


Brain Microvascular Hemodynamic Responses to Induced Seizures

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SUMMARY Arteriolar diameters and venular erythrocyte velocities in the small pial vessels on the surface of the cat brain were measured by TV methods during induced epileptic seizures through a cranial window. Grand mal seizures maximally dilated arterioles and increased venular erythrocyte velocity up to 400%. High positive correlation existed between changes in CSF hydrogen ion concentration and pial arteriolar diameter, suggesting metabolic regulation of CBF through CSF/interstitial fluid hydrogen ion alterations during the seizure.

IN BOTH IDIOPATHIC and symptomatic epilepsy, which is manifested as generalized seizures without focal onset or partial or focal seizures with generalization, consciousness is lost at the onset and apnea may develop secondary to tonic contraction of the respiratory muscles. The ability of the cerebral circulation to meet the increased metabolic demands imposed by the seizure, especially in the presence of apnea, is important clinically and has been extensively researched since the late 1930s. Until the elaborate studies by Plum et al. the answer to this question was not clear, since conflicting results of earlier investigations could not be resolved due to significant differences in experimental design. Plum's group, basing their conclusions in part on jugular venous outflow increases of twofold to fourfold and constant metabolite levels in sampled arterial and venous blood, has indicated that the metabolic demand is met in the idealized case where there is no muscular involvement in the seizure and apnea does not occur. However, the mechanisms by which the cerebral microvasculature reacts to the sudden increase in metabolism accompanying seizures have not been clearly demonstrated or completely explored in these investigations.

Various autoregulatory and vascular control mechanisms exist which have been shown to have differing degrees of influence on control of cerebral circulation in physiological and pathological states. These mechanisms may be classified in three major groups: (a) Bayliss or myogenic control — increasing arterial pressure causes an intrinsic and compensatory decrease in vascular diameter to maintain flow constant as if vascular smooth muscle tension was regulated, (b) neurogenic control — centrally mediated sympathetic and parasympathetic influences on vascular smooth muscle act to control arterial diameter in response to autonomic influences, and (c) metabolic control — products of metabolism act directly or indirectly on vascular smooth muscle to change arterial diameter and thus alter flow to maintain a constant metabolic environment around the microvasculature. The percentage contribution of these autoregulatory/control mechanisms is debated, but it is generally agreed that the vascular response to CO2 accumulation is the dominant control factor with the myogenic effect exerting a lesser influence in physiological states and the neurogenic contribution being of least magnitude. While the intense cerebrovascular effects of metabolites are well known and have been hypothetically presented as a mechanism of vasodilatation during the ictus, no direct evidence has been presented to elucidate the role of metabolites and therefore pH in microvascular control during the ictus. Similarly, no attempts have been made to separate these metabolic effects from blood pressure effects. Plum's group presented data indicating that the increase in cerebral blood flow (CBF), measured by techniques which only yield average values over extended time intervals, can be accounted for by a corresponding increase in systemic pressure, suggesting that cerebral autoregulation might be suspended in these circumstances. In order to study these effects, we developed a method for quantifying cerebrospinal fluid (CSF) pH and pial microvascular hemodynamic responses to induced seizures in the cat at constant systemic pressure, believing that the increase in blood flow in the absence of systemic pressure changes must ultimately be a consequence of substantial readjustments in the brain microvasculature.

Methods

The method for quantifying brain electricographic and circulatory hemodynamic events in a physiologically viable exposed cortex is based on the implantation of skull screws for recording the electrocorticogram (ECoG) and the substitu-

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tion of a 1-cm² plexiglass window for the calvarium over the left frontocentral cortex. The insertion of a Forbes window\(^1\) maintains a hermetically sealed brain, thus eliminating arterial-related and respiratory-related movements of the cortex which complicate microscopic observation of that surface while also allowing the animal's own CSF to peruse the cortex and fill the space between the window and pial vessels. Inflow and outflow tubes at the edge of the window permit in vivo monitoring of CSF pH and extraction of CSF from beneath the window for precision micropetite pH determinations. Magnification (400X) of the pial vessels is obtained by a combination of microscope objective magnification and video image enlargement, the microscope field being detected and transformed to an electronic waveform by a silicon-diode-matrix vidicon which is presented as a TV image (fig. 1). The resultant electronic representation of the pial vasculature was used for hemodynamic analysis. Arteriolar diameters were quantified and dynamically tracked by a video-dimension-analyzer\(^12\) while erythrocyte velocities were determined in venules by continuously extracting and cross-correlating upstream and downstream photometric signatures of flowing erythrocytes.\(^13\) Maximum cross-correlation corresponds to the most probable erythrocyte transient time between two known points in the vessel and hence is a measure of velocity. Since venule vessels are usually constant in diameter, velocity determinations are a direct measure of local blood flow.

In ten curarized cats, electrographic grand mal seizures were precipitated by repetitive auditory stimulation during either brain-equilibrated 3.5% to 4.0% inspired enflurane or intravenous injection of pentylenetetrazol one hour after general surgical anesthesia had been replaced by topical benzocaine. Vascular responses were observed during \(\beta\)-adrenergic blockade (three cats) to eliminate the neurogenic component of vasodilatation. \(\text{CO}_2\) end-tidal concentrations were held constant by controlling respiratory rate and depth. No special attempt was made to control respiratory rate and depth. Recent data supported by the work of Stromberg and Fox,\(^14\) who reported that pial arterial blood pressure varied systematically with changes in systemic blood pressure, and Shapiro et al.,\(^15\) who quantified the pressure drop in various segments of the cerebral circulation.

Increases in venular erythrocyte velocity, a manifestation of increased CBF secondary to increased cerebral arteriolar diameters or increased perfusion pressure (or both), were observed during seizures. Figure 4 shows a fourfold increase in erythrocyte velocity in a constant-diameter 35-\(\mu\) venule recorded during a seizure at constant systemic arterial pressure. Erythrocyte velocity began to increase during the early tonic phase of the seizure, reached maximum velocity during the period of postictal electrical depression, and slowly returned to the preictal value within 60 seconds after spontaneous cerebral electrical activity reappeared.

Correlation of venular velocity and arteriolar diameter responses to these seizures was 0.905 with increases in arte-
riolar diameter at constant pressure being directly related to increased venular velocity. Such high positive correlation suggests that under these experimental conditions venular erythrocyte velocity measurement is a qualitatively accurate reflection of changes in flow.

Before these hemodynamic results were correlated to CSF pH changes it was wondered whether the complete seizure process or just the increase in cerebral electrical activity that accompanied the seizure was responsible for the compensatory vascular reactions. Figure 5 reports the results of a test to determine the answer to this question. In this test, cortical spiking was driven by repetitive auditory stimulation during subconvulsive concentrations of enflurane to increase cerebral electrical activity but to avoid creating a seizure. Up to threefold increases in velocity were observed in venules that were highly correlated to the increase in electrical activity. A noticeable increase in velocity was observed after ten stimuli which reached an apex shortly after stimulation was stopped and cerebral activity was quiescent, and which then returned to pre-stimuli values within 30 seconds after spontaneous cerebral activity returned (fig. 5). This response was consistent with the macroscopic investigations of Mchedlishvili et al., who reported a 45% increase in regional cerebral blood flow related to spike activity induced by local cortical application of 0.5% strychnine, and others, who correlated changes in EEG frequency to regional CBF.

The extracellular fluid which surrounds cerebral arterioles need not necessarily be CSF. In fact, changes in CSF pH may lag behind local pH changes in other extracellular fluid because much of the CSF is not in direct contact with cerebral arterioles. Nevertheless, CSF pH was measured as the metabolic variable because the pH of this fluid was simpler to determine than the pH of the extracellular fluid and because it was the fluid under the window which could be continuously analyzed and was in close contact with the observed pial arterioles.

Enflurane-induced or pentylentetrazol-induced electrographic grand mal seizures were produced in curarized and artificially resired animals to produce the characteristic vascular response of arteriolar vasodilatation previously described while an indwelling micro-pH probe continuously measured CSF pH. During seizures, CSF pH initially decreased in apparent synchrony with the opposite-direction change in arteriolar diameter, obtained a minimum value at nearly the same time that the diameter was maximum, and then slowly returned to a normal value.

Cross-correlations of the diameter and pH waveforms were performed to assess waveform similarity. Figure 6 shows a series of cross-correlations for different imposed time shifts on the pH waveform (delaying the diameter...
waveform is computationally analogous to moving backward in time the pH waveform). This was done because the waveforms were not identical and the initial correlation was only fair (−0.703) with arteriolar diameter changes apparently leading slightly the pH changes. Had this in fact been the case, the pH change would be expected to be in the opposite (alkaline) direction than it was, since the resultant hyperemia caused by early vasodilatation would over-perfuse the vascular bed.19 Maximum cross-correlation (−0.885) occurred when the pH waveform was moved back in time 40 seconds, suggesting that the waveforms are closely associated with a delay imposed on the pH waveform. Such a time delay can be accounted for by a diffusional delay of the hydrogen ion from vascular wall to pH recording electrode, which was located in the CSF 1 to 4 mm from the arteriolar bed. Separate empirical tests of the recording system verified similar recording delays in dynamic alterations of the pH in in vitro biological fluid.

Discussion

While correlation between two events does not necessarily imply causal relationship, the hemodynamic and metabolic correlations demonstrated in this study are significant since (a) these correlations have not been previously demonstrated in a dynamic in vivo animal model bearing such a high degree of electrographic similarity to clinically observed epilepsy (b) peripheral systemic factors were carefully controlled and their effects isolated to prevent interaction with metabolic and hemodynamic variables, and (c) these correlations are consistent with the theory of metabolic regulation of cerebral blood flow which has been shown to have a significant and sometimes dominant influence on control of CBF.

This study primarily has shown high positive correlation between changes in CSF hydrogen ion concentration and pial arteriolar diameter. Arteriolar diameters and venular erythrocyte velocities were the hemodynamic variables measured by television methods during induced epileptic seizures and were observed through a small plexiglass window implanted in the cat cranium. Changes in these variables were also highly correlated. Enflurane-induced or pentylentetrazol-induced electrographic grand mal seizures maximally dilated arteriolar diameters and increased venular erythrocyte velocity up to 400%. The absolute change in these variables was smaller during enflurane-induced seizures due to pre-seizure autoregulatory vasodilatation in response to enflurane-induced systemic hypotension. These changes were produced at constant systemic arterial pressure in the presence of a β-adrenergic blocking agent and were, in turn, highly correlated to changes in the pH of CSF surrounding the arterioles, suggesting metabolic regulation of CBF through CSF/interstitial fluid hydrogen ion alterations during the seizure. It should be noted that there was no rapid move-

Figure 4. Electroencephalographic (EEG) and venular erythrocyte velocity correlates during an enflurane-induced seizure.

Figure 5. A subconvulsive increase in cortical electrical activity was produced during enflurane anesthesia by repetitive auditory stimulation which led to an increase in venular erythrocyte velocity qualitatively similar to the responses seen during complete seizures.
The fact that changes in the pH of the fluid surrounding cerebral arterioles can alter their diameter has been unquestionably proved and is taken by most investigators to be the basis of the metabolic theory of cerebral regulation of blood flow. The more modern view is that held by Lassen who now believes extracellular pH to be the decisive factor in the determination of CBF. His theory, and the essentially similar one given by Gotoh et al., predict that if extracellular bicarbonate concentration is decreased, then low pH and cerebral vasodilatation will result, even if arterial PCO₂ is normal. Lassen presumes that vascular smooth muscle acts like a CO₂ electrode and that it is the intravascular CO₂ and the extracellular HCO₃⁻ which determine the pH around and inside the smooth muscle cell. That this mechanism is correct is supported by the clinical facts that cerebral vasodilatation is found in diabetic coma with normal arterial PCO₂, that low CSF pH and increased CBF have been demonstrated at high altitude and that the adaptive CSF pH changes which occur in response to chronic metabolic acidosis or alkalosis are followed by corresponding CBF changes. The local, pH dependent control of arteriolar diameter demonstrated by Wahl and the local control of caudate blood flow regulated by artificial bicarbonate concentrations of ventricular perfusion fluid strengthen the argument for local metabolic control of CBF.

The metabolic variable pH was so highly correlated to the observed hemodynamic changes during the seizure when other flow regulatory mechanisms had been controlled or inhibited it is taken as evidence that the metabolic regulation of flow is the dominant regulatory mechanism in effect during the seizure. It is specifically concluded that the local metabolic environment of the arteriole, as reflected in CSF pH, is directly responsible for control of cerebral arteriolar diameter and, hence, CBF during pharmacologically induced electrographic grand mal seizures in the cat. Increases in systemic blood pressure secondarily increase CBF in metabolically dilated arteries.

The distinction between pressure and metabolic effects was made because the macroscopic data of Plum et al. indicated that cerebral autoregulation was suspended during the seizure and that increased CBF followed both increases in systemic arterial pressure and passive arteriolar dilatation. By contrast, our findings indicated that vasodilatation was caused by an active arteriolar response to changes in CSF/extracellular fluid pH due to increased metabolic activity accompanying the seizure and that increases in systemic blood pressure secondarily increased blood flow in metabolically dilated cerebral arterioles.

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Cerebral Manifestations of Ergotism
Report of a Case and Review of the Literature

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SUMMARY A patient with diffuse and focal cerebral dysfunction was found to have absent peripheral pulses. Cerebral angiography revealed evidence of an arteritis with bilateral high grade carotid stenosis. When there was no laboratory confirmation of the arteritis, an iatrogenic etiology (ergotism) was suspected. This was later confirmed by the patient. The pertinent literature on ergotism is reviewed, and it is emphasized that ergotism may develop in patients on therapeutic doses of the drug.

There was no history of congenital or rheumatic heart disease, local neck trauma or infection, hypertension, diabetes or hyperlipidemia. The patient was not taking oral contraceptives or any other medication. There was no family history of heart disease, stroke, hypertension, or diabetes.

On admission the temperature, pulse and respiration were normal. Blood pressure was 110 mm Hg by palpation on the right and unobtainable on the left. Examination of the lungs, heart and abdomen was normal. There were bilateral subclavian pulses but no axillary, brachial, or radial pulses. Carotid pulses were palpable and there were no bruits. There were weak femoral pulses but none below the groin. All extremities were pale and cold. Neurologically, the patient was lethargic but arousable; she was confused and disoriented to time and place with a short attention span and exhibited marked emotional lability: she was not aphasic. Examination of the fundi was unremarkable. There was a dense left homonymous hemianopia, a left hemisensory deficit, and a left hemiplegia (as marked in the arm as in the leg). There was a left Babinski sign without a reflex preponderance.

Hematocrit, hemoglobin, white blood cell count, differential and platelet count were all normal. Sedimentation rate was 12 mm per hour. Kaolin partial thromboplastin time was slightly shortened and there was mild elevation of factors II and V; otherwise, the coagulation profile was normal. Sodium, potassium, chloride, CO₂, calcium, phosphorus, total protein, albumin, direct and indirect bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine phosphokinase, uric acid, fasting blood sugar, two-hour postprandial sugar, cholesterol, triglycerides, VDRL, T3, T4, serum and immune electrophoresis, antinuclear antibody and lupus preparations were all normal. Urinalysis revealed no protein or red cells. Skull films, chest x-ray, and flat plate of the abdomen were normal. Electrocardiogram and echocardiogram were normal. Electroencephalogram (done one day after admission) revealed 1.5 to 4 cycles per second.

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