Clinical Note

Changes in Baseline Cerebral Blood Flow in Humans Do Not Influence Regional Cerebral Blood Flow Response to Photic Stimulation

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The effect of changes in baseline regional cerebral blood flow (rCBF) values on the cerebral blood flow response during neuronal activation was studied with functional magnetic resonance imaging (fMRI). Using a breath-holding challenge as a hypercapnic stimulus, rCBF alterations during photic stimulation under normo- and hypercapnia were determined in nine volunteers. With breath-holding, baseline rCBF in areas corresponding to the visual cortex significantly increased from 54 ± 5 ml/100 g/min to 85 ± 9 ml/100 g/min ($P < 0.001$). Despite this significant change in baseline flow values, the rCBF increase during visual stimulation was very similar under normo- and hypercapnic conditions (28 ± 8 ml/100 g/min versus 26 ± 8 ml/100 g/min, respectively). This study supports the notion that within wide physiologic variations, task-induced cerebral blood flow changes are independent of baseline rCBF values. J. Magn. Reson. Imaging 2000;12:757–762.

Index terms: rCBF; fMRI; normo- and hypercapnia; focal task activation; visual cortex

THE RELATIONSHIP BETWEEN the baseline cerebral blood flow (CBF) value and regional hemodynamic response to focal task activation has been previously investigated using ^{133}Xe inhalation (1) and positron emission tomography (PET) (2,3). However, it is still unclear whether the global CBF level and activation-induced regional cerebral blood flow (rCBF) changes are proportional or additive. More recently, Schmitz et al (4,5) reported that the sensitivity of focal task activation in chloralose-anesthetized and mechanically ventilated rats was marked altered by capnic preconditioning. This raises further questions about the complexity of the regulatory mechanisms associated with cerebral hemodynamic responses to vasoactive agents and focal brain stimulation. In addition to its fundamental scientific importance, understanding the relationship between the baseline flow and the rCBF change in a specific site resulting from a focal task activation can facilitate studies that require comparison among physiologic states, subjects, and groups.

Taking advantage of the elevated global CBF during a brief breath-holding (6–8), we investigated the relationship between the globally augmented CBF and rCBF response to photic stimulation using an arterial spin labeling technique based on the flow-sensitive alternating inversion recovery (FAIR) method. The vasomotor reaction to CO_2 is one of the intrinsic features of intact cerebral perfusion in the normal brain and can be used to regulate the global CBF level. CO_2 breathing is normally used for such a hypercapnic stress test. Its application to fMRI study requires the subjects to wear an MRI-compatible mask and a steady CO_2 supply.

Recent studies (6–8) have demonstrated that a brief breath-holding as short as 18 seconds is sufficient to result in significant global CBF elevation. Compared with the use of other vasoactive substances, the side effects and experimental difficulties are diminished to a minimum level in a breath-holding test.

MATERIALS AND METHODS

Nine healthy volunteers (males aged 20–36 years) were studied. All measurements were performed on a GE Signa 1.5-T echo-speed medical scanner (General Electric Medical Systems, Milwaukee, WI) equipped with an Echo-Speed gradient system. The maximum achievable gradient amplitude and slew rate were 22 mT/m and 120 T/m/sec, respectively. A custom made receiver-only birdcage coil with an elliptical cross section was used. The scanning procedure for each subject was as follows:

1. Sagittal localizer images acquired using a conventional gradient-recalled echo pulse sequence.
2. Three sets of FAIR fMRI measurements using a single-shot FAIR spiral pulse sequence with TE/TI/TR of 8/1200/3000 msec. For each set of FAIR measurements, four oblique slices with a slice

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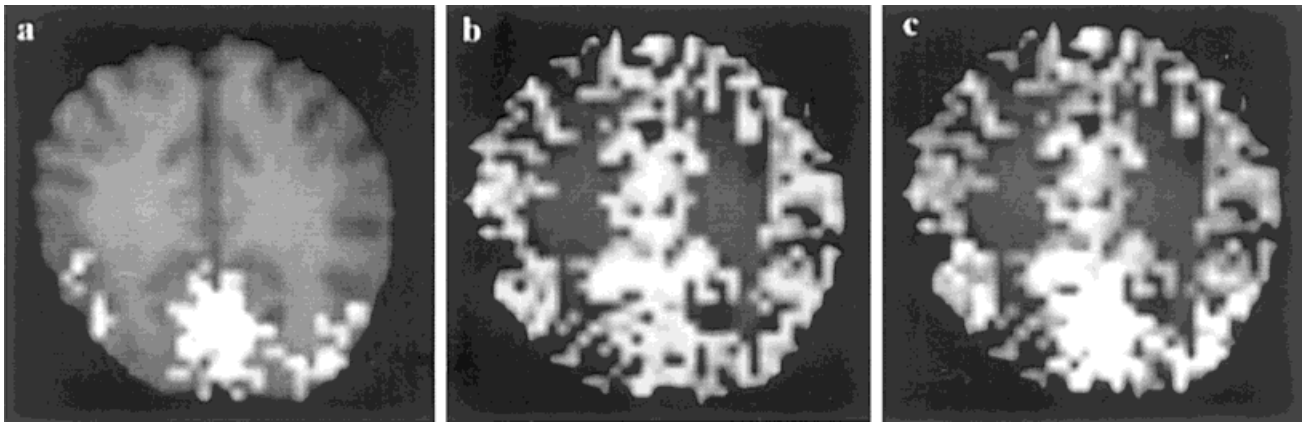

Figure 1. A representative set of FAIR activation map (grayscale *t*-score overlaid onto the anatomic image for the corresponding slice) identified by using Student's *t*-test statistics and cluster analysis to guarantee a significance level better than $P < 0.001$ and a minimum cluster size of 5 pixels. Significant rCBF increase was observed in the visual cortex during photic stimulation under normal breath (**a**, PS). A 30-second breath-holding induced rCBF increase in the entire cortical gray matter (**b**, BH). With simultaneous breath-holding and photic stimulation (BHPS), rCBF enhancement in the entire cortical gray matter was also detected. In addition to this global CBF elevation, rCBF increase in the visual cortex was further induced by the flashing checkerboard. Therefore, the significance level in the visual cortex is much higher (brighter) than other gray matter areas (**c**, BHPS).

thickness of 8 mm through the visual cortex were imaged in an interleaved fashion.

3. Fast T1 mapping of the same slices using a Look-Locker sequence with a single-shot spiral readout (9). The total scanning for T1 mapping was about 30 seconds. The designs of the spiral readout gradient waveforms (10,11) for FAIR fMRI and T1 mapping were identical. With a matrix size of 64 × 64 over a field of view of 220 × 220 mm^2, the corresponding readout window was 22.6 msec.

The activation paradigm consisted of 3 minutes of baseline data sampling followed by seven blocks of activation epochs alternating with resting periods. Both the activation and resting periods lasted 30 s. Three types of tests were investigated, viz., photic stimulation (PS) by viewing a black/white circular checkerboard flickering at 8 Hz, expiration breath-holding (BH), and simultaneous breath-holding and photic stimulation (BHPS). The start and stop of the activation were controlled by projecting the instructions into the magnet bore in front of the subject using a custom-built projection setup. During BHPS, the breath-holding was synchronized with the flashing checkerboard. All subjects were carefully instructed to perform expiration breath-holding. Care was also taken to reduce the possible bulk motion artifacts. The subjects were immobilized with foam padding to fill the space tightly between the head and the coil.

Motion artifact control was performed for each data set by subtracting consecutive time frames as a part of FAIR image processing. No observable bulk motion artifacts were detected in any of the data sets. FAIR images were calculated by magnitude subtraction of the nonselective inverted images from the selective inverted image; the temporal resolution of FAIR data was, therefore, 6 seconds per frame. All time series data were independently analyzed with Student's *t*-test statistics on a pixel-by-pixel basis. The statistical significance of the activation was assessed by *t*-score threshholding. After including a multiple comparison correction, use of a threshhold *t*-score > 3.2 guaranteed a significance of $P < 0.001$. A minimum cluster size of 5 pixels was also implemented to produce the final activation maps. This further reduces the number of false positive voxels. The mean time course was determined by taking average value of the signal intensities of all activated voxels. Time-locked averaging (12) of the mean time course was used to obtain the average dip-to-peak CBF change between activation and resting states.

The rCBF voxel values were evaluated from the FAIR data and T1 maps according to the procedure described previously (13). During simultaneous breath-holding and photic stimulation (BHPS), the CBF increase in the visual cortex was induced by the flashing checkerboard in addition to the global CBF elevation due to breath-holding. The total CBF increase in the visual cortex during BHPS was determined by using the activation map for photic stimulation under normal breathing as mask to define the region of interest. Kolmogorov-Smirnov statistics applicable to unbinned data sets were used to test the similarity between the CBF changes under normo- and hypercapnia.

Figure 2. The associated mean time courses of the relative rCBF changes in response to block trials of photic stimulation under normal breathing (PS), 30-second breath-holding following expiration (BH), and superimposing photic stimulation with breath-holding (PSBH). The sum of the disparate rCBF responses to photic stimulation (PS) and breath-holding (BH) is the same as the rCBF change induced by simultaneous breath-holding upon photic stimulation BHPS).

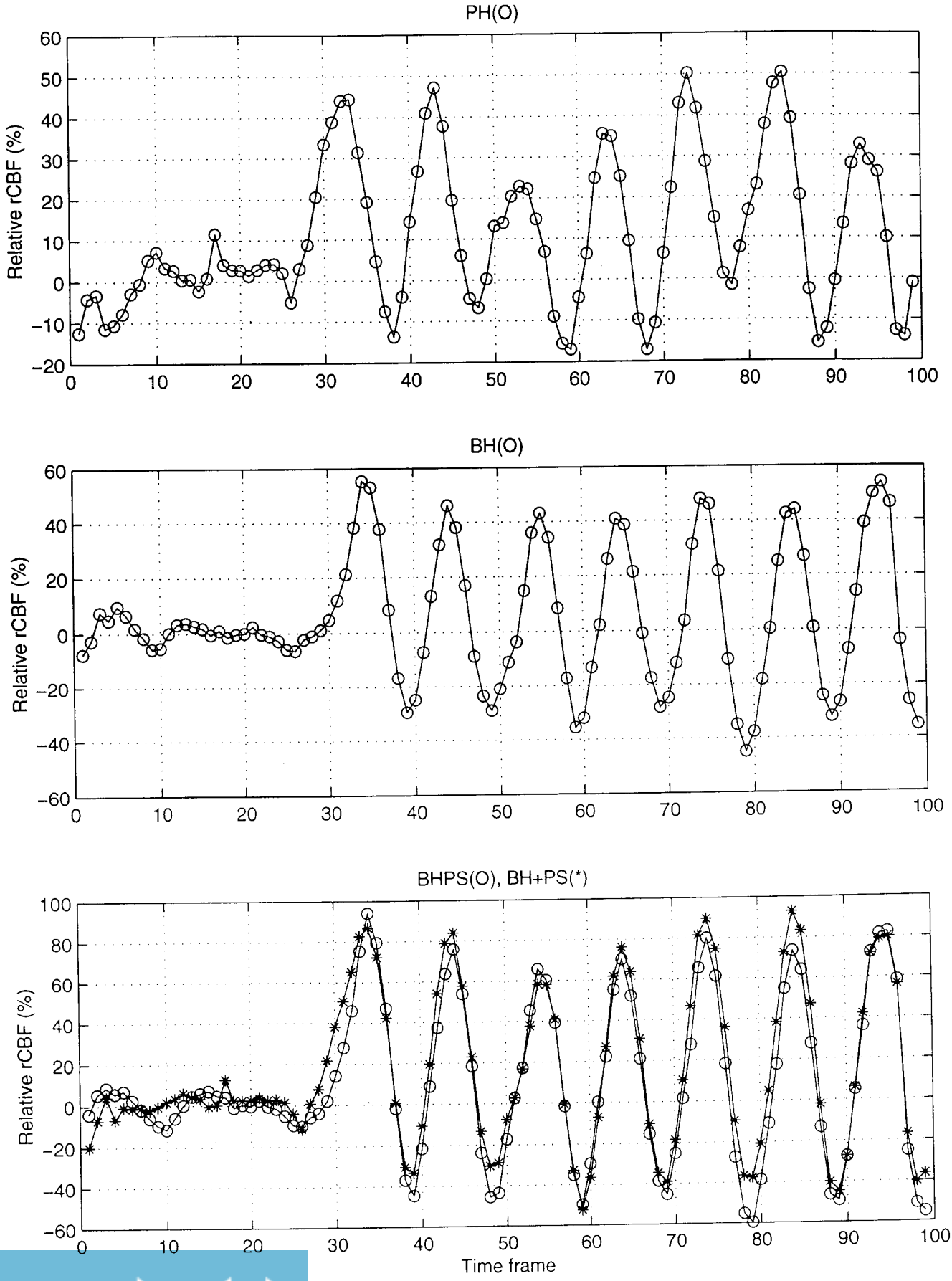

Figure 2.

Table 1
Baseline rCBF ± SD (ml/100 g/min) and Photic Stimulation-Induced ΔrCBF ± SD (ml/100 g/min) Under Normo- and Hypercapnia Conditions*

Subject no.	Normal breathing		Hypercapnia	
	rCBF	ΔrCBF	rCBF	ΔrCBF
1	46 ± 9	22 ± 5	70 ± 13	24 ± 6
2	52 ± 16	24 ± 4	84 ± 7	25 ± 5
3	62 ± 16	37 ± 6	84 ± 8	24 ± 6
4	51 ± 12	20 ± 8	91 ± 8	12 ± 6
5	55 ± 16	19 ± 6	101 ± 16	19 ± 8
6	54 ± 15	28 ± 7	79 ± 8	28 ± 5
7	61 ± 23	42 ± 7	91 ± 11	39 ± 12
8	60 ± 14	26 ± 9	84 ± 12	28 ± 8
9	51 ± 14	37 ± 13	80 ± 9	34 ± 6
Mean	54 ± 5	28 ± 8	85 ± 9	26 ± 8

*The regional cerebral blood flow change, ΔrCBF, under normal breathing was calculated as the average value of activated voxels in visual cortex. The baseline rCBF and the rCBF change induced by photic stimulation under hypercapnia were evaluated from the visual cortex area masked by the activation map under normal breath. The intrasubject standard deviation is the positive rCBF variance for all activated voxels in multiple slices. The photic stimulation-induced ΔrCBF values are peak-to-dip differences between activation and resting epochs.

RESULTS

A representative set of FAIR activation maps in one subject is shown in Fig. 1. Pertinent time courses from activated areas in Fig. 1 (in case of breath-holding only areas, corresponding to the visual cortex were used for the analysis) are depicted in Fig. 2. Repeated challenges of breath-holding induced an increase in rCBF, which was greatest in cortical gray matter and nonsignificant in white matter (Fig. 1b). During photic stimulation rCBF mainly increased in the gray matter along the calcarine fissure (Fig. 1a); however, the limited spatial resolution of the FAIR data did not allow further differentiation of the various visual areas. The absolute rCBF data for each subject and paradigm are summarized in Table 1. For the entire study population rCBF values during normal breathing in gray matter areas corresponding to the visual cortex were 54 ± 5 ml/100 g/min (range 46–62 ml/100 g/min). During a 30-second breath-holding after expiration, these values significantly increased by 31 ± 9 ml/100 g/min (range 22–46 ml/100 g/min) to 85 ± 9 ml/100 g/min (range 70&–101 ml/100 g/min)($P < 0.001$).

With simultaneous breath-holding and photic stimulation, the CBF increase in the visual cortex was induced by the flashing checkerboard in addition to the global CBF elevation due to breath-holding. As the *t*-score map shown in Fig. 1c, the significance level in the visual cortex are is much higher than in other gray matter areas. The absolute rCBF increase induced by visual stimulation was very similar ($P < 0.003$) under normo- and hypercapnic conditions (28 ± 8 ml/100 g/min during normal breathing versus 26 ± 8 ml/100 g/min during breath-holding). This indicates that the increase in rCBF during focal task activation was independent of the highly variable baseline rCBF values (Fig. 3 and Table 1).

DISCUSSION

With the development of various arterial spin tagging MRI techniques, fMRI has become an important tool to obtain CBF information during neural activation. In this study, the absolute rCBF changes during photic stimulation under normo- and hypercapnia conditions were determined using the FAIR technique. The baseline rCBF values of 54 ± 5 ml/100 g/min (range 46–62 ml/100 g/min) during normal breathing measured with the FAIR technique in this study are in good agreement with the gold standard PET reference value of 50 ml/100 g/min (14). Similarly, the average increase of rCBF during photic stimulation under normocapnia (28 ± 8 ml/100 g/min) is comparable with previous PET and fMRI studies, as shown by Fox et al (15) (27 ± 7 ml/100 g/min) and Kim et al (16) (31 ± 11 ml/100 g/min).

The most important finding in the present study was that the magnitude of the absolute rCBF increase during photic stimulation was very similar under normo- and hypercapnic conditions. While previous PET (2), Xe (1), and fMRI studies (17) based on CO_2 breathing produced similar findings, Shimosegawa et al (3) reported that the rCBF in the visual cortex was linearly dependent on baseline flow values (proportional model). Possibly, baseline flow values had already reached a maximum during CO_2 inhalation in the later study, limiting a further flow increase during functional activation. In support of this assumption, the highest baseline flow level was also associated with the smallest rCBF increase during visual stimulation in the present study. However, the exact point of exhaustion of the capacity for vasodilation and increase in CBF still remains to be defined in healthy volunteers. In an earlier study of our group (18), we demonstrated that local CBF changes during visual stimulation were independent of highly variable baseline flow values under normal condition. The results from this study indicate such independence also exists under hypercapnic conditions with higher baseline CBF. With graded hypercapnia measurement using CO_2 breathing, it should be possible to probe the ultimate capacity for vasodilation of the cerebral cortex.

From a physiologic standpoint, our results indicate that coupling of CBF to either neuronal activation or artery tension of CO_2 ($PaCO_2$) underlies two independent regulatory systems. Local changes in perfusion due to increased neuronal metabolism appear to occur automatically irrespective of already existing flow levels. With respect to the results of this study, the independence of metabolically and chemically mediated CBF changes might also be found under dynamic conditions.

The vasomotor response of the cerebral vasculature to CO_2 provides a practical method to regulate the baseline CBF level in the normal brain. CO_2 breathing is commonly used for such a hypercapnic stress test to map vascular reactivity. For fMRI study, an MRI-compatible mask must be used. Recent studies (6–8) on hemodynamic response to breath challenge using fMRI have shown that breath challenge is a reliable alternative approach to CO_2 inhalation. In this study the previously established breath-holding maneuver (6–8) was

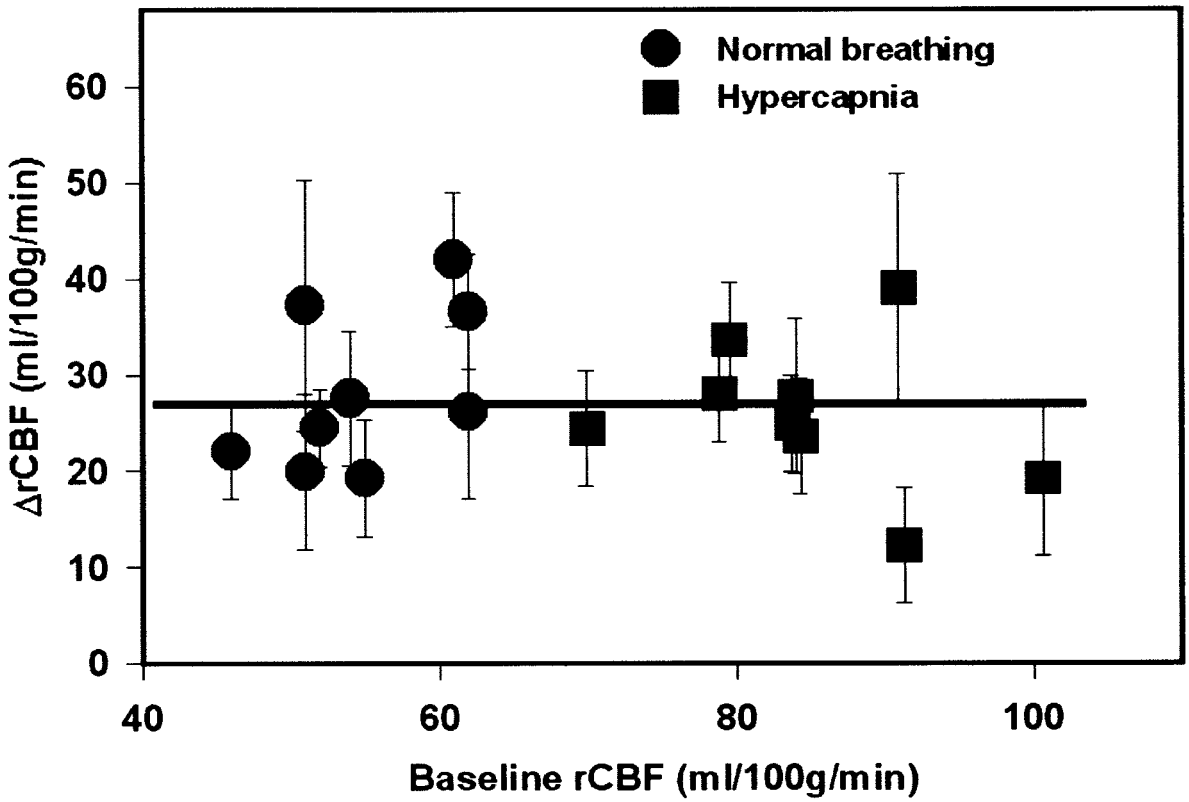

Figure 3. The absolute rCBF changes in visual cortex associated with photic stimulation as a function of the baseline CBF regulated by hypercapnia elicited by breath-holding after expiration. Despite the intersubject variability, the absolute rCBF increase induced by the same visual stimulation is statistically constant at different levels of baseline CBF regulated by respiration challenge.

used to alter baseline rCBF values. The observed global augmentation of CBF in gray matter during a repeated breath-holding of 30 seconds agrees very well with the results from previous studies (6–8). With the onset of breath-holding following expirations, CBF in gray matter was promptly elevated as a result of the rising $PaCO_2$. The major event associated with a brief breath-holding after expiration is hypercapnia (6–8). Although it is possible to change baseline CBF values with such a simple respiratory maneuver, potential shortcomings of this technique, especially with respect to the present results, should be noted. In contrast to CO_2 inhalation, changes in baseline flow values cannot be achieved to arbitrary levels during short periods of breath-holding.

CONCLUSIONS

The global augmentation of baseline CBF elicited by hypercapnic conditioning and rCBF response to focal task activation are physiologically independent. Regional CBF increases due to neuronal activation and hypercapnia combine additively. Since we only used a mild hypercapnic stress, future studies will have to clarify whether a point of exhaustion of CBF increase can be found and defined well in humans.

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