Comparison of Local Cerebral Blood Flow Determined by Thermal and Hydrogen Clearance

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SUMMARY Local cerebral blood flow (ICBF) was measured simultaneously in ten cats with (1) a large surface thermal diffusion probe resting on the cortex and (2) hydrogen clearance curves from implanted electrodes surrounding the thermal probe. A close correlation was found between ICBF values obtained by the two methods. Since hydrogen clearance is accepted as quantitative, the data suggest that the thermal diffusion technique is a reliably quantitative means of measuring local cerebral blood flow.

The heat clearance method for determining local cerebral blood flow (ICBF) may be useful for monitoring clinical patients. In 1973, Carter and Atkinson described a surface thermal probe which incorporates a Peltier stack and may be safely and conveniently applied to the brain surface during craniotomy. The method allows continuous monitoring of ICBF for detection of rapid changes. This probe has been used in both laboratory and clinical settings and has been shown to be a reproducible and apparently quantitative means of measuring flow.

A major criticism of the heat clearance method has been its lack of reliable quantitation. Although data derived by heat clearance are related in a linear way with ICBF determined by Krypton washout, previous investigations have indicated that the slope of the line is different in different preparations, and the intercept differs under different recording conditions.

To examine further the quantitative capability of the surface thermal probe, we have compared it to a hydrogen clearance method for simultaneous measurements of flow rates under a variety of conditions. The hydrogen clearance technique was selected because it has been widely accepted as quantitative, and it can be repeated frequently.

Methods

General Preparation

Ten mongrel cats (2.3–4.2 kg) were initially anesthetized with Ketamine hydrochloride (10 mg/kg IM, Bristol Laboratories) for placement of arterial and venous catheters. Arterial blood pressure and blood gases were monitored. Anesthesia was maintained with increments of intravenous pentobarbital (10–15 mg/kg) and pancuronium (0.2 mg/kg) as needed. The animals were placed on a ventilator (Harvard small animal respirator), and the PO$_2$ was maintained from 80 to 100 torr. PCO$_2$ was manipulated from 25 to 50 torr to change ICBF. The rectal temperature was maintained from 36.5°C to 38.5°C with an electric heating blanket. A right parietal craniectomy was performed, and the thermal flow probe was placed on the cortex. Three
platinum-iridium electrodes for measuring hydrogen clearance were inserted in zones surrounding the thermal probe. 1CBF values derived by hydrogen clearance were compared to a simultaneous measurement taken by the thermal probe. Approximately ten sets of flow values were compared in each animal. Different rates of flow were obtained by pCO$_2$ manipulation (from 25 to 50 torr) with ventilator changes and systolic blood pressure manipulation (from 30 to 220 torr) with intravenous infusion of metaraminol bitartrate (10 mg/50 mm/5% dextrose in water) and sodium nitroprusside (10 mg/100 ml 5% dextrose in water). Only flow values associated with monoexponential hydrogen clearance curves and a constant blood flow as measured by thermal probe were used for comparison.

Thermal Probe

The thermal probe used in these experiments is an updated version of the one described by Carter and Atkinson in 1973$^2$ and elaborated on elsewhere.$^{3-5}$ The probe consists of a Peltier stack with L-shaped gold plates arranged so that the voltage output is proportional to the temperature difference between the plates. The probe weighs 1.5 gm and is 13 mm in diameter. Activation of the stack creates a temperature gradient between the plates which brackets the ambient cortical temperature. Blood flow increments cool the heated plate, warm the cold plate, and cause a decrease in thermocouple voltage output. This voltage is correlated to blood flow according to a previously described calibration curve.$^3$ This calibration curve was used in the present experiments to determine flow rates for specific voltage outputs. At the conclusion of each experiment, the cat was sacrificed with intravenous potassium chloride, and zero flow voltages were recorded. Dead brain values (zero flows) had a mean of 316 microvolts with a standard deviation of 10.46.

H$_2$ Clearance

Three platinum (70%)-iridium (30%) electrodes 0.25 mm in diameter with a 2 mm bare tip were placed obliquely to a depth of 1–2 mm in the cortex surrounding the thermal probe. A subcutaneous stainless steel screw was used as a reference electrode. The electrode signal was conducted by flexible 0.02 mm diameter wire. In preliminary experiments, a heavier wire was used which caused excessive movement of electrode tip with resultant cortical injury. Electrodes were polarized at +0.65 volts according to a modification of the voltage clamp circuit of Willis et al.$^8$ Hydrogen gas (approximately 7%) was given via endotracheal tube. Hydrogen saturation was attained without changes in blood pressure, blood gases, or local blood flow as measured by the thermal probe. The first 40 seconds of the desaturation curve was disregarded to avoid problems of recirculation.$^5$ The signal was fed into a Grass Polygraph (Model 7), and the curves were digitized by an online calculator (Hewlett Packard Model 9815A). These data were fed into a Tektronix 4052 computer and 4662 digital plotter. Flows were calculated by a monoexponential least squares program and the function plotted to check the fit of the curve to the data.

Results

Ten experiments were conducted. Ninety-nine pairs of blood flow determinations were compared. Six values were discarded on the basis of instability of thermal readout or multieponential hydrogen clearance. All suitable values were plotted in figure 1. The overall correlation coefficient was 0.823. Correlation coefficients from the individual experiments ranged from 0.70 to 0.99. The last five experiments, carried out with lightweight wire leads to minimize injury by hydrogen electrodes, had correlations of 0.94 or better (fig. 2). Despite the fact that individual experiments had a high degree of correlation, the grouping of experiments, even restricting selection to those experiments with Rho > 0.9, yielded different correlation lines. Pooling of data from the last five experiments gave a Rho value equal to 0.87.

The overwhelming majority of hydrogen desaturation curves were monoexponential with only three multieponential curves discarded out of two hundred and eighty recorded. All flow values were compatible with grey matter flows ($\geq 40$ ml/100 gm/min under initial conditions). However, each of the three electrodes gave different values during the same run. This suggests heterogenous flow beneath the thermal probe. In general, blood flow values decreased over time, as one might expect in a craniotomy situation. Values obtained from the hydrogen clearance method were generally slightly higher than those obtained by the

![Figure 1. Lease squares linear fit of cerebral blood flow for all data. Each point represents thermal CBF versus average flow value from three hydrogen probes recording simultaneously from around the thermal probe.](image-url)
Thermal CBF (ml/100g/min)

**FIGURE 2.** (a) Thermal CBF and H$_2$ CBF from representative experiment using thin wires. (b) Least squares linear fit of thermal CBF and H$_2$ CBF from same experiment.

The readout from the thermal probe was generally a smooth tracing free of artifacts, adjusting in the expected direction within a matter of seconds in response to changes in pCO$_2$ or blood pressure. Artifacts resulted from irrigation of the cortex and loss of tissue contact. Typically, irrigation with saline caused acute rises in apparent ICBF of about 20 ml/100 gm/min with return to normal in about 30 seconds. Gross pathological examination of the cortex underlying the thermal probe to examine for either damage due to pressure or thermal injury was normal. The pressure used is just enough to keep contact and involves minimal force. Thermal damage is prevented by circuitry in the probe which cuts off power if the warm plate should exceed 41.5°C. No untoward effects have been known to be attributed to the thermal probe in over 100 craniotomies.

**Discussion**

For individual experiments, the results demonstrated a close correlation of ICBF derived by thermal diffusion with ICBF determined by hydrogen clearance ($r \geq 0.94$). Cusick and Mykleburst recently reported a linear relationship between thermal and hydrogen clearance determined ICBF with a miniaturized probe incorporating both methods. In studies comparing thermal diffusion and $^{85}$Kr clearance, Betz found a close correlation of ICBF values for a given brain site. (Placement of Betz’s small thermal probe at different cortical sites gave linear correlation but with different slopes.) In fact, Betz found that for a given brain site, determinations of ICBF by thermal diffusion were reproducible (linear with same slope and intercept) over many months in chronic experiments. Investigation of ICBF by simultaneous thermal and Xenon clearance has likewise indicated a close correlation. Therefore, for a given site, this thermal conductivity technique is a quantitative method for determination of ICBF.

Geometric considerations are important in the determination of ICBF. For miniature probes (less than 2 mm diameter), the sampled volume may include varying proportions of neural tissue and vessels. Such sampling differences may underlie differences in ICBF values recorded with hydrogen electrodes from different preparations and from various sites in the same animal. The same effect may explain variations between animals recorded by Betz with a miniature thermal probe. By contrast, the thermal probe used here monitors CBF in the cortex covered by its 1.5 cm$^2$ contact surface. An averaging effect achieved by monitoring a larger tissue volume may explain the consistent CBF recorded by thermal clearance from animal to animal under initial conditions. Geometry probably accounts for the variable slope amongst experiments of the correlation line comparing thermal and hydrogen clearance ($r = 0.823$). Since thermal flow was consistent and hydrogen flow inconsistent from cat to cat, this variability appears to derive from the geometric vagaries of the miniature hydrogen electrode, not the larger thermal probe. This variability of hydrogen blood flows was seen within the range of autoregulation.

Alterations in thermal conductivity, which is related to tissue composition, would distort quantitation of ICBF. Cusick and Myklehurst suggest that thermal conductivity changes under some conditions of recording. Their investigations showed a linear relationship with constant slope between thermal and hydrogen clearance, but the intercept was altered after profound ischemia or hypertension ($> 250$ torr for 20 minutes), suggesting change in thermal conductivity.

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probe, however, was fixed to the skull with the possibility of damage to the pulsatile brain, with resultant diffusion barrier to alteration in thermal conductivity. In the present study, the data indicate that the linear relationship between thermal and hydrogen clearance is present over a wide range of 1CBF (10 ml/100 gm/min to 130 ml/100 gm/min). Thermal conductivity of dead brains (zero flow) was constant in these experiments and in other feline studies involving mannitol dehydration or profound ischemia. Betz noted constant thermal conductivity over months in chronic experiments. Thus, the balance of evidence suggests no important changes in thermal conductivity in normal tissue, even after hypotension or hypertension. Although thermal conductivities of blood, plasma and brain may not differ significantly, thermal conductivity may differ in pathologic tissues such as tumors, and thermal flow values from such tissues may not be reliably quantitative.

Summary

There is a linear relationship between local CBF determined by heat clearance and local CBF measured by hydrogen clearance. This relationship holds for a given brain site over a wide range of mean arterial blood pressures and pCO₂. Comparisons between different brain sites and animals are less secure, but the origin of this problem lies with the geometry of the hydrogen probe, not the larger thermal probe. In various experiments with different brain insults, variation in thermal conductivity (which would obscure flow determination) has not been encountered.

The results support the large surface thermal clearance probe used here for quantitative determination of 1CBF. The principal advantage of the probe is its application at human craniotomy to give a continuous assessment of local cortical blood flow.

References

Comparison of local cerebral blood flow determined by thermal and hydrogen clearance.
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