteinogram, renal and hepatic tests, fibrinogen level, lipidogram, glycemia and glicated hemoglobin) were in normal range, as mentioned in the previous medical history records. The same tests appeared within normal range upon hospital admission.

Patient 1 (47 years old) presented an ischemic stroke in the territory of left MCA, encompassing the posterior left insular cortex. Clinically, he presented proportional right hemiplegia, predominantly expressive aphasia. National Institute of Health Stroke Score (NIHSS) was 13 at the moment of evaluation.

Patient 2 (36 years old) presented an ischemic stroke in the territory of right MCA, involving the posterior right insular cortex. The clinical examination was marked by left spastic proportional hemiparesis and dysarthria. NIHSS was evaluated at 11 points.

Both patients did not benefit of thrombolysis because of delayed admission to the emergency department.

Insular epilepsy patients

We also report two focal epilepsy patients with insular involvement, followed in the Department of Neurology.

Patient 3, 31 years old male, right handed, was diagnosed with left insular epilepsy with temporal lobe involvement, since age of 4. Seizures were focal, expressed by rotatory vertigo and autonomic manifestations such as sweating and facial flushes, sometimes followed by secondary generalization and post-ictal heteroaggressivity. Brain MRI showed left insular cortex atrophy with extension to the left fronto-parieto-temporal lobes. Seizures frequency was on average 2 per month. The patient was resistant to several antiepileptic drug associations. As no eligibility for epilepsy surgery was established, vagal nerve stimulation was finally proposed in this patient.

Patient 4, 34 years old female, right handed, was diagnosed with right insular focal epilepsy, since age of 6. The seizures began with sensation of rotatory vertigo, sweating, hypersalivation and were usually followed by secondary generalization (on average one generalization every two months). There was no evident focal lesion on cerebral MRI examination. The seizures occurrence was on average 3 per month. Drug resistance after multiple antiepileptic drug combinations and no eligibility for epilepsy surgery recommended also this patient for vagal nerve stimulation.

Complementary investigations

The assessment of ischemic stroke etiology in the first two cases excluded any supra-aortic arterial trunk lesion or paroxystic atrial fibrillation in continuous ECG recordings. Supplementary investigations for a hypercoagulability state for patient 1 found a heterozygote mutation of MTHFR C677T gene, coding the plasminogen activator inhibitor PAI -1, and a homozygote form of A2 and A3 allele of EPCR (endothelial protein C receptor). Patient 2 presented a heterozygote form of MTHFR A1298C gene mutation. Complete cardiac evaluation of both patients excluded an embolic cause or a patent foramen ovale.

Methods

Continuous ambulatory blood pressure measurement (ABPM) and ECG recordings during 24 hours using BTL Holter (series 08AE-0025901, BTL Industries Ltd, UK), BTL CardioPoint 2.21 (BTL Industries Ltd, UK) were performed in stroke patients during hospitalization. The following algorithm was used to analyze R-R interval variation: $(RR_{max} - RR_{min}) \times 100/RR_{mean}$, which is the difference between the shortest and longest RR interval during 5 minutes ECG continuous recording, in resting state, given as a percentage of the mean of all maximal and minimal peaks. RR interval variability at rest was considered abnormal when less than 10% [16].

Sympathetic and parasympathetic activity was assessed in the 4 patients by analyzing biologic parameters such as heart rate variability (HRV) using BIOPAC® Acquisition System. This is an integrated hardware and software system used for collecting and processing biologic signals (AcqKnowledge software package, version 3.9.1.6). Biologic parameters were converted by BIOPAC System in numeric data and then interpreted by AcqKnowledge software that allows detecting, measuring and automatic analysis of the registered signal. The data was afterwards processed using Kubios HRV program, version 2.2 (Biosignal Analysis and Medical Imaging Group, University of Eastern

Finland), which evaluates HRV in both time and frequency domain.

Several parameters were considered for quantifying the heart-rate variability. The standard deviation of the heart rate - Standard Deviation of Normal-to-Normal beat (SDNN), is the square root of its variance, recorded during an interval of 5 minutes. The coefficient of variation of the heart rate reflects the influence of the parasympathetic and sympathetic system on heart rate modulation [17, 18].

The pNN50 indicates the proportion of differences in consecutive, so-called normal-to-normal RR intervals that are longer than 50 milliseconds (ms) and reflects the percentage of such intervals in comparison to the total number of analyzed intervals. The pNN50 is a parameter of parasympathetic activity [17, 18]. Similarly, the square root of the mean squared differences of successive NN intervals (RMSSD) reflects parasympathetic activity. The coefficient of variation and the RMSSD are the most valuable time-domain parameters for routine evaluation at rest as they provide highly reproducible results and are not influenced by mean resting heart rate.

We also assessed frequency domain parameters, that assign bands of frequency and then count the number of NN intervals that match each band: high frequency (HF) from 0.15 to 0.4 Hz (characteristic to parasympathetic activity), low frequency (LF) from 0.04 to 0.15 Hz (represent both sympathetic and parasympathetic activities, depending on more complex mechanisms) and the very low frequency (VLF) from 0.0033 to 0.04 Hz (influenced by the thermoregulatory and renin-angiotensin system).

We used the LF/HF ratio to describe the sympatho-vagal balance and also the normalized units for the LF and HF (LFnu, HFnu), that remove the VLF from the estimation.

Five minutes ECG during rest was recorded using BIOPAC System in all four patients after 20 minutes of supine position in a 22°C atmosphere, without any previous physical effort.

Results

Stroke patients

In patient 1 (left MCA stroke), even from the first 48 hours after stroke onset, clinical monitoring showed low blood pressure values (80/50 mmHg) that imposed hemodynamic rebalance, and sinus bradycardia, not signaled before the stroke (Figure 1). The tilt-test, conducted two weeks after stroke, highlighted orthostatic hypotension (decrease from 102/64mmHg in supine position to 80/49mmHg after 3 minutes in orthostatic position).

We noticed a mean heart rate of 66 beats/min on a 24 hours period (Table 1), slowing down to as low as 49 beats/min. The 24-hour ABPM registration reflected the tendency towards low blood pressure values, frequently ranged between 80-90mmHg (Figure 1).

For patient 2 (right MCA stroke), we noticed sinus tachycardia, that imposed afterwards beta-blocker treatment, with a mean heart rate of 94 beats/min, reaching even to 159 beats/min (Table 1), while the 24-hour ABPM recording revealed high blood pressure levels, not present before the stroke (Figure 1). The most frequent systolic blood pressure value was between 140-150mmHg, with 24-hour monitoring suggesting the presence of a non-dipper tensional profile with high arterial pressure values during the night. The "tilt-test" was negative for orthostatic hypotension.

Comparing the 24-hour ABPM results for the two insular stroke patients (Table 1), we observed higher values of the arterial pressure in patient 2, associating higher heart rates, possibly related to a sympathetic hyperactivation, in contrast to a vagal tonus predominance in patient 1.

We completed our evaluation of the two stroke patients with the HRV analysis after 5 minutes ECG recordings in resting state, illustrated in Figure 2, in order to verify the sympatho-vagal imbalance, firstly indicated by the Holter ECG and ABPM recordings.

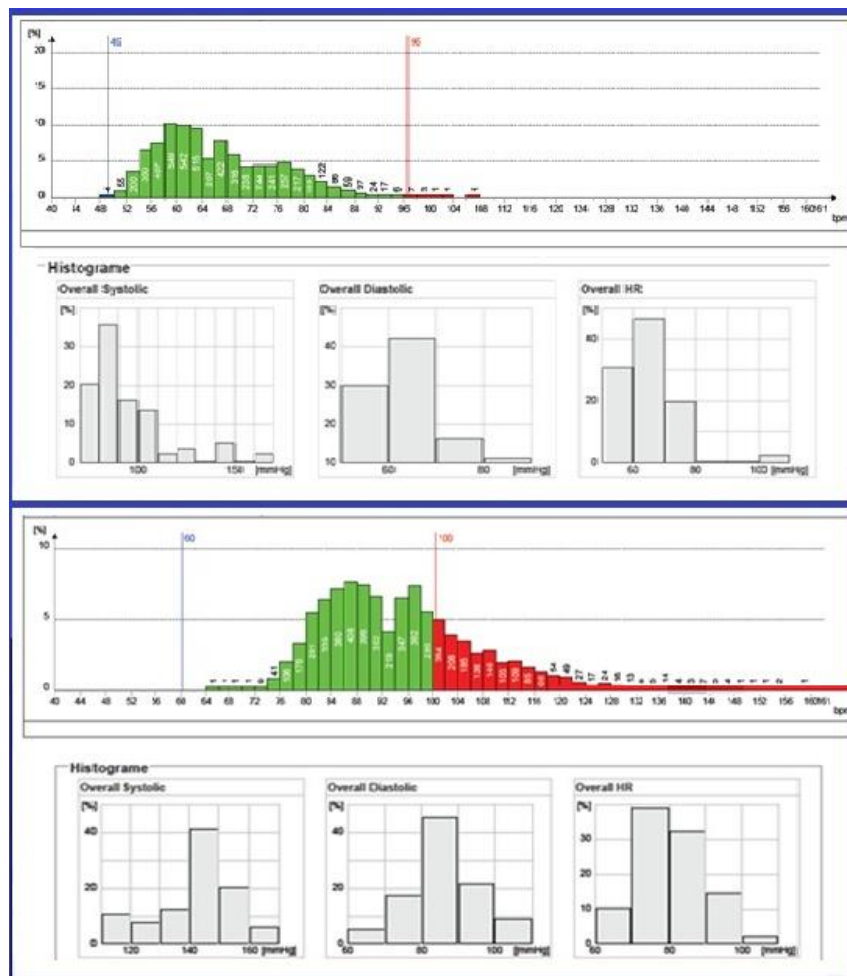


Fig. 1. Histogram of heart rate and blood pressure values during 24-hour recordings
Above: Patient 1 (left insular ischemic stroke). Below: Patient 2 (right insular ischemic stroke)

Table 1. Parameters for blood pressure and ECG recordings for stroke patients

Parameters for 24-hour blood pressure and ECG recordings	Patient 1 (left insular stroke)	Patient 2 (right insular stroke)
Total heart beats recorded	86 172	124 524
HR max/min	106/49 (beats/min)	159 /65 (beats/min)
Mean HR	66 (beats/min)	94 (beats/min)
Mean HR awake	69 (beats/min)	97 (beats/min)
Mean HR sleep	60 (beats/min)	91 (beats/min)
Tachycardia (%)	<1%	33%
Mean systolic arterial pressure (max percentage /24h)	80-90 mmHg (35%)	140-150 mmHg (42%)
Mean diastolic arterial pressure	60-70 mmHg (42%)	60-70 mmHg (44%)
Day/night variation	Dipper profile	Non-dipper profile

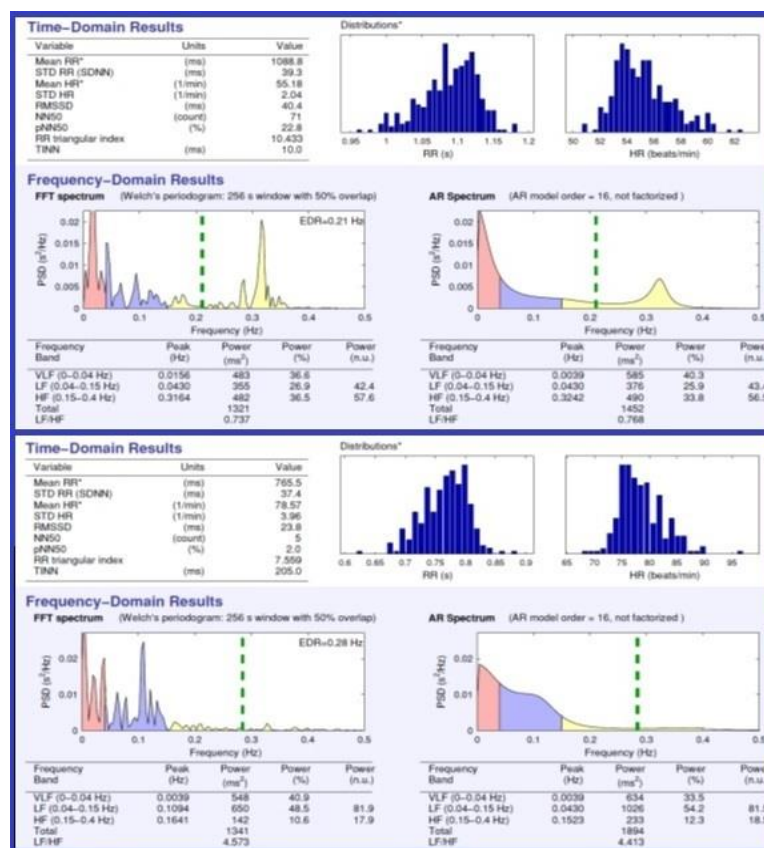


Fig. 2. Heart rate variability parameters using Kubios software.

Above: Patient 1 (left insular stroke) - parasympathetic predominance. Below: Patient 2 (right insular stroke) - sympathetic predominance

Table 2. Heart rate variability parameters in the four patients.

HRV parameters (time and frequency domain)	Patient 1 (left insular stroke)	Patient 2 (right insular stroke)	Patient 3 (left insular epilepsy)	Patient 4 (right insular epilepsy)
Mean RR (ms)	1088.8	765.5	791.8	670
SDNN (ms)	39.3	37.4	88.4	41.5
Mean heart rate (beats/min)	55.18	78.57	76.49	89.84
RMSSD	40.4	23.8	111.5	20.1
NN50 (count)	71	5	28	11
pNN50 (%)	22.8	2.0	6.8	2.4
LFnu	42.4	81.9	43.7	73.9
HFnu	57.6	17.9	55.0	26.0
LF/HF	0.737	4.573	0.795	2.843

Comparing the HRV parameters obtained from the two stroke patients (Table 2), we observed a higher mean heart rate and shorter RR interval duration in the second stroke patient, corresponding to the ECG Holter results.

Comparative data presented in Table 2 suggest that patient 1 with left insular ischemic stroke had a parasympathetic predominance (higher values of RMSSD, NN50, pNN50 and HFnu), while patient 2 with right insular ischemic stroke had a more pronounced sympathetic tone (lower values of RMSSD, NN50, pNN50 and HFnu, higher LF/HF ratio).

Epileptic patients

Both epileptic patients had normal blood pressure values, no orthostatic hypotension and were evaluated in similar conditions, having a monthly neurological follow-up. A good adherence to treatment was noticed and no cardiac side-effect was reported from the beginning. At least one day seizure-free before the recordings were considered in both patients.

The continuous ECG recordings for the HRV assessment are illustrated in Figure 3 for the left insular epilepsy and right insular epilepsy patients. Comparative data presented in Table 2 suggest that patient 3 with left insular epilepsy had a parasympathetic predominance (higher values of RMSSD, NN50, pNN50 and HFnu, lower LF/HF ratio),

while patient 4, with right insular epilepsy had a more pronounced sympathetic activity (lower values of RMSSD, NN50, pNN50 and HFnu). We also found low heart rate variability in patient 4 (7.8%), using the aforementioned algorithm in Methods [16]. Although both patients had similar clinical features, in the inter-ictal period we observed a different sympato-vagal balance, according to the cortical lateralization of the epileptic focus.

Cardio-autonomic outcome

Both stroke patients presented favorable outcome with marked improvement of neurological deficit, given their young age.

However, the autonomic response was different in these two patients. In the case of patient 1 (left insular stroke) we noticed low blood pressure values, bradycardia and orthostatic hypotension, explained by vagal hyperactivity. Heart rate variability, calculated by the algorithm mentioned, was within normal values (15%) [16].

Patient 2, with right MCA stroke and insular involvement, presented abnormal blood pressure values and a tendency towards sinus tachycardia suggestive for sympathetic predominance. We found low heart rate variability (8.62%) in this patient. In the context of post stroke cardiac dysautonomia, this patient presented impaired adaptability to effort.

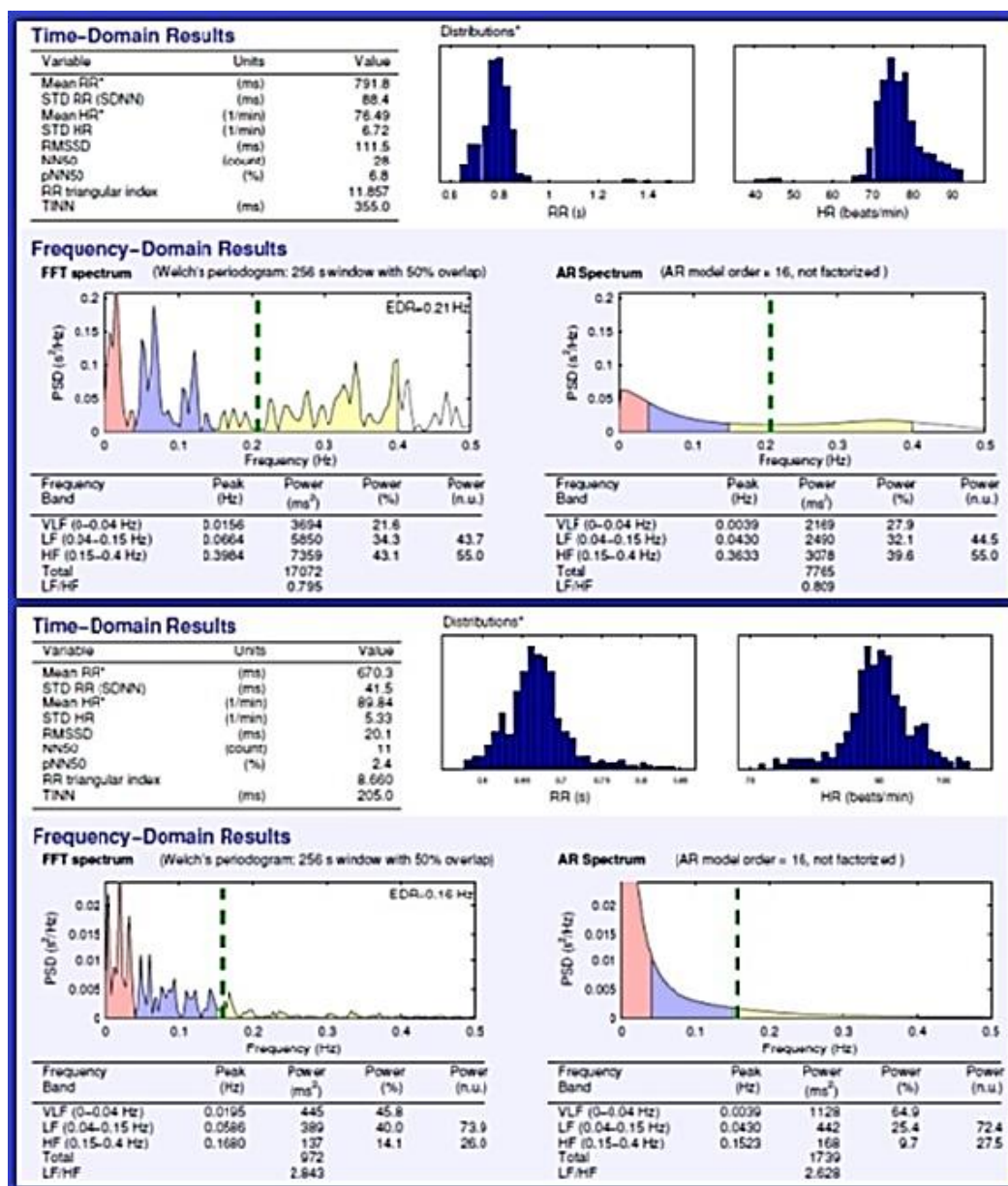


Fig. 3. Heart rate variability parameters using Kubios software

Above: Patient 3 (left insular epilepsy) - parasympathetic predominance. Below: Patient 4 (right insular epilepsy) - sympathetic predominance

Discussions

The physiological variability of the heart rate - the variation of the interval between consecutive heart beats over time - is indicative of the heart's ability to adjust to circulatory changes and serves as an important parameter for the assessment of autonomic functions [19]. The HRV is a standard measure of cardiac autonomic function which noninvasively reflects

sympathetic/parasympathetic balance using ECG recordings. The high frequency (HF) domain is a marker of parasympathetic activity whereas the low frequency (LF) domain is thought to represent both sympathetic and parasympathetic activities. A close relationship is known to exist between increased sympathetic activity and decreased parasympathetic activity with a consequent tendency to cardiac arrhythmia. It is known that the low HRV is associated with a higher

risk of arrhythmia [17, 20] and accompanies increased sudden cardiac death risk. Several investigators have reported decreased HRV in patients with stroke, which is found not only in the acute phase, but also one to six months after the event [21-23].

Post-stroke outcome and the prognostic of the patients can be highly influenced by autonomic nervous system disruption. HRV, as a non-invasive method to assess the sympatho-vagal balance, and beside other markers (troponin augmentation, BNP, QTc prolongation), may help in preventing cardiac fatal arrhythmia occurrence in neurologic patients. Studying HRV in the first 6 months post ischemic stroke can be useful in identifying cardiac dysautonomia and sympathetic overactivation during physical effort commitment to motor deficit rehabilitation, as a potential source of complications of patients' clinical outcome.

Studies regarding sympato-vagal imbalance using HRV spectral analysis in neurologic patients during night-recordings are insufficient, new data may be added to polysomnography and continuous blood pressure monitoring (ABPM). Observing autonomic nervous system during night in acute state of stroke patients would offer new perspectives on preventing unfortunate vascular events. It is not yet clear if post stroke ECG modifications are a consequence of direct autonomic innervation or secondary to high circulating catecholamine levels.

Cerebral involvement in cardiac dysfunction in neurologic patients has become more evident [24], but the frequency and circumstances of cardiac dysfunction in patients' evolution is still unclear. We found decreased HRV in the right-sided insular stroke patient, sympathetic predominance in right insular stroke and epileptic patients, and parasympathetic predominance in left insular stroke and epileptic patients.

Insular cortex involvement in central control of autonomic nervous system is sustained by several animal and human studies. The importance of the insular cortex in the control and representation of the cardiovascular autonomic state was also demonstrated by stimulation and electrophysiological studies in animals. In

rodents, right posterior insular cortex ablation determined increased heart rate and blood pressure [25]. In rats under urethane anesthesia a connection between the posterior insular cortex and the baroreceptor gain was evidenced, depending of the cortical lateralization [26]. The occlusion of MCA in rats determined myocytolysis, increased blood pressure and circulating norepinephrine levels, especially when right insular cortex was involved [27].

Not only animal studies have confirmed a lateralization in the control of the autonomic nervous system, but also human studies. In epileptic patients with drug refractory seizures who underwent intracarotid amobarbital injections (wada test), it was noticed sympathetic tonus predominance in the right hemisphere and parasympathetic predominance and up-regulation of baroreceptor sensitivity in the left hemisphere [28].

Intraoperative electrical stimulation of the insula determines cardiovascular activity modifications, which appear to be lateralized. Stimulating the right insular cortex results in tachycardia and hypertension, while left insular cortex stimulation ensure bradycardia and arterial hypotension [29]. In left handed individuals there is a specific lateralization regarding hemispheric dominance, opposite from right handed ones [30].

Using continuous ECG monitoring in first ever acute ischemic stroke patients, Colivicchi et al. [31] observed that the right insular cortex involvement associated significantly lower values of SDNN, standard deviation of the root mean square of difference of adjacent normal to normal RR intervals and higher LF/HF. These results confirm our findings that in the right ischemic stroke patient there is higher sympathetic tonus predominance.

When comparing different cortical localizations and the influence on cardiovascular system, the right insular cortex lesion was associated with more premature ventricular contractions and premature supraventricular contractions complex than left sided ischemia and with more non sustained ventricular tachycardia and supraventricular tachyarrhythmia than all other localizations [31].

The exact role played in cortical modulation of autonomic nervous system and the lateralization impact depending on the hemispheric localization are still debated. The relationship between insular ischemic stroke and cardiac events could be explained by complex and extended insular connections with different autonomic centers and the limbic system.

In the above presented stroke and epileptic patients, data suggest that there are differential cerebral impacts on autonomic function that depend on the side of the brain. But the hemispheric lateralization of autonomic control, experimentally observed in some other studies after insular stimulation, could be reduced or reversed [29]. This phenomenon could be explained by the predominance of the autonomic activity from the contralateral, non lesioned hemisphere. Furthermore, it was proposed that not all the insular cortex has a homogenous influence on the autonomic function. The cardiosympathetic centers are located in the anterior, medial, and superior parts of the insula, and the posterior insula and inferior parietal lobe are responsible for inhibiting and modulating the cardiosympathetic outflow of other parts of the insula [32]. An ischemic lesion involving the inferior parietal and posterior insula can disrupt the connection between the parietal lobe and autonomic centers in the brain, causing an autonomic imbalance and possible activation of the cardiosympathetic system, and predispose patients to increased risk of cardiac arrhythmia [33].

There is evidence that right insular cortex plays a role in modulating sympathetic autonomic control and that left insular cortex in parasympathetic control [34, 35]. This interpretation may represent an oversimplification of a more complex interaction between simpato-vagal balance and hemispheric lateralization, since it is known that some insular tractus realise interhemispheric connections. Moreover, insular lesions are usually a part of a larger stroke in the middle cerebral artery territory [12].

On the other hand, the cortical lateralization hypothesis may seem rather mechanical and not fully explain the complex

interaction of the autonomic nervous system with other exterior influences like endocrine or neuro-hormonal system [36, 37].

Conflicting results regarding specific autonomic roles of the insular cortex justifies further studies using functional imaging in order to better understand insular lateralization, vagal tonus modifications, and other cerebral structures involved in cardiac dysautonomia post stroke or in insular epilepsy. In our case report, we observe the same sympatho-vagal balance depending on the hemispheric lateralization in ischemic stroke (destructive lesion) and epilepsy patients (discharging lesion). Both lesions involve generators of oscillatory neural activity. Data from both experimental and human studies suggests that changes in oscillations patterns and subsequent changes in molecular and cellular mechanisms are involved both in stroke and in epilepsy lesions [38-42]. In stroke, the reduction of cerebral blood flow, as well as the progression of tissue damage may impact directly the power of several oscillatory bands, therefore opening the perspective of new predictive biomarkers based on brain neural dynamics after stroke [43]. In epilepsy, epileptiform events seem to result from complex interactions between neuronal networks with various patterns of neuronal firing (inhibitory and excitatory activity) and dynamical evolution of synchronization [42]. Therefore, detection and mapping of the oscillatory dynamics reflecting initiation and propagation of seizure activity is considered more and more as an effective modality for epilepsy focus diagnosis and invasive treatment guidance [41].

Therapeutic perspectives

Randomized trials are needed for confirmation of the benefits of beta-blockers or ACE inhibitors to stabilize the sympatho-vagal balance in patients prone to neurogenic heart disease and fatal cardiac arrhythmia. The role of cardio-defibrillator in order to decrease mortality rate can be discussed. Multiple clinical trials documented significant survival benefit of implantable cardioverter defibrillator in certain subsets of patients (experiencing decreased left ventricle ejection fraction

secondary to cardiomyopathy, sustained ventricular arrhythmias, etc.) with high risk of sudden cardiac death [44, 45]. However, progress in cardiac monitoring protocols in stroke and epilepsy units, but also pragmatic analysis of cost-effectiveness issues are still necessary to determine the precise use of defibrillator in patients with documented ventricular dysrhythmias.

Preventing sympathetic hyperactivity and secondary cardiac arrhythmia by rising vagal activity could be achieved by transcranial magnetic stimulation [46, 47]. Future studies should clarify whether the vagal nerve stimulation can be a feasible strategy in post-stroke rehabilitation. In animal models, experimental studies showed that vagal nerve stimulation and rehabilitative training enhanced the forelimb recovery after ischemic stroke [48].

It is known that patients with epilepsy can experience disrupted heart rate variability and changes in its circadian rhythm with negative clinical consequences such as dysrhythmias and possibly sudden unexpected death in epilepsy (SUDEP) [49]. Therefore, in epilepsy patients, vagal activity alteration, indicative of cardiac autonomic control, can be used as a prediction marker for seizures recurrence. If this technique would be validated, HRV could be included as a warning sign for seizures. Both ictal tachycardia and ictal bradycardia occur most frequently in association with mesial temporal lobe sclerosis and both are associated with other brain abnormalities such as cortical dysplasia, heterotopia and cortical lesions [50-53]. Apparently, ictal tachycardia occurs more frequently with seizures originating in the temporal lobe [51, 54] and mesial lobe seizure onset is more likely to cause increased heart rate [51, 55]. It has been shown that seizure activity in focal brain lesions influence anatomically and functionally interconnected areas, by propagating along specific neural networks that characterize the underlying epilepsy syndrome [56]. Certain autonomic symptoms experienced during or post-seizure may provide lateralization and localization hints of the seizure onset zone. Therefore, increased cardiac sympathetic tone in patients with left temporal lobe epilepsy it seems consistent with the presumed

asymmetric representation of autonomic function as described in earlier reports [25, 29, 57]. Furthermore, interictal autonomic lateralization with impaired parasympathetic activity and predominant sympathetic activity in left temporal lobe epilepsy has been mentioned in chronic epilepsy [58, 59]. Our major aim was to assess cardiac variability in two neurological conditions (stroke and epilepsy), involving insula, on the right and on the left. We considered the comparison of insular effects based on the laterality of the lesion, in order to highlight central modulation effects on heart rate variability in patients at risk for cardiac events [60]. To our knowledge, the evidence to support an effect of seizure lateralization on heart rate in the literature was inconclusive [61], but it was suggested that events with increase in heart rate are more highly influenced by the right anatomic structures [62-65].

In this respect, further studies regarding cardiac dysautonomia and insular epilepsy are needed on larger study groups.

New integrative therapeutic strategies in neurocardiology can offer different perspectives for vagal nerve stimulation on renal denervation practice in neurologic patients [66-70]. Our data aims to strengthen the need of careful cardio-vascular monitoring of these fragile patients, by including in routine clinical protocols, autonomic activity markers as reliable predictors for potentially life-threatening, but preventable events.

VNS stimulation, based on vagus nerve anatomical and functional impact on higher nervous structures, may modulate autonomic parameters, including heart rate variability in epilepsy patients [71]. Vagus nerve stimulator implantation was applied, according to international consensus, unilaterally, on the left, subclavicular side, in order to minimize potential cardiac complications, such as dysrhythmia. It is known that the left and right cardiac motor fibers of the vagus nerve innervate the heart asymmetrically, with fibers originating from the left vagus nerve supplying the atrioventricular node (causing decremental conduction) and those from the right vagus nerve innervating the sinoatrial node (reducing depolarization rates and producing bradycardia) [72-74].

It is already proven that VNS effects appear progressively after the initiation of the stimulation (which usually is set one month after the surgical implantation procedure, for post-surgery safety reasons). As shown by Ben-Menachem et al. [75], in one of the first studies to assess clinical efficacy of VNS, 14 weeks after VNS stimulation, patients receiving therapeutic VNS stimulation experienced seizure frequency reduction by about one third (30.9% reduction). To reach the therapeutic threshold (which is usually considered at 2 mA), the stimulation is gradually increased by steps of 0.25 mA, in average every 2 weeks. Our data was recorded on the immediate post-intervention period, accessional phase of stimulation (maximum 0.5 mA of stimulation), not yet considered therapeutic. However, evaluation after 3 months of progressive VNS therapy (when patients reached the 2 mA threshold) showed decreased number of seizures in both patients, especially in the fourth patient with right focal insular epilepsy. An improvement of the sympathetic/parasympathetic balance was noticed, using the same recording procedure as described in Methods, with a parasympathetic predominance markedly increased in the fourth patient. These data were not included in the article, as it was beyond this paper scope. We focused on one time-point observation of insular activity before the actual VNS clinical effects were clearly installed. Monthly follow-up was performed post-VNS intervention. Given the lack of different time-points observations in the post-VNS period, it is difficult to consider the decrease of seizure frequency noticed in these patients after 3 months, as specifically related to VNS modulation. This issue is, of course, interesting to look for in further studies dedicated to VNS-related modulation effects in larger group of epileptic patients.

Conclusions

In conclusion, these four clinical cases illustrated insula's involvement in lateralizing autonomic control and strengthened the importance of identifying pertinent evaluation parameters of possible future cardiac

arrhythmia in post stroke and epileptic patients.

Regarding stroke patients, we would like to emphasize the strong clinical impact of dysautonomic cardiac phenomena in the absence of any cardiovascular history. In the two epileptic patients, we confirm the same type of lateralization as in stroke patients. There are few studies regarding cortical lateralization of the sympatho-vagal dominance in epileptic patients and the autonomic control dysregulation. Taking this into consideration, HRV represents a useful tool that could be used as a marker to assess the sympatho-vagal balance in dynamics of acute stroke and can be a prognostic factor in stroke or epilepsy involving the insular cortex.

Elaborating prognostic scores, depending on the presence and magnitude of autonomic dysfunction, is necessary in order of a global management of neurological patients.

Limitations of the study

Although the research has reached its aims, there were several unavoidable limitations. First, this research was conducted on a very small number of patients. A second limitation is the difficulty to consider only the insular lesions as responsible for the results, as it is known, the insular cortex is part of a complex modulatory network. However, the semiology of the patients reflected lateralized insular origin. In epilepsy patients, stereo-electroencephalography studies should assess the insular lateralized cardio-autonomic implications more accurately. Another limitation concerns the modulation of autonomic parameters by VNS stimulation in epilepsy patients and its specific impact on cardiac activity. Even though highly interesting, this was not the main focus of this paper. Further data, with previous baseline (pre-VNS) monitoring of cardiac variability, together with timely observations on the modulation of the autonomic responses, while progressively increasing VNS stimulation intensity, according to clinical well-established protocols, would be, of course, of great interest for further in-depth studies on drug resistant epileptic patients implanted with VNS device.

Conflicts of Interest

The authors declare that they have no competing interests.

Consent

Written informed consent was obtained from the patients for publication of this case report.

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