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Functional Cerebral Hyperemia Is Unaffected by Isovolemic Hemodilution

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Background: **The cerebral hyperemic effect of hemodilution is well known; however, its mechanism and potential modifying effect on the functional hyperemic response to neuronal activation are unclear. The authors investigated the effects of isovolemic hemodilution on vibrissal stimulation–induced changes in cerebrocortical laser Doppler flow and tissue oxygen tension in the rat.**

Methods: **The hyperemic response to whisker stimulation was assessed in the whisker barrel cortex of 12 rats anesthetized with chloralose–urethane before and after hemodilution. Graded, isovolemic hemodilution was performed by three repeated withdrawals of 3 ml blood with replacement of equal volume of 5% serum albumin. Measured systemic hematocrit values were 39.3 ± 1.3% (control), 29.5 ± 1.0%, 22.3 ± 1.5%, and 17.0 ± 1.6% (after the three hemodilution steps). Arterial blood pressure was maintained at control levels with an infusion of methoxamine. Unilateral whisker stimulation was performed with a mechanical actuator at 8 Hz, and 10 cycles of 10 s on–30 s off periods. In six control animals, shed blood was immediately reinfused, resulting in no change in hematocrit, and whisker stimulation was performed using the same timeline as in the other animals. In six additional experiments, resting cerebral cortical oxygen tension was measured using the phosphorescence quenching technique following the same hemodilution protocol.**

Results: **Graded hemodilution increased baseline laser Doppler flow by 5.5 ± 0.9%, 13 ± 1.6%, and 23.7 ± 2.2%. Vibrissal stimulation transiently increased laser Doppler flow by 17.0 ± 2.0%. The hyperemic response was unchanged after hemodilution and was identical to that seen in the control group in all conditions. Tissue oxygen tension increased slightly but significantly with hemodilution at a rate of 1.4 mmHg per 10% hematocrit change (r = 0.83). Mean arterial pressure, arterial oxygen tension, carbon dioxide tension, and *p*H were within normal limits in each experimental group and were not different from control during hemodilution.**

Conclusions: **The results suggest that an increase in baseline flow during hemodilution maintains cortical oxygen supply and consequently preserves the normal functional hyperemic response.**

THE brain's exclusive dependence on glucose oxidation and its inability to store oxygen and glucose as metabolic substrates necessitates a tight control system for cerebral blood flow as a function of neuronal activity and metabolism. Neuronal activation is coupled to an increase in regional cerebral blood flow within seconds, and the hyperemia is maintained as long as the neuronal activity stays enhanced. As the supply and transport rate of glucose exceed the replacement demand, the hyperemia is postulated to subserve the need to satisfy an increased demand for oxygen in the activated cerebral region. Why the hypermetabolism may be smaller than the relative increase in blood flow[1] remains a paradox. Clues to solve this problem may be provided by paradigms in which the oxygen transport capacity of blood is experimentally altered before neuronal activation to reveal an effect of the former on the magnitude of the resulting blood flow response. A straightforward and frequently applied clinical maneuver to change blood oxygen-carrying capacity is hemodilution.

It is well known that hemodilution, especially isovolemic hemodilution, produces marked increases in cerebral blood flow in both humans and experimental animals.[2–4] Isovolemic hemodilution is believed to enhance oxygen and glucose delivery to the brain of anemic patients.[5,6] Based on the consistent increase in flow (the hyperemic response), hemodilution has been considered useful in the treatment of cerebral ischemia induced by stroke or in the prevention of vasospasm after subarachnoid hemorrhage.[7] It is unclear, however, whether hemodilution with its consequent hyperemic effect may influence the capacity of the cerebral circulation to respond to additional functional stimuli provided by endogenous or exogenous neuronal activation.

To investigate this question, we measured the changes in laser Doppler flow (LDF) in the rat whisker barrel cortex at rest and during whisker stimulation at graded levels of isovolemic hemodilution. Mechanical stimulation of the facial vibrissae result in consistent neuronal activation and localized functional hyperemia of the corresponding area of the somatosensory cortex and has been widely used in various rodent species.[8–13]

For further insight, we measured intracortical tissue oxygen tension (Po_2) that directly reflects the status of cerebral tissue oxygen supply in control and hemodiluted conditions. We hypothesized that an acute reduction in arterial hematocrit will interfere with normal cerebral oxygen supply and therefore enhance the hyperemic response to neuronal activation. Alternatively, if moderate hemodilution increased oxygen delivery, then an attenuation of the functional response will be seen. Finally, during severe hemodilution, profound hyperemia will prevent further increases in flow during neuronal activation.

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Materials and Methods

Animal Preparation

This study was approved by the Institutional Animal Care Committee of the Medical College of Wisconsin. Eighteen male Sprague-Dawley rats weighing 250–350 g were used. During surgery, the animals were anesthetized with 1.5–2.0% halothane in 30% O_2–70% N_2, tracheotomized, paralyzed with gallamine (80 mg administered intraperitoneally), and artificially ventilated. Femoral arterial and venous lines were placed for the measurement of arterial blood pressure, for arterial blood samples, blood withdrawal, and for the infusion of drugs. After surgery, halothane administration was discontinued, and anesthesia was maintained with the mixture of urethane (50 mg/ml) and α-chloralose (5 mg/ml) infused at a rate of 3–4 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} during experiments. Arterial blood pressure, end-tidal carbon dioxide, and inspired oxygen concentration were continuously monitored (POET II; Criticare Systems, Waukesha, WI). The rate and volume of ventilation were adjusted to maintain the end-tidal carbon dioxide at 35 mmHg, adjusted if necessary according to the arterial blood gas value.

Laser Doppler Flow and Oxygen Tension Measurement

The animal's head was secured in a 30° rotational stereotaxic apparatus. Three translucent cranial windows were prepared for the measurement of LDF, Po_2, and temperature, respectively. The skull was thinned to translucency over the left somatosensory cortex using a dental drill. During the drilling, the bone temperature was maintained with cool saline to avoid tissue heating. An LDF probe (Oxford Array; Oxford Optronix, Oxford, United Kingdom) was stereotaxically positioned over left somatosensory cortex (2.5 mm caudal and 6.5 mm lateral to bregma), and the position was further adjusted until a maximum flow response was seen after whisker stimulation. For the measurement of intracortical oxygen pressure, in separate animals (n = 6), a fiberoptic sensor (OxyLite; Oxford Optronix) was inserted using a micromanipulator into the parietal cerebral cortex to 1 mm depth. LDF was measured as before, using the cortical surface probe, in close proximity to the Po_2 sensor. Brain temperature was monitored through the third window in the contralateral hemisphere. For Po_2 and temperature measurements, the remaining bone membrane and underlying dura were slit open before probe insertion.

The principle of tissue Po_2 determination is based on the measurement of decay times of the fluorescence of ruthenium molecules. The fluorescence decay time, measured in microseconds, varies inversely with the local tissue oxygen. The fluorescent molecules are encased in an insertable probe of 300 μm diameter, attached to a light guide of 200 μm diameter. The Po_2 probes are individually precalibrated by the manufacturer, and the calibration details are provided with each probe. Before their use, the calibration data are entered into the signal-processing unit.

Whisker Stimulation

The right vibrissae were cut to a length of approximately 3 cm from the face and fitted through a mesh screen connected to a galvano-mechanically actuated arm. The screen was positioned approximately 1 cm from the rat's face, making sure that no facial hair was in contact with the mesh screen during stimulation. The screen was moved in the fronto-caudal direction, and the maximum displacement was 3 cm. The stimulator was controlled with a timing circuit and set for 10 s on, 30 s off trains, at frequency of 8 Hz and repeated 10 times in each run. The stimulation was performed before and 5 min after each hemodilution step.

Hemodilution Protocol

Graded, isovolemic hemodilution was performed in 12 animals by three consecutive withdrawals of 3 ml of arterial blood and immediately replaced by the same volume of 5% serum albumin. In the control group (n = 6), the shed blood was reinfused instead of serum albumin, resulting in no change in arterial hematocrit. A sample of 500 μl blood from that withdrawn at each of the three hemodilution steps was used for blood gas–hematocrit determinations. Before the beginning of the hemodilution protocol, heparin (400 units) was injected through the arterial line subsequently used for blood withdrawal. The inside walls of the plastic syringe used to collect the shed blood were precoated with heparin. For retransfusion, the shed blood was kept warm at 37°C. Methoxamine, an α_1-selective adrenergic agonist, was infused to maintain mean arterial blood pressure at baseline level. The rate of infusion was adjusted as needed in the range of 1–15 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}. In most experiments, methoxamine infusion was necessary at the most severe hemodilution step only. Specific α_1 agonists exert no direct effect on the cerebral vasculature.[14]

Data Analysis

Baseline LDF was determined from the average of data points sampled during a 10-s period before whisker stimulation. LDF data during stimulation were taken from a 5-s period with a 3-s delay after the onset of stimulation. All LDF data were expressed in percent of control baseline LDF in each animal. The percent LDF response was then calculated as the difference between prestimulation and stimulation LDF values and averaged (mean ± SEM; n = 6) across all 10 stimulation cycles. Intracortical Po_2 values were obtained in physical units of millimeters of mercury and presented as mean ± SEM

Table 1. Physiologic Parameters in Three Experimental Groups

	Baseline	Step 1	Step 2	Step 3
Hemodilution LDF group				
Hct	39.3 ± 1.3	29.5 ± 1.0	22.3 ± 1.5	17.0 ± 1.6
MAP	117 ± 6	113 ± 6	113 ± 6	109 ± 4
Pa_{O_2}	146 ± 12	160 ± 6	159 ± 6	150 ± 7
Pa_{CO_2}	36.4 ± 3.4	34.1 ± 1.4	34.2 ± 1.0	35.9 ± 1.3
pH	7.40 ± 0.05	7.40 ± 0.01	7.40 ± 0.01	7.35 ± 0.01
Control LDF group				
Hct	42.3 ± 1.3	41.8 ± 1.2	40.8 ± 1.3	40.3 ± 1.6
MAP	118 ± 5	118 ± 4	118 ± 5	114 ± 4
Pa_{O_2}	151 ± 5	150 ± 3	145 ± 9	151 ± 11
Pa_{CO_2}	34.7 ± 1.5	34.0 ± 1.4	34.5 ± 1.8	34.5 ± 1.8
pH	7.40 ± 0.01	7.40 ± 0.02	7.37 ± 0.02	7.38 ± 0.02
Hemodilution P_{O_2} group				
Hct	42.6 ± 1.6	35.5 ± 1.7	25.9 ± 1.5	18.7 ± 1.5
MAP	122 ± 5	122 ± 5	119 ± 6	118 ± 8
Pa_{O_2}	124 ± 8	123 ± 7	125 ± 8	131 ± 10
Pa_{CO_2}	34.6 ± 1.1	34.8 ± 1.3	35.1 ± 0.9	34.8 ± 1.3
pH	7.43 ± 0.03	7.39 ± 0.02	7.37 ± 0.02	7.34 ± 0.02

LDF = laser Doppler flow; Hct = arterial hematocrit (%); MAP = mean arterial pressure (mmHg); Pa_{O_2} = arterial oxygen pressure (mmHg); Pa_{CO_2} = arterial carbon dioxide pressure (mmHg).

(n = 6). Statistical analysis of baseline LDF changes was determined with repeated-measures analysis of variance with the stimulation train (control and hemodiluted) as within factors. Linear regression was performed using statistics software NCSS 2000 (NCSS, Inc., Kaysville, UT), which provides significance values for the regression coefficients. A P value < 0.05 was chosen as significant throughout.

Results

Physiologic Data

All physiologic variables, except by design hematocrit, were stable during the experiments (table 1). In particular, with the use of methoxamine infusion, baseline mean arterial pressure levels were maintained at all levels of hemodilution. Importantly, no decrease in arterial P_{O_2} occurred, thus avoiding hypoxemia.

Effects of Hemodilution on Resting and Whisker Stimulation–Induced Laser Doppler Flow Responses

Basal LDF increased progressively by 5.5 ± 0.9%, 13.0 ± 1.6%, and 23.7 ± 2.2% after the three dilution steps, respectively (fig. 1). The absolute baseline LDF in control and three hemodilution levels were, respectively, 625 ± 59, 659 ± 64, 718 ± 68, and 794 ± 87 perfusion units. Whisker stimulation produced a transient LDF increase of 16.9 ± 2.0%. Hemodilution did not alter the LDF response to whisker stimulation (fig. 2). As shown in table 2, the average LDF responses were identical at all hemodilution steps. In the control group, which had no change in hematocrit, the LDF responses were identical to that seen in the hemodiluted group and showed no change after repeated blood withdrawal–reinfusion maneuvers.

Effects of Hemodilution on Cerebral Oxygen Tension Levels

Baseline intracortical P_{O_2} was measured in an additional group of subjects. Resting levels of 15.5 ± 1.5 mmHg P_{O_2} increased during hemodilution to 16.8 ± 1.6, 17.5 ± 1.6, and 19.4 ± 1.8 mmHg at the three dilution steps, respectively (fig. 3). Additional normalization of the P_{O_2} data was performed to reduce animal-to-animal variance and facilitate regression analysis. The mean P_{O_2} values from all hematocrit levels in each animal were averaged to obtain one mean P_{O_2} value per animal. The deviations of mean P_{O_2} in each animal from a grand mean from all data were subtracted from the

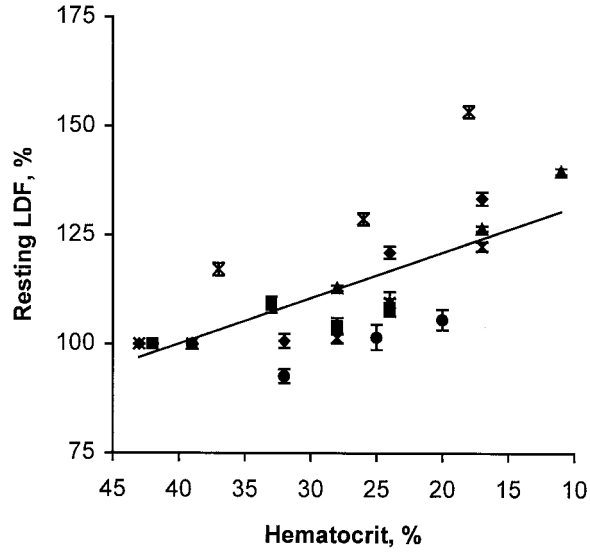

Fig. 1. Effect of isovolemic hemodilution on resting cerebrocortical laser Doppler flow (LDF). Different symbols correspond to different experiments. Resting LDF increases significantly with a decrease in arterial hematocrit. Line shows linear regression to all data (r^2 = 0.678).

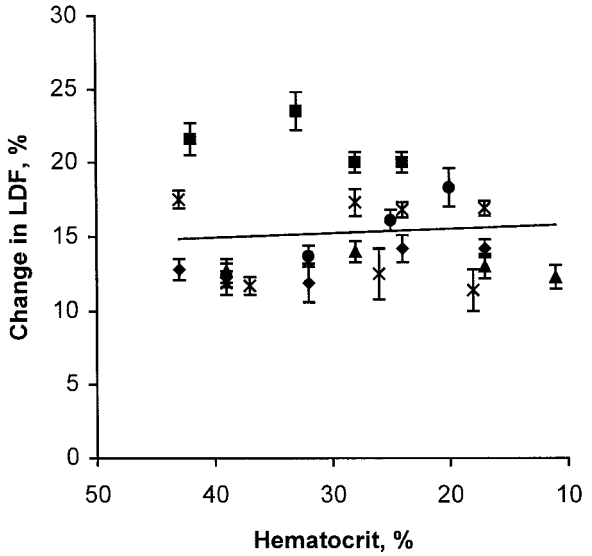

Fig. 2. Effect of isovolemic hemodilution on the whisker stimulation–induced response of cortical laser Doppler flow (LDF). LDF data (mean ± SEM) are expressed in percent of control baseline values in each animal. Different symbols indicate data from different experiments. The cerebrocortical hyperemic response to whisker stimulation was unchanged after hemodilution. Linear regression: $r^2 = 0.051$.

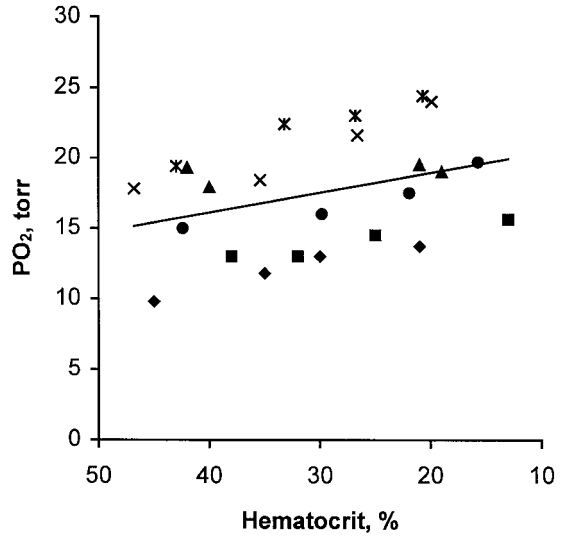

Fig. 3. Effect of isovolemic hemodilution on cerebrocortical tissue oxygen tension (P_{O_2}) in six rats. The increase in P_{O_2} with decreasing hematocrit is statistically significant. Linear regression: $r^2 = 0.689$.

measured P_{O_2} values in each animal. Linear regression revealed a P_{O_2} change of 1.4 mmHg per 10% hematocrit change with correlation coefficient of $r = 0.83$, confirming the small but significant ($P < 0.001$) increase in cerebral tissue P_{O_2} during hemodilution.

Discussion

The major findings of this study are that isovolemic hemodilution significantly increased resting LDF but did not alter the functional hyperemic response to whisker stimulation. In addition, hemodilution did not reduce cortical tissue P_{O_2}; rather, a small but consistent increase in tissue P_{O_2} was produced. These results demonstrate that acute reductions in arterial hematocrit to levels as low as 17% are hemodynamically compensated by increasing resting LDF such that cerebral oxygen transport is maintained and the neuronal activity–flow coupling is preserved.

Table 2. Cerebrocortical Hyperemic Response to Whisker Stimulation in Two Experimental Groups

	Baseline	Step 1	Step 2	Step 3
Hemodilution group				
Hct	39.3 ± 1.3	29.5 ± 1.0	22.3 ± 1.5	17.0 ± 1.6
LDF change	17.0 ± 2.0	17.0 ± 1.9	17.0 ± 1.5	16.0 ± 1.7
Control group				
Hct	42.3 ± 1.3	41.8 ± 1.2	40.8 ± 1.3	40.3 ± 1.6
LDF change	17.0 ± 1.7	17.9 ± 2.1	18.3 ± 2.2	17.1 ± 1.6

Hct = arterial hematocrit; LDF = laser Doppler flow (%).

Effect of Hemodilution on Resting Laser Doppler Flow

Consistent with the well-established phenomenon of hemodilution-induced cerebral hyperemia, we observed that cortical LDF progressively increased with the reduction of arterial hematocrit. The observed increase in LDF, reaching approximately 25% on average, was small compared with that reported in other studies.[4,15–19] It should be emphasized that LDF measures the perfusion rate of erythrocytes, not of whole blood. In LDF, the frequency of monochromatic laser light is Doppler-shifted by moving erythrocytes in the microcirculation, which results in widening of the detected light spectrum. Weighted by the fraction of back-scattered Doppler-shifted light that reflects the concentration of moving erythrocytes, the volumetric perfusion rate of erythrocytes is derived. Thus, when arterial hematocrit is reduced, LDF may show smaller changes in flow than do most other techniques that measure plasma flow or whole blood flow. A deviation between the changes in LDF and in blood flow measured by the hydrogen clearance technique in severe hemodilution has been reported by Kramer *et al.*[20]

The fact that LDF reflects erythrocyte perfusion should not be viewed as a technical limitation, but, rather, as an advantage in that LDF reflects convective oxygen transport to cerebral tissue more closely than does whole blood flow. Thus, because arterial P_{O_2} was unchanged during hemodilution, the resting LDF data in this study predict progressively improved tissue oxygenation with reduced arterial hematocrit.

It is also important to note that in the current rat experiments, mean arterial blood pressure was maintained even at the lowest levels of arterial hematocrit. This is critical because, should blood pressure decrease during severe hemodilution, the increase in flow may be

reduced or obliterated, as we observed in preliminary studies and as reported by other investigators.[21] Rodents are generally more sensitive than larger mammals to hypoxemia and anemia with respect to their cardiovascular stability. Thus, blood pressure support is important for the full hyperemic effect of hemodilution in this species.

Effect of Hemodilution on Resting Cortical Tissue Oxygen Tension

Consistent with the observed change in resting LDF, cortical tissue Po_2 increased, although modestly, during hemodilution. This trend was evident even as mean arterial hematocrit decreased as low as 17%, suggesting that the so-called "optimum" hematocrit is definitely lower than the generally assumed value of 30%.[3] This finding is consistent with the observations of Bauer *et al.*,[22] who demonstrated that neuronal function and high-energy phosphates in the brain were preserved at a systemic hematocrit of 6.1%. Ulatowski *et al.*[19] concluded that oxygen transport in the brain is well regulated and independent of alterations in systemic hematocrit. How can tissue Po_2 be upheld despite such a dramatic reduction in arterial hematocrit? As previously discussed, our LDF data indicate an enhanced erythrocyte perfusion rate in the microcirculation, suggesting that cerebral microvascular hematocrit is unaffected by a change in systemic hematocrit. Recently, in an intravital microscopic study of the cerebral microcirculation, we demonstrated that the linear density of erythrocytes in cerebrocortical capillaries remained independent of arterial hematocrit as low as 15%.[3] In fact, both velocity and perfusion rate by erythrocytes increased with hemodilution in the capillary network. Rheological mechanisms that augment the rate of entry of erythrocytes into capillaries may contribute to this effect.[23]

The current Po_2 data have some further implications regarding the possible mechanism of hemodilution-induced hyperemia. Hemodilution reduces both blood viscosity and oxygen content, and either or both may contribute to the hyperemia. A long-standing question has been which of these two factors plays the primary role. The importance of reduced viscosity is supported by data on pial artery diameter and vascular resistance.[24,25] On the other hand, blood exchange with oxygen carrier solutions suggests an important role for blood oxygen content.[18,26,27] Because arterial Po_2 remained normal during hemodilution, it could not provide an error signal to maintain steady state hyperemia. It is then difficult to see by what cellular mechanisms a change in oxygen content could be sensed in the absence of a change in Po_2. Furthermore, because tissue Po_2 is not reduced, the role for a metabolic signal is unlikely. A recent study by Tomiyama *et al.*,[17] demonstrating the absence of an effect of the adenosine triphosphate–regulated potassium channel antagonist glibenclamide on the cerebral hyperemic response to hemodilution, suggested that the latter was not mediated by a hypoxic signal. Taken together, is seems likely that both blood viscosity and intravascular oxygen affect cerebral perfusion in such a way that reduced viscosity augments and increased Po_2 attenuates the hyperemic effect.

Effects of Hemodilution on Functional Hyperemia

Whisker stimulation in the rodent is a well-established model of functional cerebral hyperemia of the somatosensory barrel cortex.[8,9] The mechanism of functional hyperemia has not been fully elucidated. In essence, two major theories prevail; the original metabolic theory introduced by Roy and Sherrington[28] and the direct neuronal theory.[10,29] The latter hypothesizes cerebral vasodilation coupled directly to a change in neuronal activity, whereas the former would rely on an intermediate metabolic signal. Various mediators have been proposed to play a role in the coupling of neuronal activity to regional cerebral blood flow, including K^+,[30] H^+,[31] adenosine,[11,32] and nitric oxide.[12,33] The degree to which functional hyperemia depends on an increase in oxidative *versus* anaerobic metabolism remains controversial.[1,13,34] Regardless of the exact mechanism, the assumption that some increase in neuronal metabolic need during enhanced neuronal activity is plausible, and that neuronal activation may depend critically on the preservation of functional hyperemia to increase the supply of substrate, particularly oxygen and glucose.

At the outset of this study, we hypothesized that an acute reduction of the oxygen-carrying capacity of arterial blood by isovolemic hemodilution would interfere with cerebral oxygen supply and would therefore bring about a greater-than-normal increase in cerebral perfusion during neuronal activation. However, in light of our findings of enhanced erythrocyte perfusion and maintained cortical Po_2, it is not surprising that functional hyperemia failed to increase after hemodilution. Because the Po_2 measurements were performed after the whisker stimulation study was complete, we did not anticipate the absent effect of hemodilution on functional hyperemia. Thus, from the current data it may be concluded that after hemodilution, the normalization of basal cerebral oxygen supply, with an enhancement of erythrocyte perfusion, leaves the functional hyperemic response unchanged. This interpretation is consistent with the view that microvascular or tissue oxygen may influence the magnitude of the hyperemic response. Because the latter remains nearly constant during hemodilution, a normal increase in erythrocyte perfusion during neuronal activation is sufficient to satisfy the supposed increase in metabolic demand. If, alternatively, the hyperemic response does not depend on oxygen delivery and oxygen metabolism, as Wolf *et al.*[13] suggest, but on other factors, then these results can be simply taken to indicate that an acute increase in baseline perfusion produced by

the hemodilution maneuver does not interfere with the coupling mechanism of functional hyperemia.

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