
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.1-6 Until the elaborate studies by Plum et al.8,9 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,8 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,5,10 and have been hypothetically presented as a mechanism of vasodilatation during the ictus,4 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-
tion of a 1-cm² plexiglass window for the calvarium over the left frontocentral cortex. The insertion of a Forbes window 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 perfuse 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 micropipette pH determinations. Magnification (400×) 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 while erythrocyte velocities were determined in venules by continuously extracting and cross-correlating upstream and downstream photometric signatures of flowing erythrocytes. 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 β-adrenergic blockade (three cats) to eliminate the neurogenic component of vasodilatation. CO₂ end-tidal concentrations were held constant by controlling respiratory rate and depth. No special attempt was made to control systemic arterial pressure during the seizures. Early seizures in the protocol were associated with elevations in systemic pressure. Subsequent seizures, however, were free of such changes in blood pressure, presumably due to depletion of catecholamine stores by the earlier seizures.

Results

In early qualitative measurements of arteriolar caliber changes during induced seizures, arteriolar vasodilatation was noted to begin during the early tonic phase of the discharge, reach maximum diameter by the end of the clonic phase and begin to return to preictal diameters early in the postictal period of electrical silence. As figure 2 displays, vascular reactions were repeatedly and closely associated with electrocorticographic activity. While elevations in systemic arterial pressure accompanied the seizure in some instances, that was not always the case; blood pressure changes were not correlated with arteriolar diameter changes, either directly or inversely, the latter being expected if autoregulation was maintained. Although autoregulation appeared to be suspended during the seizure, arteriolar dilatation did not appear to be simply a passive reaction to increased arteriolar intraluminal pressure.

The first seizure in figure 2 was associated with an increase in blood pressure coincident with the start of vasodilatation but vasodilatation began in the second and third seizures at the same electrocorticographic point but at different blood pressure levels. In the third seizure, systemic arterial pressure was constant during the tonic and clonic phases of the seizure. Note that in the second seizure, constriction back to preictal diameters began in the early postictal phase while the blood pressure was slowly rising. The thesis that arterioles are passively dilated by increases in systemic blood pressure during the seizure seems to be unsupported by these data. Figure 3 provides additional support for the previous statement by giving ten preictal and early postictal arteriole diameters along with the mean systemic arterial pressure present at the time diameters were measured. An average 8.5% increase in arteriolar diameter occurred between the two measurements during constant or, in three vessels, decreased systemic pressure levels between preictal and postictal measurements. That systemic pressures are a reliable reflection of cerebral perfusion is supported by the work of Stromberg and Fox, who reported that pial arterial blood pressure varied systematically with changes in systemic blood pressure, and Shapiro et al., 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 arterial 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-μm 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-

**Figure 1** Typical cortical vascular field consisting of a branched arteriole and a venule. White squares on the venule represent video sampling windows used in the determination of erythrocyte velocity. The windows are separated by 20 μ.
EEG
pentylenetetrazol

FIGURE 2 Electroencephalographic, arteriolar diameter and systemic arterial pressure responses during three pentylenetetrazol-induced electrographic grand mal seizures. The consistency of electrocorticographic and vasomotion correlations in the face of varied pressure responses suggests a dynamic metabolic influence on arteriolar diameter.

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 pentylenetetrazol-induced electrographic grand mal seizures were produced in curarized and artificially respirated animals to produce the characteristic vascular response of arteriolar vasodilation 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

FIGURE 3 Arteriolar diameter increases during enflurane-induced seizures at constant or, in three vessels, decreased postictal versus preictal systemic mean arterial pressures. Deep levels of enflurane anesthesia are responsible for systemic hypotension. Diameters increased an average 8.5% between preictal and early postictal measurements.
FIGURE 4  Electroocorticographic (ECoG) and venule erythrocyte velocity correlates during an enflurane-induced seizure.

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. 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 time 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-
diameter and CSF pH changes during a seizure. Maximum cross-correlation occurred when the pH waveform was changed in time to compensate for the delay in its recording created by hydrogen ion diffusion from arteriole to pH recording electrode.

The fact that changes in the pH of the fluid surrounding cerebral arterioles can alter their diameter has been unquestionably proved and is taken as evidence that the metabolic regulatory mechanism is in effect. That 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 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.

**Acknowledgment**

The authors gratefully acknowledge the assistance of Mr. Don Walker and Ms. Karen Chass.

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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 respirations 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, lactic 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

THE TOXIC EFFECTS OF ERGOT on the peripheral vasculature are well recognized, but the toxic effects of ergot on the cerebral vasculature are less well known. This paper describes the neurological and angiographical manifestations of ergotism in a patient, and reviews the pertinent literature.

Case Report

A 36-year-old, right-handed white woman awoke confused on the morning of admission, and had a left hemiparesis. At age 17, the patient had migraine headaches characterized by a prodrome of scintillating scotomata followed by a right or left hemianopic headache terminated by nausea. For 20 years she had been taking ergotamine tartrate suppositories (Cafergot®) with good symptomatic relief. For the three weeks prior to admission she had been under unusual emotional stress and noted a sharp increase in the frequency of her headaches. However, she denied taking more than half a suppository (1 mg of ergotamine) a day. One week prior to admission she consulted a physician because of leg cramps. He found absent pulses below the groin and, unaware of the history of ergot usage, prescribed a vasodilating agent, nylidrin hydrochloride (Arlidin®), without symptomatic relief. Nylidrin was discontinued a few days later. On the day prior to admission, the patient was unusually drowsy and that night had difficulty climbing stairs and getting into bed. She awoke at 6 A.M. on the day of admission and was unable to move her left side.

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Brain microvascular hemodynamic responses to induced seizures.
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Stroke. 1976;7:83-88
doi: 10.1161/01.STR.7.1.83

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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