NeuroImage: Clinical 11 (2016) 667–677

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Respiratory challenge MRI: Practical aspects

Fiona C. Moreton[a], Krishna A. Dani[a], Colin Goutcher[b], Kevin O'Hare[b], Keith W. Muir[a,*]

[a]Department of Neurology, Institute of Neurosciences and Psychology, University of Glasgow, Queen Elizabeth University Hospital Glasgow, 1345 Govan Road, Glasgow G51 4TF, United Kingdom
[b]Department of Neuroanaesthesia, Institute of Neurological Sciences, Queen Elizabeth University Hospital Glasgow, 1345 Govan Road, Glasgow G51 4TF, United Kingdom

ARTICLE INFO

Article history:
Received 14 February 2016
Received in revised form 11 April 2016
Accepted 3 May 2016
Available online 6 May 2016

Keywords:
Cerebral blood flow
Cerebrovascular reactivity
Magnetic resonance imaging
Respiratory challenge
Review

ABSTRACT

Respiratory challenge MRI is the modification of arterial oxygen (PaO_2) and/or carbon dioxide ($PaCO_2$) concentration to induce a change in cerebral function or metabolism which is then measured by MRI. Alterations in arterial gas concentrations can lead to profound changes in cerebral haemodynamics which can be studied using a variety of MRI sequences. Whilst such experiments may provide a wealth of information, conducting them can be complex and challenging. In this paper we review the rationale for respiratory challenge MRI including the effects of oxygen and carbon dioxide on the cerebral circulation. We also discuss the planning, equipment, monitoring and techniques that have been used to undertake these experiments. We finally propose some recommendations in this evolving area for conducting these experiments to enhance data quality and comparison between techniques.

Contents

1. Introduction . . . 668
2. Rationale . . . 668
   2.1. Gases . . . 669
      2.1.1. The physiology of gas transport . . . 669
      2.1.2. Carbon dioxide . . . 670
      2.1.3. Oxygen . . . 670
3. Technique . . . 670
   3.1. preparation . . . 670
      3.1.1. Exclusions . . . 671
   3.2. Standardization of testing conditions . . . 671
   3.3. A trial run . . . 671
   3.4. The respiratory challenge . . . 671
      3.4.1. Ventilatory techniques . . . 671
      3.4.2. Fixed inspiratory challenge . . . 672
      3.4.3. Rebreathing . . . 672
      3.4.4. Dynamic end-tidal forcing . . . 673
      3.4.5. Prospective end-tidal targeting . . . 673
      3.4.6. Motion artefacts . . . 673
   3.5. The environment and equipment . . . 673
      3.5.1. Monitoring . . . 673
      3.5.2. Gas delivery . . . 673
4. MRI sequences and examples of use in brain disease . . . 674
   4.1. BOLD signal: fMRI and SWI . . . 674
   4.2. Perfusion . . . 674
   4.3. Dual echo imaging (BOLD and perfusion) . . . 674
   4.4. Cerebral blood volume: VASO . . . 675
   4.5. Other . . . 675
5. Recommendations . . . 675

* Corresponding author at: Institute of Neuroscience and Psychology, University of Glasgow, Queen Elizabeth University Hospital Glasgow, Glasgow G51 4TF, United Kingdom.

http://dx.doi.org/10.1016/j.nicl.2016.05.003

6. Conclusions . . . 675
Author contribution statement . . . 675
Conflict of interest . . . 675
Acknowledgements . . . 675
References . . . 675

1. Introduction

Alterations in the arterial partial pressure of oxygen (O_2) and carbon dioxide (CO_2) lead to changes in cerebral blood flow and vasculature (Kety and Schmidt, 1948a), and this response, when used in combination with a variety of imaging techniques, has been used to study brain physiology and disease for many years (Aaslid et al., 1989; Battisti-Charbonney et al., 2011; Novack et al., 1953). Magnetic resonance imaging (MRI) is a safe, non-invasive, repeatable technique with high spatial resolution, which can provide detailed structural and functional information about the brain. In this paper, we define respiratory challenge MRI as the modification of arterial oxygen (PaO_2) and/or carbon dioxide ($PaCO_2$) concentration to induce a change in cerebral function or metabolism which is then measured by MRI. This approach has been used for some time for optimization and calibration of fMRI sequences (Hoge, 2012), but there is increasing interest in the use of functional and/or perfusion MRI to examine brain pathophysiology. In particular, cerebral blood flow, oxygenation, metabolic rate and microvascular function in diseases such as stroke (Dani et al., 2010), dementia (Cantin et al., 2011), epilepsy (Kalamangalam et al., 2012) and brain neoplasm (Hsu et al., 2010; Yetkin and Mendelsohn, 2002).

A number of approaches have been explored. These can range from simple modification of respiratory rate, including breath hold (Hsu et al., 2010) and hyperventilation, to complex modelling of both respiratory parameters and brain signal change (Mutch et al., 2012; Shen et al., 2011). Whilst excellent articles reviewing the rationale and uses of these procedures are available (see Krainik for a recent review of functional imaging of brain perfusion (Krainik et al., 2013)), there are significant practical challenges in undertaking these methods. The aim of this review is to [1] review the rationale for respiratory challenge MRI in brain disease, [2] discuss techniques, equipment, monitoring and planning such experiments, and [3] propose some recommendations for optimization of these studies.

2. Rationale

The human brain employs an elegant system of regulation of cerebral blood flow (CBF) to ensure adequate delivery of O_2 and nutrients to brain tissue, according to need and regardless of changes in blood pressure, oxygenation or other factors. CBF is determined by the following equation:

$$\mathrm{CBF} = \frac{Cerebral perfusion pressure\ (CPP)}{Cerebrovascular resistance}.$$

Normal global CBF is around 50 mL/100 g/min (Kety and Schmidt, 1948b) with higher values in grey compared to white matter (Leenders et al., 1990) (see Table 1 for further definitions). However, CBF varies according to age, time of day, anatomical area and neuronal activity in order to maintain adequate nutrient delivery. The principle mechanism by which CBF is adjusted according to demand is by changing cerebrovascular resistance. This is governed by small cerebral vessels, particularly pre-capillary arterioles (<100 μm) (Wei et al., 1980), which are able to change calibre in response to a number of stimuli, a process known as cerebrovascular reactivity (CVR). Capillaries may also have an important role in vasoreactivity through the action of pericytes (Hall et al., 2014). If CVR is impaired, then increased CBF will not occur when required by brain activity.

Whilst a variety of methods exist for measuring CBF, there are difficulties in obtaining accurate, quantifiable CBF measurements, including interindividual variability (Leenders et al., 1990), external factors (Laurent et al., 2006), and inaccuracies in modelling methods (Eskey and Sanelli, 2005). Large patient groups or large disease-related effects may be needed to detect differences in baseline CBF in disease states.

Table 1
Definitions and relevant normal values.

Parameter	Abbreviation	Definition	Normal values
Cerebral blood flow	CBF	The volume of blood passing through the brain parenchyma in a defined time i.e. rate. This is usually defined in units of millilitres per 100 grams per minute.	~50 mL/100 g/min
Cerebral blood volume	CBV	The fraction of a tissue volume occupied by blood	4–6 mL/100 g
Cerebral metabolic rate for oxygen	$CMRO_2$	The amount of oxygen consumed by 100 g of brain in 1 min.	~3.5 mL/100 g/min
Cerebrovascular reactivity	CVR	Cerebral blood flow, or BOLD signal changes in response to stimuli usually measured as a percentage change in signal per change in CO_2/O_2	
Arterial gas concentration	PaO_2 $PaCO_2$	Partial pressure of oxygen or carbon dioxide in arterial blood i.e. gas molecules dissolved in plasma.	PaO_2: 11–13 kPa $PaCO_2$: 4.7–6 kPa
End-tidal gas tension	EtO_2 $EtCO_2$	The partial pressure or maximum concentration of oxygen or carbon dioxide at the end of an exhaled breath.	EtO_2: 16–17% $EtCO_2$: 5% (4.6–5.6 kPa)
Fraction of inspired gas	FiO_2 $FiCO_2$	The fraction or percentage of oxygen or carbon dioxide in the air that is breathed by the subject. Normal air has an FiO_2 of 0.21	FiO_2: 0.21 (21%) $FiCO_2$: 0.0004 (0.04%)
Oxygen saturation	SaO_2 SvO_2	The percentage of haemoglobin molecules which are oxygenated in arterial blood.	95–100%
Oxygen content	CaO_2	The amount of oxygen in the blood and therefore available for tissues.	20 mL O_2/dL
Cerebrovascular resistance		The resistance to the passage of blood created by arterioles and capillaries.	
Autoregulation		Cerebral vascular bed alters vascular resistance to maintain blood flow in the face of changes in systemic blood pressure to match metabolic needs.	
Vascular steal		A stimulus results in the redistribution of blood flow from regions of exhausted cerebrovascular reactivity (maximally dilated vessels) to areas with preserved vasodilatory capacity.	