# Correction for Blood Pressure Improves Correlation between Cerebrovascular Reactivity Assessed by Breath Holding and 6% $CO_2$ Breathing

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*Background:* Changes in cerebral blood flow velocity to hypercapnia are associated with changes in systemic blood pressure (BP). These confounding BP-dependent changes in cerebral blood flow velocity cause misinterpretation of cerebrovascular reactivity (CVR) results. The objective of the study was to determine the relationship between CVR assessed by breath holding and 6% $CO_2$ breathing after correcting for BP-dependent changes in cerebral blood flow velocity. *Methods:* In 33 patients of uncomplicated type 2 diabetes mellitus, CVR was assessed as percentage changes in cerebral blood flow velocity and cerebrovascular conductance index. *Results:* Percentage change in cerebral blood flow velocity during breath holding was positively correlated with that of during 6% $CO_2$ breathing ($r = .35$; $P = .0448$). CVR during breath holding and 6% $CO_2$ breathing were better correlated when expressed as percentage changes in cerebrovascular conductance index ($r = .49$; $P = .0040$). Similarly, breath-holding test results expressed as percentage changes in cerebral blood flow velocity correctly identified only 37.5% of the poor reactors to 6% $CO_2$ breathing. However, when the breath-holding test results were expressed as percentage changes in cerebrovascular conductance index, 62.5% of the poor reactors to 6% $CO_2$ breathing were correctly identified indicating a better agreement between the test results obtained by the 2 methods. *Conclusion:* Cerebrovascular response to breath holding is better correlated with that of 6% $CO_2$ breathing when changes in cerebral blood flow velocity were corrected for associated changes in BP. **Key Words:** Cerebrovascular reactivity—breath holding—hypercapnia—breath-holding index—cerebrovascular conductance index.


## Introduction

Measurement of cerebral blood flow responses to altered partial pressure of $CO_2$ in the arterial blood has been widely used to assess cerebrovascular reactivity (CVR). Besides being used as a clinical and research tool to assess the functional reserve in cerebral vasculature, CVR measures have been shown to predict the risk of subsequent stroke in patients with carotid artery stenosis.[1,2]

Cerebral blood flow responses are commonly measured noninvasively using transcranial Doppler ultrasonography that reliably quantifies the changes in cerebral blood flow in terms of changes in flow velocities.[3,4] Alteration in the arterial partial pressure of $CO_2$ used for inducing cerebral blood flow responses is brought about by various methods including a 30-s breath hold, hyperventilation followed by rebreathing, or breathing of air enriched with $CO_2$ for a fixed duration of time.[5,6] Estimation of CVR by breath holding has been practiced

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as a simple, less cumbersome, and inexpensive alternative to the more technically challenging methods involving breathing of $CO_2$-enriched air.[5]

Estimation of CVR by measuring middle cerebral artery blood flow velocity (MCAV) to hypercapnic stimulus has been shown to be influenced by concurrent changes in systemic arterial blood pressure (ABP) which may result in the misinterpretation of CVR test results.[6,7] Multiple methods have been advocated including the estimation of CVR as changes in cerebrovascular conductance index (CVCi) that normalizes the changes in MCAV to the changes in perfusion pressure.[6,8] Changes in ABP are mostly because of hypercapnia-induced activation of sympathetic nervous system[6,8]; however, estimation of CVR by breath holding may also involve blood pressure (BP) changes induced by straining leading to "Valsalva"-like responses in ABP.[9] CVR assessed by breath-holding method has been reported to have poor long-term reproducibility,[10] which could be because of the differential BP responses at various time points of measurement and its influence on changes in MCAV.

It is clinically relevant to assess the correlation and agreement between CVR test results obtained by breath holding and more standard tests based on breathing of $CO_2$-enriched air before using it as a cheap and effective alternative to the conventional tests. CVR estimated by breath-holding method has been reported to correlate with that by breathing of $CO_2$-enriched air by a few studies in the past.[5,11,12] However, none of these studies had taken into account the influence of concurrent changes in ABP on the CVRs estimated. We hypothesized that the interpatient variability in the BP response to varying hypercapnic stimulus administered may affect the correlation in CVR determined by the 2 methods. The differences are likely to be more pronounced in patient groups with impaired autoregulation of cerebral blood flow to changes in ABP as is the case of type 2 diabetes mellitus (DM) patients.[13,14] The objective of the present study was to determine the relationship between CVRs estimated by breath holding and breathing of 6% $CO_2$ in patients with type 2 DM after correcting for ABP-induced changes in MCAV.

## Materials and Methods

The study was conducted in 33 patients of uncomplicated type 2 DM. The study was approved by the Ethics committee for research on human subjects, All India Institute of Medical Sciences, and all experimental procedures were performed after obtaining prior informed consent from the participants. Recruitment of patients was done from September 2010 to April 2012. The diagnosis of type 2 DM was done as per American Diabetes Association criteria. Male patients within the age range of 35-60 years were included in the study. After careful clinical and laboratory evaluation, patients diagnosed with various comorbidities including hypertension, ischemic heart disease, stroke, any acute or chronic respiratory disorder, tobacco use, and those with resting MCAV greater than 100 cm/s were excluded. This ensured the participation of a relatively homogenous group of patients who could safely perform 6% $CO_2$ breathing for CVR assessment. The study was approved by the ethics committee for research on human subjects, All India Institute of Medical Sciences, New Delhi (ref. no. IESC/T-249/2010).

### *Assessment of CVR*

The right middle cerebral artery (MCA) was insonated through the transtemporal window with a 2-MHz probe using the MultiDop T2 ultrasound machine (DWL Elektronische Systeme, Singen, Germany). The probe was positioned and stabilized using a head fixation band to record the mean MCA blood flow velocity (monitoring program QL software 2.5; DWL Elektronische Systeme). Beat-to-beat BP was noninvasively recorded by "volume clamp method" from right middle finger using Finometer (Finometer model 2; FMS, Amsterdam, The Netherlands).

CVR was assessed by 2 methods: first by steady-state technique of breathing of 6% $CO_2$[8,15] and then by breath holding for up to 30 seconds.[16,17] The patients rested in sitting position for 15 minutes with continuous monitoring of ABP, electrocardiogram, and MCAV to establish a baseline. The patients were then asked to breath the gas mixture (6% $CO_2$, 21% $O_2$, balanced by nitrogen), via Bain circuit (set at 2.5 times of their minute ventilation) for 2 minutes during which MCAV, ABP, and electrocardiogram signals were continuously acquired. After 15 minutes of rest breathing atmospheric air, subjects were asked to hold their breath for 30 seconds after normal inspiration. Subjects who were not able to hold their breath for 30 seconds held breath as long as they could, and the variability in the holding time was taken care by considering the changes in the MCAV and conductance values per unit time of apnea.

MCA blood flow velocities were quantified from the envelope of the spectral Doppler waveforms. Mean blood flow velocities were calculated by dividing the area under the curve of each velocity waveform by the time duration of the same waveform. In 6% $CO_2$ breathing protocol, maximum percentage change in MCAV with reference to baseline was calculated from the average of 8-12 (corresponding to 1 respiratory cycle) consecutive MCAV waveforms recorded following the attainment of plateau (indicating the attainment of a steady state) in the blood flow velocity response. Similarly, percentage change in MCAV during breath holding was computed from the average of MCAV waveforms recorded during the final 3 seconds of breath hold.[16] Breath-holding index (BHI) was calculated as percentage change in MCAV with reference to baseline divided by the duration of breath hold.