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Cerebrovascular reactivity by quantitative magnetic resonance angiography with a co_2 challenge. Validation as a new imaging biomarker

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ABSTRACT

Assessment of cerebrovascular reactivity (CVR) is essential in cerebrovascular diseases, as exhausted CVR may enhance the risk of cerebral ischemic events. Transcranial Doppler (TCD) with a vasodilatory stimulus is currently used for CVR evaluation. Scanty data are available for Quantitative Magnetic Resonance Angiography (QMRA), which supplies higher spatial resolution and quantitative cerebral blood flow values. Aims of our pilot study were: (a) to assess safety and feasibility of CO_2 administration during QMRA, (b) evaluation of CVR under QMRA compared to TCD, and (c) quantitative evaluation of blood flow from the major intracranial arterial vessels both at rest and after CO_2.

CVR during 5% CO_2 air breathing was measured with TCD as a reference method and compared with QMRA.

Fifteen healthy subjects (age 60.47 ± 2.24; male 11/15) were evaluated at rest and during CO_2 challenge. Feasibility and safety of QMRA under CO_2 were ensured in all subjects. CVR from middle cerebral artery territory was not statistically different between TCD and MRI ($p > 0.05$). Mean arterial pressure (MAP) and heart rate (HR) increased during QMRA and TCD (MAP $p = 0.007$ and $p = 0.001$; HR $p = 0.043$ and $p = 0.068$, respectively). Blood flow values from all intracranial vessels increased after CO_2 inhalation ($p < 0.001$).

CO_2 administration during QMRA sessions is safe and feasible. Good correlation in terms of CVR was obtained comparing TCD and QMRA. Blood flow values significantly increased from all intracranial arterial vessels after CO_2. Studies regarding CVR in physiopathological conditions might consider the utilization of QMRA both in routine clinical settings and in research projects.

1. Introduction

The vasodilatory response of the cerebral resistance vessels is known as cerebrovascular reactivity (CVR) and is crucial in cerebrovascular diseases [1,2].

The full range of CVR, including the end stage increase in oxygen extraction fraction, can only be assessed by positron emission tomography (PET) using oxygen-15-labeled tracers [3]. However, PET is not widely available and has a failure rate for obtaining adequate quantitative data [3–5] in a range between 20% and 40%. Alternatively, although limited to the evaluation of vasodilatation, Transcranial Doppler (TCD) examination with acetazolamide

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injection, CO_2 inhalation or breath-holding [6–8] is a non-invasive, cheap technique for CVR assessment [2].

CO_2 provokes vasodilatory effects mostly on the peripheral vascular bed, particularly at the small cortical vessels [9,10] and TCD can pick up the increase in blood flow velocities (i.e. CVR) which reflect parallel changes in cerebral blood flow [11] in larger cerebral vessels [12] during the hypercapnic challenge. Furthermore, TCD allows an evaluation of collateral supply in subjects with carotid steno-occlusion [13,14], aiding in the distinction between normal and compromised hemodynamic state. TCD has a poor spatial resolution and CVR is currently measurable only by both middle cerebral arteries.

Magnetic resonance imaging (MRI), particularly quantitative magnetic resonance angiography (QMRA), has been introduced as a potential novel technique for CVR evaluation, in particular it has been utilized in cerebrovascular diseases [15,16].

QMRA provides quantitative data on cerebral blood flow (CBF) [17], the evaluation of the effects of age and sex on CBF [18], and the distribution of CBF into the circle of Willis [19]. Furthermore, QMRA has a high spatial resolution and is not invasive.

The aim of this pilot study was to standardize QMRA before and after CO_2 administration as a less invasive and repeatable technique for obtaining quantitative data regarding cerebral blood flow and CVR in healthy subjects. Primary aims were (a) to ascertain the safety and feasibility of CO_2 administration during MRI session, (b) to evaluate CVR under QMRA compared to TCD, this latter taken as a reference method and (c) to evaluate quantitatively overall blood flow from the major intracranial arterial vessels both at rest and after CO_2 administration.

2. Subjects and methods

2.1. Subjects and clinical assessment

After local Ethics Committee's approval, we prospectively enrolled fifteen healthy subjects – volunteer hospital staff and/or patients' relatives – in a 50–75 years age-range in a 2-year period. All participants signed a dedicated informed consent.

Exclusion criteria included poor insonation of the temporal bone window, heart failure (NYHAS > 3), severe chronic obstructive pulmonary disease, cardiac arrhythmias, epilepsy, presence of intracranial anatomic variants of the circle of Willis, cerebral arteriovenous malformations and/or aneurysm, carotid atheromatosis, any central nervous system malformation, claustrophobia or an overall MR non-compatibility. Furthermore, the occurrence of headache, chest oppression or any other intolerance during inhalation of the mixture of air with 5% CO_2 during TCD examination was considered as an exclusion criterion for the following MRI, and, therefore, for the enrolment in the study protocol. Intracranial vessel diameter < 2 mm did not allow to correctly identify or analyze flow-data under QMRA, thus ruling out the individual from the study.

Age, sex, history of hypertension, dyslipidemia, smoking habits, diabetes and heart disease were recorded in all subjects.

2.2. Experimental procedure – Transcranial Doppler

Transcranial Doppler was performed by an experienced neurologist (LC) in neurosonology at the Fondazione IRCCS Neurological Institute C. Besta in Milan. Mean flow velocity (MFV) of both middle cerebral arteries (M1 segment) was continuously recorded throughout the session with a 2 MHz Transcranial probe, fastened to the temporal window by a proper probe holder (Multi-Dop T, DWL Elektronische Systeme, Sipplingen, Germany). Depth of insonation varied between 45 and 60 mm and was selected to obtain the best signal. TCD was considered the reference method for the cerebrovascular reactivity in our study.

The subject wore a ventilation mask with two one-way valves tightly secured to the face so as to avoid any leakage. The input valve delivered room air or a mixture of air with 5% CO_2, the output valve was connected to a capnometer (Philips Intellivue MP70, Philips Healthcare, The Netherlands) for the constant monitoring of end tidal CO_2 ($EtCO_2$). Arterial blood pressure was assessed through a cuff manometer every 2 min throughout the procedure. Heart rate (HR) and peripheral arterial oxygen saturation were continuously monitored with pulse oximetry placed on a finger.

In order to avoid any complications due to hypercarbia, respiratory and hemodynamic safety thresholds were established and any value higher than 30% from baseline in $EtCO_2$ or mean arterial blood pressure (MAP) was considered a reason to stop the procedure and allow subjects to breath fresh air with the addition of oxygen at a 0.4 fractional inspiratory O_2 concentration (0.4 FIO_2) for 5 min.

Each subject lay in a quiet, comfortable and dimly-lit room, with low background noise. In the pre-test phase the subject breathed room air for about 10 min. Afterwards, the input valve was switched to the mixture of air with 5% CO_2 until steady $EtCO_2$ and MFV were obtained (on average 2 min). Each session was stored in the hard disk of the TCD for subsequent off-line analysis. Basal MFV data were averaged from the spectral outline of the monitoring curve across the last 2 min of the pre-test phase and hypercapnic MFV values across the last 30 s of inhalation of the mixture of air with 5% CO_2.

The same method was applied to data evaluation regarding HR (obtained from MFV spectral display) and $EtCO_2$, both in the pre-test and hypercapnic phases. Since blood pressure (BP) monitoring was intermittent, we averaged the values in the pre-test phase and those closest to the maximal MFV in the hypercapnic phase. MAP values, as resulting from 1/3 systolic BP + 1/2 diastolic BP, were used in all calculations.

CVR was calculated as the percent increase in MFV from both middle cerebral arteries per unit increase in $EtCO_2$ according to the formula [20]:

$$\text{CVR index} = \frac{[\text{MFV hypercapnic} - \text{MFV pre-test}) \times 100/\text{MFV pre-test}]}{[EtCO_2 \text{ hypercapnic} - EtCO_2 \text{ pre-test}]}.$$

TCD was performed before MRI in order to evaluate a) the possible occurrence of adverse events under CO_2 and b) the time needed to obtain steady $EtCO_2$ and MFV in each subject. This latter information was paramount to establish the time of maximal response during QMRA. The mean time interval between TCD and MRI sessions was 29.8 ± 7.4 min.

Apart from the pre-test phase in which the subject breathed room air for about 10 min, the mean time for the entire TCD study was 358 ± 17 s.

2.3. Experimental procedure – Quantitative Magnetic Resonance Angiography (QMRA) and Blood Flow Measurement

The subjects underwent quantitative flow measurements of the major intracranial arteries by Quantitative Magnetic Resonance Angiography on a 1.5 T MR (Siemens, Magnetom Avanto), using an eight-channel phased-array head coil. The technique of blood flow quantification by QMRA was based on a method of three-dimensional (3D) vessel localization that allows the identification of the vessel of interest, the selection of the vessel segment, and the determination of the slice orientation to improve the accuracy of phase-contrast magnetic resonance (PCMR) angiography, as described by Zhao et al. [21].