

Association between clinical condition and F-waves changes in the acute phase of stroke

Associação entre condição clínica e alterações das ondas-F na fase aguda do acidente vascular cerebral

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ABSTRACT

Objective: To relate F-waves with clinical and laboratory exams in the acute phase of stroke. **Methods:** Inclusion criteria for this cross-sectional study were: hemiplegia, absence of previous cranial trauma, myopathy, diabetes, alcoholism or other known causes of peripheral neuropathy, and normal sensory and motor conduction. The National Institutes of Health Stroke Scale (NIHSS) score, glycemia, glucosilate hemoglobin, and CPK were obtained at admission by routine blood exams. After hospital admission, the F-wave latencies and persistence were obtained from the deep peroneal nerve using symmetrical techniques. **Results:** Evaluation of 20 individuals – mean age 66 years, 50% male and 85% Caucasian – showed association of F-wave persistence with glycemia ($r = 0.71$; $p < 0.001$) and NIHSS categorized (NIHSS 1-7 = 65.0 x NIHSS 9-23 = 100; $p = 0.004$). Multivariate analysis found only association of F-wave persistence with glycemia $\beta = 0.59$ (0.44–0.74); $p < 0.001$.

Conclusion: The increase in the persistence of F-waves are associated with hyperglycemia in the acute phase of stroke.

Keywords: stroke; brain waves; electrophysiology.

RESUMO

Objetivo: Relacionar as ondas-F com exames clínicos e laboratoriais na fase aguda do acidente vascular cerebral (AVC). **Métodos:** Os critérios de inclusão para este estudo transversal foram: hemiplegia, ausência de trauma craniano, miopatia, diabetes, alcoolismo ou outra causa conhecida de neuropatia periférica, além de condução sensorial e motora normal. O National Institutes of Health Stroke Scale (NIHSS), glicemia, hemoglobina glicada e CPK foram obtidos na admissão por meio de exames de rotina. Após a admissão hospitalar, a latência e persistência das ondas-F foram obtidas por meio da estimulação do nervo fibular profundo utilizando técnicas simétricas.

Resultados: Foram avaliados 20 indivíduos – média de idade 66 anos, 50% homem e 85% caucasianos – apresentaram associação univariada da persistência das ondas-F com glicemia ($r = 0.71$; $p < 0.001$) e NIHSS categorizado (NIHSS 1–7 = 65.0 x NIHSS 9–23 = 100; $p = 0.004$). Na regressão multivariada foi encontrado associação somente entre persistência de ondas-F com glicemia $\beta = 0.59$ (0.44–0.74); $p < 0.001$. **Conclusão:** O aumento da persistência de ondas-F está associado com maior nível de glicemia na fase aguda do AVC.

Palavras-chave: acidente vascular cerebral; ondas encefálicas; eletrofisiologia.

Stroke often leads to a significant decrease in patient quality of life, yet it has been the subject of few electrophysiological studies^{1,2}. Following the pioneering work of McComas et al.³, electromyography studies showed that changes in muscle fiber density occur during the chronic phase of stroke^{4,5}, and that positive sharp waves and fibrillation are observed two to three weeks after stroke^{6,7}. However, few studies have used electrophysiological examinations to evaluate F-wave alterations in the acute phase of stroke.

F-waves are late muscle responses elicited by the firing of antidromically stimulated motor neurons⁸. F-wave measurements are helpful in evaluating conduction along the entire

length of peripheral motor neuron axons, including the most proximal segment⁹. Mesrati and Vecchierini¹⁰ reported that F-wave changes occur in central nervous system (CNS) diseases, and concluded that F-waves are absent during the acute phase of CNS lesions but persist in the chronic phase in association with spasticity and hyperreflexia. Alterations in F-waves are associated with major severity of the CNS diseases and a poor long-term motor prognosis¹⁰.

In the only study that investigated the relationship between level of consciousness and F-waves, it was concluded that F-waves may be useful as an objective measure of the severity of consciousness impairment, but an association

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between the neurological condition and laboratory exam results was not reported⁸. Given that stroke is a main cause of chronic incapacity in adults, F-wave alterations in the acute phase of stroke could be important for future prognostic studies. Therefore, we hypothesized that the persistence of F-waves correlates with the severity of stroke in the acute phase. The aim of this study was to describe F-wave alterations in the acute phase of stroke and to evaluate their association with clinical and laboratory exam results.

METHODS

Study design, setting and participants

A single-center cross-sectional study was conducted in accordance with the principles of the Declaration of Helsinki¹¹. Patients were selected following approval of the study protocol by the Institutional Review Board of the Botucatu Medical School (UNESP). All participants or their legal representatives were aware of the study objectives and provided written informed consent.

The study included 20 individuals with a stroke diagnosis that was confirmed by CT-scan or MRI. The individuals were admitted to the stroke unit of Universidade Estadual Paulista (UNESP) between March 2012 and November 2013, and were included only if they met the following eligibility criteria: first stroke event, presence of hemiparesis with scores ≥ 1 in items 5 or 6 of the National Institutes of Health Stroke Scale/Score (NIHSS), absence of previous cranial trauma, absence of previous myopathy, absence of diabetes (glycated hemoglobin $< 6.5\%$) as specified by the expert committee on the diagnosis and classification of diabetes mellitus¹², absence of alcoholism and other known causes of peripheral neuropathy, and normal sensory and motor conduction in all four limbs as measured by conventional electrophysiological techniques⁹.

Variables

Exposures

The independent variables of clinical condition were: age (years), race (non-Caucasian vs. Caucasian), glycemia (mg/dL), glycated hemoglobin (HbA1c, %), creatine phosphokinase (CPK, U/L), NIHSS score upon admission (total score), and type of stroke (ischemic vs. hemorrhagic). Glycemia, HbA1c, and CPK were measured by routine laboratory examination. The NIHSS was administered prior to the electrophysiological examination and aimed to quantify the severity of the neurological condition and was subdivided into 11 items: consciousness level, speech, language, visual field, unilateral spatial neglect, ocular movement, strength, coordination, and sensitivity. Each item was scored on a scale from 0 to 4, where a higher score was associated with a poorer neurological clinical condition³. Stroke was classified as either ischemic or hemorrhagic by

means of a CT-scan or MRI evaluation according to international guidelines.

Outcomes

The outcomes of the electrophysiological examination after admission were: F-wave persistence and latency. The temperature of the lower limb was maintained above 32°C and F-waves were measured from the deep peroneal nerve using symmetrical techniques on the hemiparetic side. Analysis time was set to 10 ms/cm with a sensitivity of 200 μV and the band-pass filter was set to 20–3,000 Hz. A minimum of two series of 16 supramaximal stimuli were applied to the deep peroneal nerve at the head of the fibula and it was captured in the *extensor digitorum brevis* muscle in order to determine the persistence and latency of F-waves. The minimum amplitude to evoke a positive response (i.e., F-waves) was 10% of the amplitude of the M-wave. The examination was performed by a single examiner, who was certified by the Brazilian Society of Clinical Neurophysiology. All independent variables were measured upon admission to the stroke unit, and the outcomes were measured within 24–48 h.

Statistical methods

The univariate association between each clinical exposure and electrophysiological outcome was analyzed using non-parametric tests (Spearman and Mann-Whitney). The exposures most strongly associated ($p < 0.0083$ by Bonferroni correction, $\alpha = 0.05/6$) with the outcomes were included in a model of multiple linear regression. The number of independent variables associated with each outcome was 6 in the univariate regression model. After adjustment of the model, the Shapiro-Wilk diagnostic did not reveal any violation of the presuppositions of normality and homoscedasticity. Significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 21.0 (IBM, Chicago, Illinois, USA).

RESULTS

Over the course of this study, only 20 of the 168 individuals recruited met the study eligibility criteria. The principal reasons for exclusion of individuals were: absence of hemiparesis (18 patients), presentation of cranial trauma (8 patients), previous myopathy (2 patients), previous diagnosis of diabetes (57 patients), history of alcoholism (24 patients), previous presentation of peripheral neuropathy (36 patients), and presentation of abnormal sensory and motor conduction before F-wave examination (13 patients).

The characteristics of participants in this study are displayed in Table 1. The majority of patients were Caucasian (85%) and presented with hyperglycemia (78%) and ischemic stroke (75%) at admission.

The latency of F-waves was not significantly associated with any clinical or laboratory exam result (Table 2). However, the persistence of F-waves was significantly correlated with glycemia ($r = 0.71$; $p < 0.001$; Figure A) and NIHSS scores (NIHSS 1–7 = 65.0 \times NIHSS 9–23 = 100; $p = 0.004$; Figure B).

The exposures most strongly associated with our outcomes were included in the multivariate regression model (Table 3). Glycemia was the most important predictor for an increase in the persistence of F-waves ($p < 0.001$), with each 1 mg/dl of glycemia augmenting the persistence of F-waves by 0.59% [$\beta = 0.59$ (0.44–0.74); $p < 0.001$].

Table 1. Characteristic of participants (n = 20).

Variable	Participants
Age (years)	66 (26–88) ¹
Gender	
Male	10 (50.0%)
Female	10 (50.0%)
Race	
Non-Caucasian	3 (15.0%)
Caucasian	17 (85.0%)
NIHSS	
1–7	15 (75.0%)
9–23	5 (25.0%)
Glycemia (mg/dL)	96.5 (61.0–172.0) ¹
HbA1c (%)	5.6 (5.2–6.0) ¹
CPK (xx)	86.5 (24.0–225.0) ¹
Type of stroke	
Ischemic	15 (75.0%)
Hemorrhagic	5 (25.0%)
F-waves	
Persistence (%)	81.2 (8.0–100.0) ¹
Latency (ms)	43.7 (30.7–50.0) ¹

¹Values in median; HbA1c: glycated hemoglobin; NIHSS: National Institutes of Health Stroke Scale.

Table 2. Association between F-waves and clinical and laboratory exams.

cPK (U/L)	Persistence	p	Latency	p
Age (years)	$r = 0.31$	0.181	$r = -0.008$	0.975
Race				
Non-caucasian (n = 3)	87.5 (81.2–84.0)	0.241	42.5 (41.1–48.4)	0.791
Caucasian (n = 17)	80.0 (8.0–100.0)		44.3 (30.7–50.0)	
NIHSS				
1–7 (n = 15)	65.0 (8.0–84.0)	0.004	44.7 (30.7–50.0)	0.407
9–23 (n = 5)	100 (81.3–100.0)		43.2 (37.0–44.8)	
Glycemia (mg/dL)	$r = 0.71$	< 0.001	$r = 0.10$	0.672
CPK (U/L)	$r = -0.32$	0.158	$r = 0.30$	0.188
Type of stroke				
Ischemic (n = 15)	80.0 (8.0–100.0)	0.292	43.2 (30.7–48.4)	0.965
Hemorrhagic (n = 5)	81.2 (40–100.0)		44.3 (37.0–50.0)	

NIHSS: National Institutes of Health Stroke Scale; CPK: Creatine phosphokinase.

DISCUSSION

The generation of F-waves is dependent upon the excitability of motor neurons. An increase in the persistence of F-waves indicates alpha motor neuron hyperexcitability, whereas a reduction in the persistence of F-waves indicates hypoexcitability¹³. In the acute phase of stroke, F-wave persistence is significantly reduced on the paretic side. In our study, the mean F-wave persistence was 81.2%. Other studies have reported that F-wave amplitudes and persistence are decreased in clinically involved limbs, and this finding is compatible with observations of decreased central excitability (*e.g.*, decreased tone and reflexes) in patients who are studied early after stroke^{14,15}.

In the acute phase of stroke, F-waves may be absent owing to the hyperpolarization of spinal motor neurons; however, in the late phase, many authors report that F-waves are increased (100%) owing to the augmentation of central nervous system excitability, the disinhibition of supraspinal descending pathways, and a slow conduction period¹⁰. A higher persistence of F-waves in the acute phase of stroke may be related to a poorer neurological outcome¹⁵. Several trials have reported an association between the NIHSS score and functional outcome^{16,17}, but an association between the persistence of F-waves and NIHSS scores was not significant in the final model of regression in this study. Some studies have reported differences in F-wave latencies observed on the normal side versus the paretic side¹⁸, whereas other studies did not observe any differences between the normal and paretic sides^{19,20,21}. In this study, we did not find any differences in F-waves latencies between the normal and paretic sides.

Regarding the biochemical variables in our study, the majority of patients presented with hyperglycemia in the acute phase of stroke. This effect may be related to the elevation of catecholamines during ischemia or alternatively the activation of the hypothalamic-pituitary axis and suprarenal glands, which can lead to activation of the

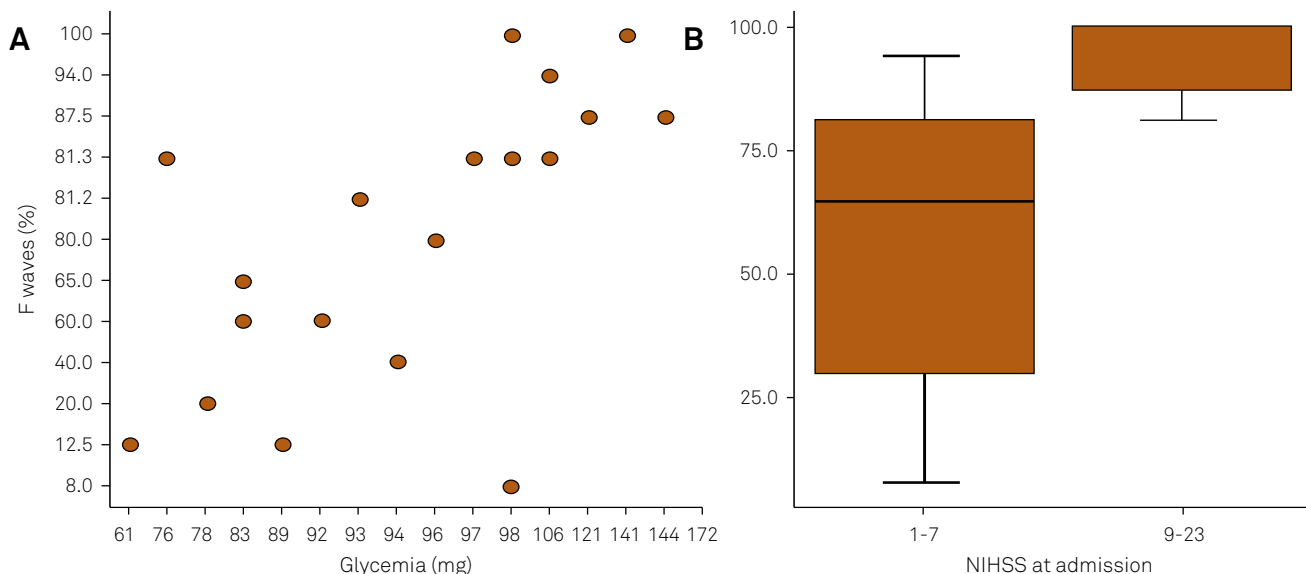


Figure. (A) Scatterplot of F-waves versus glycemia; (B): Boxplot of the association between F-waves and stroke severity.

Table 3. Linear regression adjusted to account for the F-wave persistence as a function of glycemia and NIHSS.

Variable	β	SE	p	CI 95%
Glycemia	0.594	0.070	< 0.001	0.448 0.741
NIHSS (9-23)	17.921	14.645	0.237	-12.848 48.689

R²aj = 82.1; pSW = 0.261; NIHSS: National Institutes of Health Stroke Scale; β : estimated coefficient; SE: standard error; CI: confidence interval.

sympathetic nervous system, elevated glucocorticoid production, and stimulates the production of glucose by glycogenolysis, glyconeogenesis, proteolysis and/or lipolysis^{22,23}. Hyperglycemia in the acute phase of stroke may play a role in ischemic neuronal damage²⁴ and, additionally, hyperglycemia is associated with a poorer long-term prognosis^{25,26,27}.

Hyperglycemia has been reported to alter nerve conduction in some preclinical studies^{28,29}. In clinical studies, acute hyperglycemia did not alter nerve conduction velocities and amplitudes³⁰, but chronic hyperglycemia has been hypothesized to be more detrimental to nerves³¹. The relationship between hyperglycemia and nerve conduction is therefore controversial in the literature, and no study to date has reported a relationship between the persistence of F-waves and an acute glucose disorder. Therefore, we postulate the hypothesis that hyperglycemia leads to neuronal hyperexcitability and exacerbated brain damage after cerebral ischemic injury.

The suggestion that F-waves are a useful prognostic indicator in the acute phase of stroke requires further study in a larger patient sample and with follow-up examination of patients in the chronic phase of stroke. The principal limitation of our study is the small sample size. The methodological rigor of the adopted inclusion criteria was a barrier to the recruitment of patients. Additionally, electrophysiological evaluations were operator-dependent and therefore limited our ability to screen patients. The long-term prognosis was not evaluated in this manuscript. Despite the limitations of our study, we report a novel finding in a Brazilian population of the principal alterations of F-waves in the acute phase of stroke, and these results provide useful parameters for future research studies.

We conclude that increases in the persistence of F-waves are associated with hyperglycemia in the acute phase of stroke.

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