SUMMARY  The current state of the art of noninvasive measurement of regional cerebral blood flow (rCBF) by inhalation of \(^{133}Xe\) gas is briefly reviewed. Apparatus is now available commercially so that printouts of rCBF values for gray and white matter flow of both cerebral hemispheres, and probably the brain stem and cerebellum, are available within 30 minutes after 1 minute inhalation of 5-6 mCi of the gas mixed in air. The printout is in the form of a brain map which shows normal values. Normal values reported in volunteers are available commercially so that changes in rCBF can be easily repeated and are reproducible so that changes in brain function such as sleep, attention, activation, speech, hearing, performance of tasks and the normal aging process are reviewed. Noninvasive rCBF measurements have some practical clinical and investigative applications in the evaluation of pathological states such as cerebrovascular disease, the dementias, migraine, epilepsy, narcolepsy, and head injuries. Despite certain technical limitations of the \(^{133}Xe\) inhalation method, which are described, rCBF measurements show promise for future screening of patients at risk from cerebrovascular disease, early identification of stroke-prone individuals, evaluation of methods of prevention, as well as measurement of the effects of medical and surgical treatment.

FIVE YEARS AGO, at the Eighth Princeton Conference on Cerebral Vascular Diseases, Posner outlined the requirements for an ideal method for measuring cerebral blood flow in human subjects.\(^5\) These included the following criteria for the ideal technique: 1. noninvasive, 2. measure flow instantaneously, 3. be repeatable, 4. measure total and regional flow, 5. measure substrate metabolism, 6. measure intracranial, extracranial and venous flow, 7. not require hospitalization, and 8. not entail use of radioactive materials. While some of the requirements given remain to be attained, considerable progress has been made in achieving the remainder.\(^2-4\) Measurements today can be made in a safe and reliable manner without discomfort. Apparatus is now available commercially which can be used for measurement of mean total as well as regional cerebral blood flow which is important in disorders such as migraine and occlusive disease of the internal carotid artery, where extracranial, as well as intracranial flow, are likely to be altered.

Methodological Considerations

As an indicator for measuring rCBF, \(^{18}Xe\) may be administered safely by inhalation of a mixture of 5-7 mCi/liter in air for 1 minute by means of a face mask. \(^{18}Xe\) as a radioactive indicator has many advantages: it is readily available commercially in the United States; it is relatively safe, easy to store and dispense, and requirements for its radiation safety are well established.\(^11\) It has a half-life of 5.3 days, is chemically inert and the partition coefficients for gray and white matter in normal brain tissues are known. When inhaled it passes rapidly from the lungs as a bolus into the arterial blood and is uniformly distributed via the heart to all parts of the brain. Measurements of regional blood flow may be made which include the brain stem, the diencephalon, the cerebellum and both cerebral hemispheres.

Values for regional blood flow are calculated by 2 compartmental analyses of the curves recorded from the head by

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collimated probes during a 10-minute desaturation period using a modification of the Fick principle. More than 16-32 probes may be used for better regional localization of flow patterns. The end-tidal 133Xe curves are recorded from the mask and if cardio-pulmonary function is normal and in equilibrium with the arterial blood they are used for correction of recirculation. The radioactive gas 133Xe emits both gamma and x-ray activity, so that desaturation curves of gamma activity comes primarily from brain, subtraction of gamma and x-ray activity, so that desaturation curves of gamma activity comes primarily from brain, subtraction of gamma plus x activity are slightly lower. White matter flow values (Fw) are of 18.3 ± 1.7 ml/100 g/min and values for percentage weight of gray matter are 41.7 ± 6.1%. Mean flow gray values, recorded from the posterior cranium and believed to represent flow from brain stem and cerebellum, are higher, 101 ± 21 ml/100 g brain/min. Reproducibility testing of serial rCBF measurements of flow gray values at rest in a lighted laboratory is —2.5%.

Most investigators who have experience with the 133Xe inhalation method agree that gray matter flow values are reliable and reproducible although they vary from one region to another depending on the regional state of brain activity. Because of the technical problems relating to possible extracerebral contamination already mentioned, further experience with measurements of Fw are necessary before their reliability can be universally accepted. In general, Fw values tend to remain relatively constant during physiological activity while Fg values vary directly with the regional functional state of the brain. Changes in Regional Blood Flow During Speech, Visuospatial Tasks, Reasoning and Arousal

Measurements of rCBF provide a useful way of measuring regional cortical activation patterns in human subjects during tests of higher cortical function. The anterior frontal regions, particularly in the left hemisphere of right-handed individuals, tend to show higher Fg values during concentration and attention to a new task. With habituation to the task, these Fg increases in the frontal regions are no longer seen. Increases in frontal blood flow also subside with relaxation in apprehensive and anxious individuals and in all subjects after repeated rCBF measurements. For this reason, careful explanation of the procedure to patients and volunteers, with an interval for acclimatization to the laboratory environment, is important before steady state measurements are begun. There is no comparable decrease in the Fg response of cortical regions which are activated by a stimulus (such as the posterior portions of the hemispheres during visual problem solving) even after habituation to the task. During speech activated increases are seen in both Broca’s and Wernicke’s areas in right-handed individuals. While the subject is listening to spoken words, through earphones, these increases in Fg values are in the region of Heschl’s gyrus.
Effects of Alertness, Relaxation and Sleep

The Fg values also show correlation with simultaneous EEG recording. When subjects are alert, with beta and muscle activity rather than alpha activity recorded from the EEG, Fg values of both frontal and presumably brain stem-cerebellar regions are usually increased compared to measurements made in the relaxed state with the eyes closed and alpha activity seen in the EEG. With subjects awake in a quiet relaxed state in the dark (or with the eyes covered), with the ears plugged (or while listening to intermittent white noise presented through earphones), and the EEG showing alpha activity and little EMG activity, lower mean hemispheric Fg values with less interregional variation of Fg values are seen compared to values measured during states of alertness, arousal and attention. Flow values recorded over the posterior cranium are also reduced in these circumstances.

In Stages I and II of sleep there is a significant reduction of mean Fg values compared to the relaxed but awake state with the most marked reductions recorded over brain stem-cerebellum. In normal subjects, during rapid eye movement (REM) sleep, Fg values are increased particularly in the region of the brain stem-cerebellum. During slow wave sleep Fg values uniformly decrease.

In general, mean hemispheric Fg values are greater with the eyes open than with the eyes closed, suggesting that opening the eyes enhances arousal and alertness. In carrying out tasks, the regional increases of Fg occasioned by the task are enhanced if there is a reward for the correct performance of the task.

Testing Cerebrovascular Functional Reserve

In order to test cerebrovascular functional reserve, two rCBF measurements were carried out, the first in quiet darkness and the second 30–40 minutes later during cerebral activation with audio-visual stimulation, such as counting, conversation, watching figures move, and listening to music.

At rest in quiet darkness with the eyes closed and the ears plugged, mean Fg values in normal right-handed volunteers were: left hemisphere $79.0 \pm 12$ ml/100 g/min and right hemisphere $79.6 \pm 13$ with Fg values highest in both frontal regions. Cerebral activation increased Fg of the left hemisphere by $+13.9\%$ and of the right by $11.4\%$. Flow values recorded from what is believed to be the brain stem and cerebellum were increased by $+20\%$. Significant Fg increases were also seen in left frontal, parietal and inferior temporal regions, and in right frontal and temporal regions. The increases of flow in the right temporal region are attributed to sound stimuli.

Significant correlations were observed between a decline in hemispheric mean Fg and advancing age. The correlation was positive at different ages for both resting values and values during activation, both sharing parallel regression lines (fig. 2). This indicates that the cerebral functional reserve (ability to increase blood flow during brain work) is maintained among normal aging subjects despite a progressive decrease in Fg and gray matter weight which are usually the normal accompaniments of advancing age.

When cerebrovascular functional reserve was tested in patients with multi-infarct dementia there was no change of Fg during activation. In a group of patients with occlusion of the left internal carotid artery Fg increased by only $3\%$ in the left hemisphere but by $10\%$ in the right hemisphere.

Testing Vasodilator Responsiveness to Carbon Dioxide in Aging Subjects and Stroke

The well-known cerebral vasodilator response to inhalation of carbon dioxide has been tested in normal and aged subjects. It has been shown that there is a progressive decrease in CO$_2$ responsiveness with advancing age. The effects of vasodilator responsiveness to carbon dioxide may also be used as a test in patients with stroke where CO$_2$ responsiveness may be expected to be regionally decreased.

Testing Autoregulation in Cerebrovascular Insufficiency

It has been suggested that a simple, safe and noninvasive method of testing cerebral autoregulation is to make the first rCBF measurement with the patient lying flat and the second measurement with the patient tilted 30° (head-up). This can reduce mean arterial blood pressure by approximately
10 mm Hg. Such postural reduction of cerebral perfusion pressure does not alter rCBF values in normal volunteers. It has been reported that in patients with transient ischemic attacks in the verteobasilar territory, Fg values become reduced with tilting, indicating impaired autoregulation. The reduced values were most evident from the posterior cranial (brain stem-cerebellum) and the inferior temporal and occipital regions. During tests of autoregulation in patients with transient ischemic attacks in the carotid territory some patients showed a reduction of Fg values in the territory of the middle cerebral artery but as a group the Fg values were not significantly reduced compared to steady state values obtained in the horizontal position.

Clinical Application of Noninvasive Measurements of Cerebral Blood Flow

Stroke and Cerebrovascular Disease

A number of reports have appeared concerning the application of rCBF measurements in patients with stroke and related cerebrovascular disorders. Because the partition coefficient of infarcted brain tissue is not known, the analysis of initial slope indices has been proposed in such instances. When this is the case measurements of the fast and slow components of flow should more correctly be referred to as F1 and F2 rather than Fg and Fw. It has been shown that in zones of infarcted brain with abnormally reduced flow there may be small compartments of hyperemic or fast flows. As a result, the computer may ascribe spuriously high values to F1, unless the decreased proportionality (or reduced weight of F1) is recognized. This phenomenon has been termed "slippage." If initial slow indices, tissue weights and mean flow values are correctly proportionality (or reduced weight of F0 is recognized. This phenomenon has been termed "slippage." But if initial slope indices, true tissue weights and mean flow values are correctly measured and considered, potentially misleading overestimates of F1 values, due to small zones of regional hyperemia, may be recognized.

In general, following cerebral infarction, F1, W, and mean flow values are all reduced. Following temporary cerebral ischemia with recovery, zones of increased flow (indicated by increased F1 values, increased mean flow values but normal W, values) represent areas of reactive hyperemia. If F1 values are reduced below 38 ml/100 g/min and mean flow values below 23 ml/100 g/min, the prognosis for functional recovery of that area of the brain is poor, particularly if values remain reduced below these levels for several days.

For about 3 weeks following unilateral regional cerebral infarction such as may result from middle cerebral artery occlusion, rCBF values tend to be reduced bilaterally and symmetrically due to the phenomenon known as diaschisis. After this time interval, flow values tend to remain reduced in the area of infarction, but return to normal levels in other areas, such as the opposite hemisphere.

In right-handed individuals stroke leading to dysphasia is usually associated with rCBF reductions of F2 and flow indices in the left hemisphere in either Broca's or Wernicke's areas or both. Attempts at speech by dysphasic patients produce abnormal or decreased activation patterns of flow in the cortical speech areas.

In patients with occlusive disease of the carotid arteries, Fg values are often reduced in the carotid distribution of the affected hemisphere. It is often accompanied by a pattern of hyperemia in the region of the ipsilateral posterior cerebral artery and ischemia in the contralateral posterior cerebral artery territory. Following carotid endarterectomy, Fg values have been observed to increase toward or above normal values.

After subarachnoid hemorrhage from rupture of an intracranial sacular aneurysm or other causes of intracranial bleeding, serial measurements of rCBF may be of value in determining the time course of resultant cerebral vasospasm. In those patients developing vasospasm, Fg values become reduced beginning about the fourth day after rupture and increase toward normal between the second to fourth week. Normal pressure hydrocephalus may be suspected if there is progressive reduction of Fg and mean flow values. This complication may be confirmed by the prompt increase of rCBF that occurs after reducing CSF pressure by removal of 15 ml of cerebrospinal fluid.

In patients with cerebral arteriovenous malformations (AVM), rCBF values are greatly increased in the regions of brain occupied by the malformation but there may be reduced flows in bordering zones. If there is rupture of an AVM with intracerebral hemorrhage, flow values become reduced in the zone of the hematoma. In such cases, serial measurements of rCBF are useful in determining whether the AVM has functionally destroyed itself by the hemorrhage or if residual malformation persists with the liability of recurrent rupture.

Migraine and Vascular Headaches

A potentially useful application of rCBF measurements in clinical practice is in the objective evaluation and management of patients with migraine and related vascular headaches, particularly since the inhalation method permits an index of extracranial flow (EFI) derived from the formula

\[ \text{EFI} = \frac{F(\gamma - x)}{F}\gamma \cdot 100 \]

where extracranial flow is estimated as the percentage contribution of extracerebral tissues to cephalic flow. During the headache interval, and for 3-4 days after the headache, in patients with classic or common migraine, the mean Fg values are significantly higher than during the headache-free interval or compared to age matched normal volunteers. The average Fg increase in migraineurs studied serially during the headache and headache free intervals, 5-14 days later, showed average Fg increases of 31.4 ± 16% during the headache. Highest Fg values are usually found in the region of maximum head pain. Serial measurements made in migraineurs as the headache progressed in severity showed corresponding increases in Fg with the maximal percentage increases usually found in left frontal and right parietal regions.

Patients with migraine, studied up to 48 hours after the headache in patients with classic or common migraine, the mean Fg values are significantly higher than during the headache-free interval or compared to age matched normal volunteers. The average Fg increase in migraineurs studied serially during the headache and headache free intervals, 5-14 days later, showed average Fg increases of 31.4 ± 16% during the headache. Highest Fg values are usually found in the region of maximum head pain. Serial measurements made in migraineurs as the headache progressed in severity showed corresponding increases in Fg with the maximal percentage increases usually found in left frontal and right parietal regions.

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In patients with sublingual ergotomine during the headache, reduced rCBF values coincident with reduction of the headache.
In patients with complicated migraine, Fg values measured up to 18 hours after the headache had subsided showed reduction correlating with the neurological deficit while all other regions showed marked increases. In classic migraine, rCBF measured during the prodrome showed a significant reduction in the occipital regions correlating with the photopsias described clinically.

Patients with cluster headaches also showed marked increases in Fg values in both hemispheres compared with the headache-free interval, particularly in the fronto-temporal region on the side of the headache pain. The extracranial flow indices were also significantly increased during both cluster and migraine headaches compared to normal controls, indicating an increase in extracranial blood flow and/or blood volume. In patients with muscle contraction headache rCBF values during the headache interval were not significantly different from those of normal controls.

Alzheimer's Disease and Multi-Infarct Dementia

Compared to age-matched normal subjects, patients with Alzheimer's disease or dementia secondary to multiple episodes of cerebral ischemia (multi-infarct dementia) showed significantly reduced mean hemispheric indices of flow. The reduction varied directly with the severity of the dementia but in advanced cases mean flow, gray flow and flow. The reduction varied directly with the severity of the dementia but in advanced cases mean flow, gray flow and cerebral blood volume were diffusely reduced throughout the dementia but in advanced cases mean flow, gray flow and cerebral blood volume were diffusely reduced throughout the frontal-temporal region on the side of the head pain. The extracranial flow indices were also significantly increased during both cluster and migraine headaches compared to normal controls, indicating an increase in extracranial blood flow and/or blood volume. In patients with muscle contraction headache rCBF values during the headache interval were not significantly different from those of normal controls.

Epilepsy and Seizure Disorders

It is well known that epileptic seizures are associated with increased cerebral blood flow. In patients with focal epilepsy, who had focal EEG discharges during simultaneous rCBF recording, significant focal increases in Fg of 30–120% have been reported which correlated anatomically with the appropriate clinical and EEG focus. During either auditory or visual hallucinatory experiences reported by patients associated with psychomotor epilepsy (complex partial seizures) Fg increases were apparent in the temporal regions. Fg decreased as the hallucinations subsided with anticonvulsant therapy. Serial measurements of rCBF show that the Fg increases varied directly with the degree of the paroxysmal activity present in the EEG.

Narcolepsy

Simultaneous measurements of rCBF combined with EEG, eye movements, submental EMG and end-tidal PCO₂ have been recorded in the awake state and during different stages of sleep in patients with narcolepsy. In the awake state, regional CBF patterns in narcoleptics are the same as in normal volunteers, but during stages I and II of sleep in narcoleptic subjects, Fg values become significantly increased compared to the awake state. This is opposite to the decrease in Fg seen in the early stages of sleep in normal volunteers. During stage II sleep in narcoleptics, the increases in rCBF were maximum in temporal regions (+40%) and from the region over the brain stem-cerebellum (+35%).

During REM sleep and stage III sleep measured in narcoleptics, the rCBF changes were not different from those seen in normal volunteers. These abnormal regional CBF increases during the early stages of sleep in narcoleptics support the view that in narcolepsy central neurogenic control of the sleep-wake cycle is the primary disorder.

Limitations of the ¹³³Xe Inhalation Method

Need for Standard Recording Conditions

Mental State. rCBF measurements must be made under standard recording conditions since the rCBF values will be influenced by the functional state of the brain, i.e. whether the subject is relaxed, asleep, or awake and apprehensive, whether quiet or talking, listening to noise or music, or performing a task such as counting.

Respiratory Function. In order to measure rCBF reliably, the patient must cooperate by wearing a tight fitting face mask and by breathing regularly. This poses problems in uncooperative or restless patients with irregular respirations. Inspection of the air curve will indicate that this problem exists and such data should be discarded as unreliable. The end-tidal PCO₂ must always be recorded during the rCBF measurements since changes in Pco₂ (and hence Paco₂) will influence rCBF values. Such changes may be a good indicator that the mask is properly fitted. In patients with advanced cardiopulmonary disease the air curve for ¹³³Xe may be sufficiently distorted to render rCBF measurements invalid.

Technical Problems. Care must be taken in interpreting the second compartment (F₂ or Fw) since loose application of the probe to the scalp or poor setting of the discriminators of the probe for gamma versus x-ray discrimination may lead to underestimates of F₂. Inspection of the regional desaturation curves for both x-ray and gamma activity separately assists in identifying this artifact.

"Look-Through" Phenomenon. Chronic cystic infarcts or other cystic lesions may not be recognized from rCBF measurements since counts derived from normally perfused overlying tissues and counts derived from desaturation after solution of the ¹³³Xe gas into the cyst fluid may give rise to apparently normal values.

Future Application of the ¹³³Xe Inhalation Method

Certain applications of the ¹³³Xe inhalation method have been briefly reviewed in which some experience has been gained up to the present time. The rCBF measurements have promise in several other areas. These include serial measurements to determine the course and influence of medical and surgical treatment on cerebrovascular disorders and cerebral trauma. Preliminary studies show that the method has value in selecting patients for carotid endarterectomy and for superficial temporal artery to middle cerebral artery bypass procedures as well as potential in evaluating the effectiveness of these surgical treatments.

The method shows promise in correlating normal functional rCBF patterns with brain work in the waking state as well as in sleep and in disorders of consciousness. The method may be useful for establishing cerebral dominance for speech, hearing, visuo-spatial perception and other in-
tective functions. It should be useful in evaluating the diagnosto and prognosis of deafness, dysphasia and other neurosensory disorders. The rCBF measurements should also be of value in estimating the nature, severity and reversibility of coma, and possibly in determining cerebral death.

The method could have additional value in screening stroke-prone individuals by tests of cerebrovascular functional reserve, CO2 responsiveness and autoregulation in patients with such risk factors as transient ischemic attacks, hypertension, hyperlipidemia and diabetes mellitus. If this proves to be so, the effects of therapeutic management of these conditions on cerebral hemodynamics may be measured, thereby enhancing understanding of the pathogenesis and prevention of strokes.

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