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Is There an Evoked Vascular Response?

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Abstract. *Event-related potentials of the brain are enhanced when stimulation is synchronized with diastolic phases of cerebral or cephalic pulse pressure waves. A cerebral vascular event has been found to be temporally consistent with the event-related potential. Averaged evoked vascular responses were measured with bioimpedance techniques from the brain and the arm. Changes in brain blood volume occurred 150 to 250 milliseconds after stimulation synchronized with diastolic but not systolic phases of the cerebral pulse pressure wave. The time course of this phenomenon defies the usually accepted characteristics of metabolic activity. The evoked vascular response may be a neurally mediated event in anticipation of altered metabolic demand, and it offers the possibility of measurement in real time.*

A major problem in assessing cerebral metabolism during mental processing is temporal resolution of measurement. The 2-deoxy-D-glucose autoradiographic techniques in animals (*1*) and the positron emission tomographic approach in human subjects (*2*) provide promising tools for localization; the temporal resolution of these procedures, however, is 30 to 40 minutes, which is unsuitable for assessing event-related mental activity. An invasive method has recently been described for measuring local cerebral blood flow in animals with a temporal resolution of 30 to 40 seconds (*3*). We now report a noninvasive method for measuring transient responses of the cerebral vasculature in the range of milliseconds in conscious human subjects. The method permits the assessment of neurogenic hemodynamics reflecting mental activity in real time.

Electrophysiological procedures, such as event-related potentials (ERP's) of the brain, are reliable temporal measures of neural function (*4*). Such ERP's measure obligatory "reflexes" of the brain linked to physical stimuli as well as endogenous responses, such as stimulus evaluation and decision time (*5*). Cardiovascular phase influences evoked responses of the brain (*6*). Stimulation synchronized with the diastolic phase derived from the carotid or ophthalmic artery augments the ERP; conversely, stimulation during the systolic phase attenuates the ERP.

These and other influences on sensory threshold (*7*) have been proposed to result from the influence of baroreceptors on higher centers of the brain (*8*). However, irrespective of cardiovascular phase, brief auditory stimuli also evoke

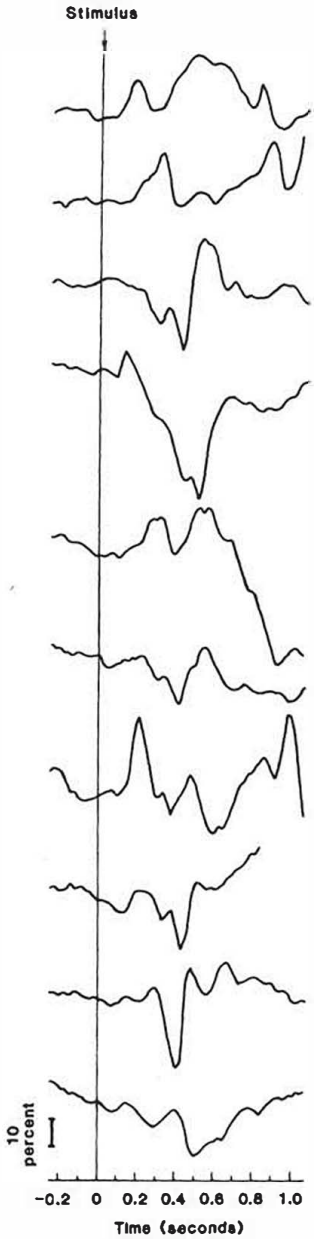

Fig. 1. Individual difference waves. Each wave is the result of subtracting 40 diastole-stimulated wave forms (250 msec prestimulus and 1250 msec poststimulus) from 40 nonstimulated wave forms. Each subject's record shows a stimulus-induced volumetric change occurring between 200 and 400 msec. Most wave forms reflect transient changes in volume without changes in flow, since impedance signals tend to return to baseline within the short sampling period. Even though the cardiac period varied considerably among the subjects, the temporal characteristics of the waves were consistent. The 10 percent change shown refers to the percentage change from the nonstimulated wave form.

transient responses in the peripheral nervous system (*9*) and change the local availability of oxygen to the brain (*10*). Additionally, studies in animal (*11*) and human (*12*) subjects demonstrate stimulus-linked responses in localized pulsatile blood-flow wave forms recorded from the thalamus, hypothalamus, and globus pallidus. Quantification and characterization of stimulus-induced hemodynamic changes have not been accomplished, and their mechanism remains uncertain. Rapid changes in blood flow are probably not the result of the action of local regulatory mechanisms, which are principally activated by metabolic end products such as carbon dioxide, but may be neurally mediated events that increase or decrease the availability of essential metabolic substrates (such as oxygen and glucose) in anticipation of altered metabolic demand (*13*).

In conscious human subjects, we have examined rapid changes in blood volume evoked by brief auditory stimuli presented during the systolic or diastolic phase of the cardiac cycle. Pulse volume wave forms were derived from the left central cerebral cortex ($N = 10$) and the left forearm ($N = 8$) through the use of impedance plethysmography.

Healthy right-handed volunteers were tested with the rheoencephalogram (REG), a measure of the volume of blood in the brain, and with impedance measures of forearm blood volume. The output of the impedance plethysmographs was amplified and filtered at low frequency (time constant, 0.45 second) on a polygraph (Grass model 79). Delivery of the stimuli and collection of blood volume wave forms were done with a computer (PDP 11/34) at a sampling rate of 1 kHz for 1250 msec.

For the REG, a small oscillating current (100 kHz, 4 mA) was applied to the scalp with silver electrodes developed for electrocardiograms placed at F_1 and 0_1. Changes in impedance, measured with silver electroencephalographic disk electrodes placed 7 cm apart on either side of C3 (left central hemisphere of the brain), reflected linear changes in cerebral blood volume. Thus, the tissue of the brain was included in an electrical circuit in the form of a volume conductor. Studies of selective cerebral arterial compression (*14*) and correlation with radioisotope methods (*15*) have established that the REG measures intracranial rather than extracranial vascular events (*16*).

Pulse volume wave forms were recorded from the left forearm with four bands of aluminum-lined Mylar tape. Current-carrying bands were placed on the bicep and just above the wrist. The current-detection electrodes were placed between the current-impressing electrodes (10 cm apart). While recording, the arm was kept at heart level on a pillow. Thus, two separate current-impressing and impedance-detecting circuits were used.

Procedures identical to earlier studies of the ERP were used to derive average pulse volume wave forms (*6*). Auditory stimuli were synchronized with systolic or diastolic components of an ophthalmic pulse pressure wave derived from a photoplethysmograph (*17*). The stimuli—450-Hz, 80-dB tones of 200-msec duration—were presented binaurally through headphones. Subjects were comfortably seated in a sound-attenuated room with 15 dB of ambient white noise. Stimuli were activated by a Schmidt trigger that detected amplitude changes in the signal from the ophthalmic photoplethysmograph (*18*). The threshold of the trigger was continuously adjusted corresponding to 25 percent of the wave form amplitude. The pulse pressure waves of the brain and the arm were averaged across 40 stimulus presentations and compared on a trial-to-trial basis with the prestimulus pulse pressure wave.

Four temporally adjacent factors of the REG were identified with a varimax rotation of the factor structure generated by principal component analysis. The first factor (which accounted for the most variance) comprised the sampling epoch between 300 and 540 msec. The second (40 to 100 msec), third (100 to 200 msec) and fourth (200 to 300 msec) factors completed the description of the wave form. These factors are consistent with the average of the individual subject waves (Fig. 1). The factor structure was not interpretable for waves evoked during systole. Thus, the evoked vascular response (EVR) can be characterized by factor analytic procedures when synchronized with diastole but not systole.

The differences between the stimulus and prestimulus waves for the arm and head placements were analyzed by a stepwise discriminant function procedure (BMD P7M). A linear combination of variables occurring at 60, 40, 260, 160, and 250 msec were selected as the most discriminating in this analysis. The stimulus and prestimulus waves for the REG alone were discriminated for 62.5 percent of the cases. For the peripheral placement, the stimulus and prestimulus were separated 37.5 and 62.5 percent, respectively (50 percent was chance).

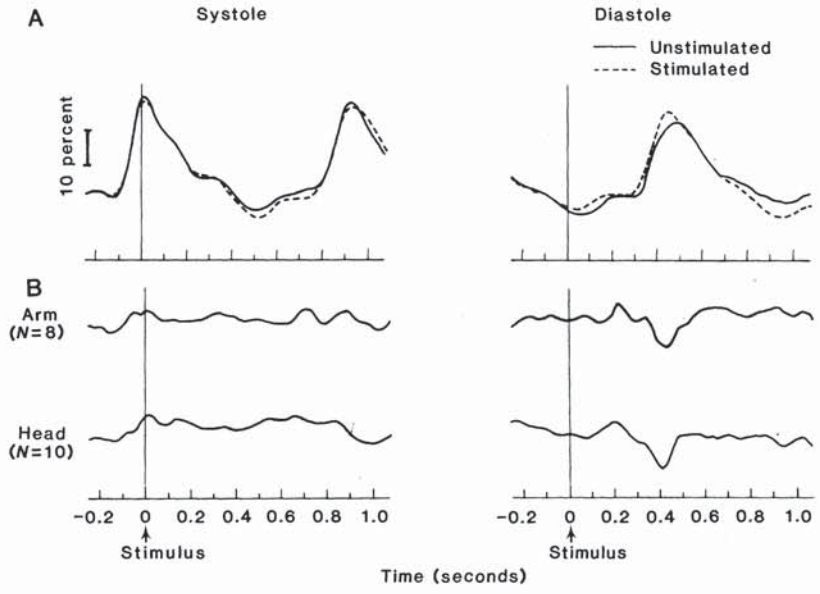

Fig. 2. (A) Averaged pulse-pressure waves from a single subject. (When the tone presentation occurred during systole, an EVR was not apparent; when presented during diastole, however, a short-latency perturbation occurred.) The bioimpedance wave forms collected in this study were not simply the mean basal impedance, Z_0, but the change in impedance with respect to Z_0, ΔZ (*20*). Therefore, differences observed between stimulus and nonstimulus conditions reflect differences in ΔZ. Further, the EVR is not simply the result of a rapid change in the capacitive reactance of tissues, as it contributes negligibly to the ΔZ signal at the applied oscillator frequency (100 kHz.). (B) Grand mean difference wave forms for the head and arm for stimulation synchronized with systole and diastole. No stimulus-linked volume change was evident in either the head or arm during systole, although similar responses occurred during diastole.

Separate analysis of diastole-triggered EVR's for the REG, however, yielded a statistically significant difference between the prestimulus and poststimulus segments (Fig. 2). Although 87.5 percent of the waves were classified accurately [$F(7, 8) = 3.92$, $P < 0.05$], only 68 percent of the stimulus and prestimulus waves were classified accurately during diastolic phase for blood volume responses of the arm. Stimulation during systole was not significantly discriminated from the prestimulus wave with any analysis.

To our knowledge, this is the first report of transient, rapid changes in a measure of the cerebral vasculature from conscious human subjects. This rapid EVR was evident only when stimulation was synchronized with the diastolic phase of the ophthalmic artery. Although the response was observed in the periphery, it did not occur reliably. The latency of the EVR defies the time course related to previously described vascular changes in response to altered metabolic activity. Thus, this response may be a neurogenically mediated vascular event in preparation for altered metabolic demand.

Enhancement of the EVR during diastole is consistent with previous reports with the ERP (*16*). Auditory stimulation synchronized with diastolic phase resulted in a 10 to 20 percent augmentation of the attentional (N1) component of the ERP. Our results suggest that rapid changes in blood volume occur according to a similar schedule and are of similar proportion (*19*). The temporal similarities between response of the cerebral vasculature and the electrical response of the brain suggest common generating mechanisms. For instance, decreased baroreceptor activity (as during diastole) is associated with increased cerebral blood flow and release from neuronal inhibiton (*13*). Our results suggest that stimulation during diastole can evoke rapid changes in cerebral vascular events and augment the ERP. The EVR may prove to be a neurally mediated phenomenon that not only yields clinically relevant information regarding the integrity of vasomotor systems but also may provide new information of brain metabolism related to detecting and processing external information in real time.

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16. A major difference among these methods is that only relative measurements are obtained with the REG, although it has the advantage of providing dynamic rather than static indices of volume. Since rapid changes in volume were of interest, the relativity of the measurement was not a problem.
17. Photoplethysmography used a reflective transducer, which combines an infrared light–emitting diode and a silicon phototransistor.
18. Tone presentation as well as data collection epochs were initiated when the amplitude-calibrated ophthalmic photoplethysmograph reached 75 percent of its maximum amplitude in either the "ascending" systolic phase or the "descending" diastolic phase. Analysis of simultaneously synchronized data collection sequences began approximately 270 msec after the R wave of the electrocardiogram, and the diastolically synchronized sequence began approximately 480 msec after the R wave.
19. It is not possible to separate the contribution of blood volume and blood flow with this procedure. Even though these two measures are related, it would be of interest to dissociate them. Our data indicate that external stimulation is related to perturbation in the cerebral vasculature. The differential contribution of volume and flow of capillaries, arterioles, venules, and major veins is not known. S. A. Radvan-Ziemnowiez [*Methods in Psychophysiology* (Williams & Wilkins, Baltimore, 1967), pp. 129–157] suggested that the REG represents blood flow contributed by the internal carotid artery. Studies of localization and of patients with known pathologies are needed to clarify this important point.
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