Normalizing cerebrovascular reactivity map via concomitant CO2 and O2 challenge

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INTRODUCTION: Cerebrovascular reactivity (CVR), referring to the ability of blood vessels to dilate upon stimulation, is an important marker of brain's vascular function (1). During the past few years, there has been a surging interest in quantitative mapping of CVR using BOLD MRI in combination with hypercapnia challenge (2-5) and to use this technique in cerebrovascular diseases (3,4) and normal aging (2,5). An undesirable feature of the current CVR mapping results is that the image shows very strong contrast in large drains (arrows in Fig. 1a), which may reduce the conspicuity of true CVR abnormalities. It is known that the over-emphasis of venous vessels is due to large amount of blood volume present in these vessels, i.e. more blood, more BOLD signal (6). We propose that the venous signal can be de-emphasized by accounting for blood volume on a voxel-by-voxel basis, which can be obtained by O2 breathing. Therefore, the first component of the present work is to demonstrate the feasibility of a "normalized CVR" mapping method, which is obtained by normalizing the CO2-CVR map with O2-reactivity map. One concern of the normalized approach is that the scan duration may be increased. Thus, the second component of this work focused on the development of a novel breathing paradigm, in which CO2 and O2 inhalation was applied simultaneously with their time courses orthogonal to each other. This allowed the acquisition of both CO2 and O2 reactivity maps without adding scan time.

METHODS: Theory of CVR normalization: According to the BOLD fMRI biophysical model (6), CO2-CVR, in the unit of %BOLD signal change per mmHg CO2, is given by Eq.[1], where 

$$M = \Delta CBF - \Delta CBF_{O2} \cdot (1 - Y_o)^{0.38}.$$  

$M$ indicates the maximum BOLD signal at a given voxel and is depending on baseline CBV, at this voxel. Similarly, the O2- reactivity can be written as Eq.[2]. By dividing CO2-CVR with O2-reactivity, the

$$\text{Normalized CVR} = \frac{CO2-CVR}{O2-\text{reactivity}}.$$  

Theoretical analysis and INTRODUCTION: Cerebrovascular reactivity (CVR), referring to the ability of blood vessels to dilate upon stimulation, is an important marker of brain's vascular function (1). During the past few years, there has been a surging interest in quantitative mapping of CVR using BOLD MRI in combination with hypercapnia challenge (2-5) and to use this technique in cerebrovascular diseases (3,4) and normal aging (2,5). An undesirable feature of the current CVR mapping results is that the image shows very strong contrast in large drains (arrows in Fig. 1a), which may reduce the conspicuity of true CVR abnormalities. It is known that the over-emphasis of venous vessels is due to large amount of blood volume present in these vessels, i.e. more blood, more BOLD signal (6). We propose that the venous signal can be de-emphasized by accounting for blood volume on a voxel-by-voxel basis, which can be obtained by O2 breathing. Therefore, the first component of the present work is to demonstrate the feasibility of a "normalized CVR" mapping method, which is obtained by normalizing the CO2-CVR map with O2-reactivity map. One concern of the normalized approach is that the scan duration may be increased. Thus, the second component of this work focused on the development of a novel breathing paradigm, in which CO2 and O2 inhalation was applied simultaneously with their time courses orthogonal to each other. This allowed the acquisition of both CO2 and O2 reactivity maps without adding scan time.

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In summary, the present work demonstrated that normalizing CO2-CVR by O2-reactivity can effectively reduce the influence of CBV on the results, thereby yielding a map that is more homogenous across tissue types. Theoretical analysis and in vivo experiment showed that normalized CVR may be a more direct index for cerebrovascular function. Furthermore, it was shown that the CO2 and O2 reactivity maps can be obtained in a single scan without increasing the study duration, using a novel breathing paradigm. Therefore, CVR normalization using concomitant CO2/O2 challenge may be a practical and promising method in clinical applications of CVR mapping in cerebrovascular diseases.