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ASSESSMENT OF HEMODIALYSIS IMPACT BY POLYSULFONE MEMBRANE ON BRAIN PLASTICITY USING BOLD-FMRI

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Abstract—*Purpose:* Hemodialysis (HD) is considered the most common alternative for overcoming renal failure. Studies have shown the involvement of HD membrane in the genesis of oxidative stress (OS) which has a direct impact on the brain tissue and is expected to be involved in brain plasticity and also reorganization of brain function control. The goal of this paper was to demonstrate the sensitivity of the blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) to characterize the OS before and after the HD session. *Patients, materials and methods:* Twelve male patient-volunteers following chronic HD for more than 6 months were recruited among 86 HD-patients. All patients underwent identical assessment immediately before and after the full HD-session. This consisted of full biological assessment, including malondialdehyde (MDA) and total antioxidant activity (TAOA); and brain BOLD-fMRI using the motor paradigm in block-design. *Results:* Functional BOLD-fMRI maps of motor area M1 were obtained from the HD patient before and after the hemodialysis session, important decrease in the intensity of brain activation of the motor area after HD, and important increase of the size of the volume of brain activation were observed, these changes are reflecting brain plasticity that is well correlated to OS levels. Individual patients MDA and TAOA before and after the hemodialysis sessions demonstrated a clear and systematic increase of the OS after HD (*P*-value = 0.03). Correlation of BOLD-fMRI maximal signal intensity and volume of activated cortical brain area behaviors to MDA and total TAOA were close to 1. *Conclusion:* OS is systematically increased in HD-patients after the HD-process. Indeed, the BOLD-fMRI shows a remarkable sensitivity to brain plasticity studied cortical areas. Our results confirm the superiority of the BOLD-fMRI quantities compared to the biological method used for assessing the OS while not being specific, and reflect the increase in OS generated by the HD. BOLD-fMRI is expected to be a suitable tool for evaluating the plasticity process evolution in hemodialysis brain patients.

Key words: hemodialysis, oxidative stress, BOLD-fMRI, brain function, functional control, plasticity.

INTRODUCTION

Hemodialysis (HD) is considered the most common alternative for overcoming renal failure (Himmelfarb and Ikizler, 2010; Farzaneh et al., 2012). However; this blood-processing procedure contributes significantly to producing oxidants and elevated markers of lipid peroxidations (Siddique et al., 2012). Malondialdehyde (MDA) is one of the major reactive substances resulting from this peroxidation (Amedeo et al., 2009) quantified by the thiobarbituric acid reactive substance (TBARS) assay, a method used for assessing the oxidative stress (OS) while not being specific (Del Rio et al., 2005; Siddique et al., 2012).

Indeed, oxygen supplied by the blood oxygenation process is behind the OS phenomena whenever the control systems of metabolites generated are suffering or corrupted (Kohen and Nyska, 2002). Thus, multiple cellular defections are observed and might result in the release of pro-inflammatory and inflammatory factors, factors that promote cell proliferation, and apoptosis and/or necrosis (Lara et al., 2004; Libetta et al., 2011). The enhancement of the cell infarct might yield later various diseases such as cardiovascular disease, cancer, inflammatory and neurodegenerative diseases (Simone et al., 2010). Besides, the brain has a very high oxidative

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Abbreviations: ANOVA, Analysis of the Variance; BOLD, blood oxygenation level dependent; BOLD-fMRI, blood oxygenation level-dependent functional magnetic resonance imaging; FRs, free radicals; HD, hemodialysis; MDA, malondialdehyde; MNI, Montreal Neurological Institute; OS, oxidative stress; ROS, reactive oxygen substances; TAOA, total antioxidant activity; TBARS, thiobarbituric acid reactive substances.

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metabolism, which is involved in producing a large amount of reactive oxygen substances (ROS). Recent papers suggested that HD has the potential of possible additional risk factor for cognitive decline (McQuillan and Jassal, 2010; Rizzo et al., 2012).

Consequently, the OS has a direct impact on the brain tissue since it is involved in most metabolic processes discussed so far (Noseworthy and Bray, 1998; Hanafy and Selim, 2012). Hence, the OS is expected to be involved in brain plasticity and also in brain function control (Kishida and Klann, 2007; Numakawa et al., 2011). Brain plasticity also known as neuroplasticity, represents the amazing ability of the central nervous system to constantly change its structure and function and make a subtle remodeling of the nervous system, it manifests as a heterogeneous spectrum of functional cortical reorganization patterns and is dependent on multiple factors (Kleim and Jones, 2008). Thus, the oxygen level in cortical brain tissue is directly involved in the brain function control (Raichle and Snyder, 2007). In addition, the blood oxygenation level-dependent (BOLD) measurement using magnetic resonance imaging was reported as a non-invasive approach allowing the assessment of the cortical oxygenation during and 'off functional' control of the brain (Sørensen et al., 2009). Indeed, the neuronal metabolism is dependent on oxygen supplies by blood because the energy production from glucose is mainly of the aerobic type (Gjedde, 2007; Kumar et al., 2012). The neuronal activity is originating increased oxygen expenditure, hence an important enhancement of the local blood flow expressed as neurovascular coupling (Girouard and Iadecola, 2006; Kikuchi et al., 2010). The increased blood flow being much more important than the increase of the consumption of oxygen, the neuronal activation is translated by a relative increase of the oxygenated hemoglobin compared to deoxygenated hemoglobin in the activated brain area (Logothetis, 2002; Logothetis and Wandell, 2004). This relative reduction in the concentration of deoxygenated hemoglobin that has a paramagnetic effect, is detected by MRI methods and is reflected as a transitional increase of the T_2^* signal (Uludag et al., 2006; Chavhan et al., 2009). This measuring approach using the principle of the BOLD contrast is known as blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) (Chen and Ogawa, 2000; Kim and Bandettini, 2012). This BOLD-fMRI methodological development was not only used to assess the brain function activity, but it was also used to assess BOLD phenomena that are directly linked to brain activity or to abundance of free radicals (FRs) and increased OS (Djamali et al., 2007). Hence, the goal of this paper was to demonstrate the sensitivity of the BOLD-fMRI to characterize the OS before and after a HD session in patients suffering from chronic renal failure, while the dialysis process was achieved using the Polysulfone membrane, also to investigate whether fMRI with a motor task is a sensitive method to detect changes in BOLD response occurring before and after HD. The hypothesis tested was the following: HD has an impact on OS as well as on brain function that can be measured with fMRI as a change in BOLD response in the primary motor area. In addition, we demonstrate the impact of HD on the OS as well as in the brain function control reorganization in the cortical area. This would be witness of brain plasticity induced by OS. Finally, we do compare the BOLD-fMRI results with earlier findings of biological assessment methods in the same patients already published in the earlier paper.

EXPERIMENTAL PROCEDURES

Patients

Twelve male patients-volunteers following chronic HD for more than 6 months were initially recruited among 86 patients following HD in the Hemodialysis Center of the University Hospital of Fez, Morocco. The age of patients ranged from 15 to 45 years old with an average age of 31.5 ± 8 years. Patient's average duration of HD before recruitment was 48.6 ± 25 months. All patients were on dialysis with three sessions per week by membranes Polysulfone. Anticoagulation used is based on sodium heparin; the dose is the same for each patient throughout the entire study. None of the HD patients received antibiotics or other medications or vitamin supplementation during the study. All subjects gave written informed consent. Patient selection was based on specific criteria of exclusion and inclusion. Diabetic, smokers and patients with episodes of infection or treatment with iron or erythropoietin injection were excluded. All patients showing inflammatory disease and/or neurological and motor disorders even minor were not included. In addition, the healthy neurological profile was a must, and serological profile viral hepatitis C, HIV and B of all patients were negative.

Also were excluded from the study patients with C-reactive protein (CRP) > 6 or those who had a history of hospitalization. During the study, one patient has shown that he is uninterested to participate in the study, while two others underwent infectious episodes that did not allow including in this study. Hence, the full study was achieved by nine patients–volunteers, and only eight HD patients were successfully studied.

The first fMRI study and biological test are performed before the HD session and the second study was performed during the same day after the HD session.

Biological assessment

All patients underwent identical biological assessment protocol immediately before starting a HD session and immediately after achieving the full HD session in the Hemodialysis Center of the University Hospital of Fez, Fez, Morocco. These consisted of assessing the markers of OS such as MDA and total antioxidant activity (TAOA). Markers of OS were determined by measuring the optical density of MDA at 532 nm and the TAOA at 600 nm by a spectrophotometer JASCO V-530 type, in the Laboratory of Pharmacology (Faculty of medicine and Pharmacy of Fez, Fez, Morocco). The detailed results were reported in Medical Doctor Thesis of one of the authors as well as in conference proceedings (Batta et al., 2010).