Measurement of Cerebral Blood Flow by Washout of Microwave Induced Heating

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SUMMARY A method is described for measurement of cerebral blood flow utilizing the washout of microwave delivered heating. Using a microwave source attenuated to achieve a brain temperature elevation of 0.5–0.75°C after a 2 second exposure in the rat, cerebral blood flow was calculated from the temperature washout curve monitored by a small thermistor implanted in the brain. The results obtained with this method were comparable to those obtained using the [14C] butanol method. To our knowledge this represents the first description of a method to deliver a blood flow “indicator” atraumatically directly into brain tissue.

SINCE 1945 when Kety and Schmidt1,2 developed the inert gas method for the measurement of cerebral blood flow (CBF), many techniques have evolved to measure flow through the brain in animals and man. Almost all “indirect” methods available have in common the fact that an “indicator” or tracer is delivered to the brain. Precapillary arteriovenous anastomosis: “Thoroughfare channels” in the brain. Arch Neurol 16: 217–224, 1967

In this study we describe a technique to measure cerebral blood flow using the thermal washout of microwave delivered heat.

Materials and Methods

Thermal Washout Flow

Adult male Wistar rats (275–325g) were anesthetized with pentobarbital 50 mg/kg i.p. After shaving, a
A small incision was made on the right side of the head, 5 mm lateral to the midline and halfway between the coronal and lambdoid sutures. With a 0.5 mm diameter drill bit, a hole was placed through the skull and dura mater. A 0.25 mm diameter temperature thermistor (Thermobead A16C4B10KB104N Thermometries Inc., Edison, NJ) was bent at a right angle 5 mm from the tip; introduced into the brain and firmly secured to the skull with a suture (fig. 1). This allowed reproducible placement of the thermistor tip in the deep gray brain mass on the right. An incision was then made in the left inguinal region and a second identical thermistor threaded into the vena cava through the femoral vein. The femoral artery was cannulated with polyethylene PE-50 tubing for withdrawal of a 150 ul. sample for arterial blood gas determinations. The incisions were closed and the animals placed prone into a lucite restraining device (Thermex, Gerling-Moore, Santa Clara, CA) without the plunger.

Using a wheatstone bridge the temperature difference between the two thermistors was monitored and amplified using a potentiometric recorder (Model 2542 Servogor S, Brinkmann Instruments, Westbury, NY). The animals in the lucite holders were placed into a microwave unit (Metabostat Model 4104, Thermex, Gerling-Moore, Santa Clara, CA). The 3.8 KW output of the unit was attenuated by placing in the pathway of the microwave an aluminum disc 0.5 mm thickness with a rectangular aperture of 3 X 3 cm cut in the center. This was previously fabricated empirically to achieve an approximate 20 fold attenuation of power and a 0.5-0.75°C increase in brain temperature after a 2 second exposure.

Twenty to thirty minutes after the beginning of anesthesia and after all the surgery was completed, the animal’s head was exposed to the microwave for a period of 2 seconds and the temperature washout recorded continuously for a period of 10 minutes. Three to five determinations were obtained in each animal. From the recorded washout curves, cerebral blood flow (ml/100g/min) was calculated from the formula:

\[ F = \frac{-\ln \left(\frac{1}{2}\right)}{t_{1/2}} \]

\( t_{1/2} \) the time taken by the curve to reach half its height was obtained from the semilogarithmic plot of the washout curves.

After the CBF determinations were completed, the animals were sacrificed with an overdose of pentobarbital and the brains removed to confirm that the thermistors had been properly positioned and that no trauma had been produced during their insertion.

In two of the above sacrificed animals, as soon as the heart stopped, the head was exposed to microwave heating for 2 seconds. Immediately after this, the animals were submerged in water at 37.5°C and the temperature difference between the two thermistors recorded for a period of 8 minutes in order to obtain zero flow values (the animals were immersed in this water in order to prevent the normal postmortem faster cooling of the head as compared to the abdomen).

Two other additional animals were exposed to the original microwave heating protocol, but repeating the exposure every 30 seconds for a total of 20 exposures each. These animals were returned to individual cages and observed for a period of 3 weeks, at the end of which they were sacrificed and the brains and eyes examined for gross evidence of microwave damage.

[14C] Butanol Flow

In order to compare the cerebral blood flow results obtained after thermal washout with a "standard" technique, a group of rats underwent blood flow deter-
minations with $^{14}$C butanol according to the technique of Van Uitert and Levy.\textsuperscript{14, 15}

In brief, the animals were anesthetized using the same pentobarbital dose used in the previous group, the left femoral artery and vein were cannulated with PE-50 tubing. The arterial catheter was connected to a 1 ml syringe attached to a Harvard pump (Harvard Apparatus Co., South Natick, MA) arranged to withdraw blood at a constant rate of 0.44 ml/min. The arterial line was also used to withdraw a 150 ul sample for blood gas determination just prior to continuous withdrawal. The pump was started and as soon as it was noted to be withdrawing at a constant rate, the animals were decapitated and the Harvard pump was stopped simultaneously. The brain was quickly removed and a 125 mm$^3$ sample of brain obtained, its center corresponding to the thermistor tip location of the previous animals. The brain specimen was weighed (grams) and dissolved for scintillation counting by adding 1.5 ml of Soluene (Packard Instruments Co., Downers Grove, IL) and placed in a metabolic incubator shaker at 60°C until fully solubilized. The arterial blood specimens were prepared for scintillation counting by adding 1 ml of a 1:1 solution of Soluene and isopropanol. The vials were then capped and placed in a metabolic shaker to solubilize the blood. They were then removed and allowed to cool in an ice tray. When cooled, 0.5 ml of hydrogen peroxide 30% was added to decolorize the specimen and make suitable for counting. The vials with brain and blood specimens were then individually mixed with 10 ml of Instagel (Packard Instruments Co., Downers Grove, IL) and placed in a counter (Tri-carb liquid scintillation spectrometer Model 3390, Packard Instruments Co., Downers Grove, IL).

Blood flow in the brain specimens was calculated using the following equation:\textsuperscript{15}

$$F = \frac{(\text{brain counts/brain mass} \times \text{arterial flow/arterial counts}) \times 100}{\text{time recorded}}$$

**Results**

In the animals subjected to postmortem microwave heating, temperature decayed very rapidly during the first 30 seconds but from then on there was no subsequent temperature drop. During preliminary studies it was also noted that a high power exposure for a short time recorded a very high peak. Long exposures with lower power (produced by attenuation as described in the Materials and Methods) decreased the height of this initial peak. From this, it was concluded that the high peak represented heating of the thermistor above that of the brain, and the initial fast decay was produced by heat dissipation into local brain tissue. In all the determinations this initial fast slope lasted 30 seconds or less and for this reason in all studies the initial 30 seconds after microwaving were not included in the final calculations. Subtraction of this 30 seconds al-

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**Figure 2.** Typical temperature difference decay curve. The arrow at 30 seconds marks the beginning of the curve analysis. Followed for a complete clearance of heat "indicator," initially delivered to the intracranial blood.

Figure 2 shows the characteristic thermal decay curve obtained. Semilogarithmic plot of all the curves showed the decay to be monoexponential (linear regression analysis $r = -0.99$ for all decay curves). The cerebral blood flow values (ml/100g/min) obtained by thermal washout can be seen in Table 1. The mean cerebral blood flow for the whole group was $55.5 \pm 7.35$ S.D. The data show that consecutive blood flow determinations in each animal showed good reproducibility.

The mean cerebral blood flow in the 12 animals that underwent $[^{14}]$C butanol flows was $52.1 \pm 5.87$ S.D. This is not significantly different from the thermal washout flows ($p > 0.1$).

The animals exposed to multiple microwaving did not show any behavioral abnormality during the 3 week period of observation. Inspection of their eyes did not reveal evidence of cataract formation and the brains appeared normal to visual inspection.

The arterial blood gases were within physiologic limits and not significantly different in the two groups. **Thermal Washout:** pH = $7.361 \pm 0.029$, PO$_2$ = $84.15 \pm 4.72$, PCO$_2$ = $37.15 \pm 2.95$. $[^{14}]$C butanol: pH = $7.351 \pm 0.028$, PO$_2$ = $88.35 \pm 9.50$, PCO$_2$ = $38.13 \pm 2.95$.

**Discussion**

Temperature is an attractive variable to measure. Like time it is one of the easiest parameters to quantify accurately and inexpensively.

Several investigators have utilized various methods to validate thermal flow techniques. Carter et al\textsuperscript{16} used a thermoelectric heat pump in the form of a Peltier stack to measure cortical blood flow. He compared these values to those obtained from $F_g$ calculations using $^{133}$Xe clearance and found a high correlation between the two methods. Using $^{133}$Xe, a linear relation was also documented in patients during surgery.\textsuperscript{17, 18} Cusick and Myklebust\textsuperscript{12} using an isothermal conductivity system with one thermistor next to a platinum H$_2$
The present technique does not offer the chance to monitor blood flow continuously which has been one of the major advantages of other thermal methods. On the other hand, calculation of flows with the present technique can be made in absolute values without need for prior calibration.

The potential toxicity of microwave heating in this situation should be negligible since it is presumed to be non-ionizing and therefore toxic effects should only result from excessive heating.23

To our knowledge the method presented here represents the first atraumatic delivery of a flow "indicator" directly into the tissue. The technique as presently described requires the traumatic introduction of a temperature measuring device into the tissue, thus limiting it applicability.

Ideally, one would be able to measure temperatures non-invasively. One possible way to obtain non-invasive temperature measurements would be using the principle that the speed at which ultrasound travels through a fluid medium is a function of temperature, propagation velocity increasing with temperature. Measurements of the time required for ultrasound to travel a fixed distance across the skull would correlate with temperature changes if other variables remained constant. It would be difficult to obtain regional information by this method.

Another possible approach would use the technique of nuclear magnetic resonance. Relaxation times of water protons are temperature-dependent and such measurements made regionally using shaped magnetic fields could provide regional flow information. This method would be completely non-invasive. The introduction of the indicator (heat) by microwave (or longer wavelength) electromagnetic induction as suggested here would be followed by a period of measurement during which a train of brief pulses of radio frequency electromagnetic energy (much too little power to produce measurable heating) would excite nuclear magnetic resonance of tissue protons. The interval between these pulses would be one or two seconds. Neither the tracer induction nor the measurement of its washout should measurably disturb the brain tissue.

Acknowledgments

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References


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<td>55.5 ± 7.35</td>
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