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Review article

Cerebrovascular reactivity measured by functional magnetic resonance imaging during breath-hold challenge: A systematic review

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ABSTRACT

Cerebrovascular reactivity (CVR) is the cerebral hemodynamic response to a vasoactive substance. Breath-hold (BH) induced CVR has the advantage of being non-invasive and easy to implement during magnetic resonance imaging (MRI). We systematically reviewed the literature regarding MRI measurement of BH induced CVR. The literature was searched using MEDLINE with the search terms breath-hold; and MRI or cerebrovascular reactivity. The search yielded 2244 results and 54 articles were included. Between-group comparisons have found that CVR was higher among healthy controls than patients with various pathologies (e.g. sleep apnea, diabetes, hypertension etc.). However, counter-intuitive findings have also been reported, including higher CVR among smokers, sedentary individuals, and patients with schizophrenia vs. controls. Methodological studies have highlighted important measurement characteristics (e.g. normalizing signal to end-tidal CO_2), and comparisons of BH induced CVR to non-BH methods. Future studies are warranted to address questions about group differences, treatment response, disease progression, and other salient clinical themes. Standardization of CVR and BH designs is needed to fully exploit the potential of this practical non-invasive method.

1. Introduction

Cerebrovascular reactivity (CVR) can be defined as the hemodynamic response by the brain's blood vessels induced by vasoactive substances. Carbon dioxide (CO_2) is a potent vasodilator that effectively increases cerebral blood flow (CBF) and cerebral blood volume (CBV) (Pollock et al., 2009), with minimal impact on tissue cerebral metabolic rate of oxygen ($CMRO_2$) (Hoshi et al., 1997; Barnes et al., 2013; Gupta et al., 2012). CVR can be characterized quantitatively in terms of temporal and amplitude responses; a larger CVR amplitude is considered a sign of better cerebrovascular health (Bright and Murphy, 2013; Glodzik et al., 2013). Low CVR has been linked to diseases such as stroke (Markus and Cullinane, 2001; Silvestrini et al., 1996b; Webster et al., 1995), cerebral stenosis (Chang et al., 2009), proximal arterial occlusion (Ziyeh et al., 2005), hypertension (Iadecola and Davisson, 2017; Leoni et al., 2011) and other cerebral artery disorders. In these disease states, cerebral arteries and arterioles are often chronically and maximally dilated, exhausting the cerebrovascular reserve that is needed for compensatory increases in CBF.

Various neuroimaging methods have been used to measure CVR, which includes transcranial Doppler ultrasound (TCD) (Kleiser and Widder, 1992), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) (Ogasawara et al., 2003). Functional magnetic resonance imaging (fMRI) measurement of CVR is currently the most popular approach because MRI is non-invasive, has adequate spatial and temporal resolution and provides a whole-brain image. A summary comparison of extant CVR measurement methods is found in Table 1.

Various other methods have been used to induce CVR such as CO_2 inhalation (Lythgoe et al., 1999) and acetazolamide injection (Inoue et al., 2014); each of these methods has its advantages and disadvantages (Table 2). For example, injection of acetazolamide can be considered invasive, can elicit different responses in different individuals (i.e. genetic polymorphisms), and might not be appropriate in certain vulnerable groups such as children, elderly, and individuals with contraindications such as liver disease (Fierstra et al., 2013; Posner and Plum, 1960). Similarly, CO_2 inhalation with a mask can be uncomfortable, particularly within the MRI head coil, and CO_2 precipitates adverse psychological symptoms such as anxiety or panic in a meaningful subset of individuals (Sanderson and Wetzler, 1990; Van

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Table 1
Comparing CVR Measurement Methods.

CVR Measurement Methods Method	Advantages	Disadvantages
fMRI	· Non-invasive · Safe · Provides whole-brain scan at high spatial resolution · A structural scan can be acquired in the same session · Readily available	· Susceptible to movement and non-movement related artifacts · Moderately expensive · Subjects in a small enclosed space
Trancranial Doppler Ultrasound (TCD)	· Non-invasive · Safe · Cheaper than most alternatives · Most common method to measure CVR · Readily available	· Low spatial resolution · Can only measure large arteries
Positron Emission Tomography (PET)	· Provides whole-brain scan at high spatial resolution	· Invasive: requires administration of radioactive tracer or contrast agent · Most expensive method listed · Subjects in a small enclosed space · Less available
Single-photon emission computed tomography (SPECT)	· Provides a whole brain scan · Subject does not have to be in a small enclosed space · Can measure reactivity over longer periods (i.e. minutes vs. seconds)	· Invasive: requires administration of radioactive tracer or contrast agent · Moderately expensive · Lower spatial resolution compared to fMRI and PET · Less available

den Hout and Griez, 1984). In addition to the discomfort of the individual, these symptoms can confound the measurement of CVR. BH without a mask or nasal cannula, although less controlled and lacking the ability to measure delivered or expired gases, offers important advantages, particularly ease of implementation, non-invasiveness, and tolerability.

Importantly, studies find no significant differences in CVR obtained from CO_2 inhalation compared to BH methods (Kastrup et al., 2001; Tancredi and Hoge, 2013). Hyperventilation or paced deep breathing methods, although equally as feasible, leads to hypocapnia-associated vasoconstriction and could be less intuitive in measuring cerebral blood vessel function. An occluded blood vessel, which has exhausted vasodilatory reserve capacity, may show good hypocapnic-related reactivity whereas it could show poor hypercapnic reactivity (Bright et al., 2011).

An important limitation of BH protocols is participant-related variability in adherence to the protocol. Some patients may have difficulty following the instructions, leading them to perform BHs differently. For example, a patient may hold their breath after inspiring when they were instructed to expire, they may not be able to hold their breath for the time allotted, or may perform an unintended Valsalva maneuver that may confound the results (Wu et al., 2015). Furthermore, equal lengths of BH across subjects does not necessarily dictate that this will lead to equal increases in partial pressure levels of CO_2 in the blood.

There are a number of ways to quantify CVR with MRI. The most common method for measuring BH-induced CVR (BH-CVR) is using T2* weighted Blood Oxygenation Level-Dependent (BOLD) contrast fMRI. The BOLD signal exploits the inherent magnetic susceptibility differences between deoxyhemoglobin and oxyhemoglobin. Paramagnetic deoxyhemoglobin has a shorter T2* decay compared to diamagnetic oxyhemoglobin, yielding BOLD-related contrast (Ogawa et al., 1990).

The increase in BOLD signal following the onset of a BH is indicative of the capacity to vasodilate, i.e. CVR. BOLD time series signals are analyzed through statistical parametric mapping and thresholding these maps (e.g. a Z-score of ≥ 2.3 with a cluster correction). This procedure

Table 2
Comparing CVR Induction Methods.

Method	CVR Induction Methods Advantages	Disadvantages
Acetazolamide	· Can determine precise amount injected · Requires little subject adherence · Considered "gold-standard" for CVR induction	· Large variability in response between subject (Fierstra et al., 2013) · Invasive; requires intravenous administration · Drug interactions and contraindications · Common side effects include: paresthesias, hearing dysfunction, nausea, diarrhea (Kristinsson, 1967; Peralta et al., 1992; Reiss and Oles, 1996)
CO_2 Inhalation	· Can measure precise amount of gas delivered/expired · Less dependent on subject adherence	· Mask can be invasive and uncomfortable for patient · Fixed fraction amount of CO_2 inspired does not lead to equal $PaCO_2$ between and within subjects (Hoskins, 1990; Prisman et al., 2008) · Does not account for differences in ventilation rates (Baddeley et al., 2000) · May induce anxiety or panic (Sanderson and Wetzler, 1990; Van den Hout and Griez, 1984).
Breath-Hold	· Easy-to implement (does not require extra equipment) · Can use nasal cannula to measure end-tidal CO_2 · Safe · Shown to be equal to other CVR induction methods	· Adherence differences can influence results · If using nasal cannula, subjects must reliably breath out of the nose (lowers ease of implementation) (Bright and Murphy, 2013) · Equal breath-hold lengths do not necessarily result in fixed amounts of $PaCO_2$
Hyperventilation/Paced Deep Breathing	· Easy-to implement (does not require extra equipment) · Safe · Shown to be equal to other CVR induction methods	· Adherence differences can influence results · Provides hypocapnic-related CVR which has uncertain utility compared to hypercapnic CVR · Assuming the task is performed equality in all subjects, the method may not necessarily lead to equal levels of $PaCO_2$ · Could lead to movement-related artifacts