Cortical Blood Flow: Thermal Diffusion vs Isotope Clearance

L. Philip Carter, M.D., Richard Erspamer, B.S., and William J. Bro, B.S.E.

SUMMARY A thermal diffusion flow probe incorporating a Peltier stack has been found to give a quantitative dynamic assessment of cortical blood flow in both the laboratory and clinical settings. Further calibration characteristics of the probe were evaluated by correlation with the fast component of Xe 1M clearance in cats. The correlation has some linear characteristics but is better defined by the equation:

\[
\text{CBF}_p = \Phi \left( \frac{1}{\Delta V} - \frac{1}{\Delta V_0} \right)
\]

Where CBF\(_p\) is flow in ml/100 g/min, \(\Delta V\) is the voltage difference of the thermocouples, and \(\Delta V_0\) is the voltage difference of the thermocouples with no flow, which was 342.8 ± 12.9 µV. \(\Phi\) describes the characteristics of the probe and was determined to be 52,431.2 ± 4796.3. The average deviation of the calculated curve from the experimental data points was ± 6.3.

The calculated \(\Phi\) differed markedly from the mean when Xe 1M fast component flows were less than 35 ml/100 g/min. This is evidence that CBF as measured by Xe 1M clearance analyzed by the bicompartamental technique loses accuracy at lower flows.

The thermal diffusion flow probe is a good device for evaluation of flow in acute ischemia models since it can delineate abrupt flow variations. Theoretically the flow probe can accurately measure flow at ischemic levels.

THE STUDY of cerebral ischemia requires cortical blood flow assessment which is continuous and accurate at reduced flows. We have employed a thermal diffusion flow probe based upon a Peltier stack to assess flow in both the laboratory and clinical environments. This technique gives a dynamic flow recording and, theoretically, should be accurate at low flows since the thermal gradient is applied directly to the cortex. In order to evaluate these recordings better we have undertaken the following study to define further the calibration and physical characteristics of the device.

The probe consists of a thermoelectric heat pump in the form of a Peltier stack with "L"-shaped gold plates soldered to the hot and cold surfaces. Copper-constantan thermocouples are fixed to the approximate center of the contact surface of each gold plate so that the output voltage from the thermocouples is proportional to the temperature difference between the plates. Thermocouple and power leads are encased in a pliable cable extending from the device which is encased in plastic. The probe weighs 1.5 g, and is 13 mm in diameter and 4 mm thick. Activation of the stack produces a temperature gradient between the plates which encompasses the ambient cortical temperature. Changes in cortical blood flow cause the thermocouple voltage to vary and this voltage is correlated with the fast component of Xe 1M clearance (\(F_g\)). Observation of the flow probe with the operating microscope has revealed that the weight of the probe causes obstruction of the pial circulation, thus leaving the probe in direct contact with the cortical capillary bed. Application of weights up to 5 g on the probe to increase probe pressure on the brain has no effect on the recording. It is therefore unlikely that the 1.5 g weight of the probe alters the flow in the cortical capillary bed. Since cortical flow is much greater than white matter flow and the probe is in direct contact with the cortex, it appears reasonable to correlate the probe with \(F_g\) in the exposed brain.

Method

Eleven mongrel cats were anesthetized with intraperitoneal sodium pentothal (40 mg/kg), paralyzed with gallamine triethiodide (20 mg) and placed on a positive pressure respirator. Additional gallamine and pentothal were given to maintain the animal on the ventilator. Bilateral craniectomies were carried out and a polyethylene cannula was threaded into the innominate artery. The flow probe was placed on the left parietal cortex and the Harshaw TASC-5 detector system was used to record Xe 1M clearance curves from the right parietal cortex. One millicurie of Xe 1M dissolved in 1 cc of saline was injected through the cannula in the innominate artery and a 15 min Xe 1M clearance curve was recorded. Only runs were analyzed that had constant cortical blood flow as measured by the probe (CBF\(_p\)) during the counting epoch. No run was accepted unless the initial counting peak was ≥ 60,000 counts per min (CPM) and ≤ 200,000 CPM. Changes in respiratory setting were used to alter PCO\(_2\) and thus CBF. At the end of each experiment cardiac arrest was produced by intravenous KCl and a dead brain or zero flow value (\(\Delta V_0\)) was obtained. The Xe 1M clearance curves were evaluated by 2 compartmental analysis and the \(F_g\) was compared to the difference between the dead brain and the thermocouple output (\(\Delta V\)) in microvolts (µV) for each run. Twenty-three Xe 1M clearance curves and 11 zero flow values were obtained.
Results

The zero flow values for the 11 animals were 325, 328, 332, 338, 340, 342, 348, 351, 360, and 367 \( \mu l \). The mean was 342.8 \( \mu l \) with a standard deviation of \( \pm 12.9 \).

The 23 \( ^{133}Xe \) clearance curves were analyzed by bicompartamental calculations. The fast component flow (F\(_f\)), slow component flow (F\(_w\)), and weights (W\(_f\) and W\(_w\)) are in the table. F\(_f\) compared to voltage difference of dead brain minus voltage difference to probe for each run (AV\(_o\) - AV) in \( \mu l \) is plotted in figure 1.

Analysis of Data

It is apparent from figure 1 that the relationship has some linear characteristics. A least squares plot of the data is shown in figure 2. This plot has a standard deviation of \( \pm 11.4 \) and the Rho value for linearity is 0.98078, a perfect linear relationship being 1.0.

Even though the linear relationship seems to describe the calibration adequately, a mathematical formula was investigated. (See fig. 3).

The model described in figure 3 is applicable to the thermal diffusion flow probe since the gold plates are insulated to prevent radiant transfer of heat. A small flange of plastic at the margins of the gold plates prevents egress of cerebrospinal fluid under the probe. Heat transfer is primarily by conduction between the gold plates and the cerebral cortex. The commonly accepted formulas for the conduction transfer of power has been discussed by numerous authors, and are as follows:

\[
Q_D = S_P K (T_H - T_B) \quad \text{and} \quad Q_{net} = S_P K (T_B - T_c)
\]

Where \( Q_D \) is power dissipated from hot plate, \( S_P \) is the coefficient of the stack, \( K \) is thermal conductivity, \( Q_{net} \) is power absorbed from cold plate and \( T_H, T_C, T_B \) are the temperatures of the hot plate, cold plate and brain respectively.

When one solves for \( T_B \):

\[
-T_B = \frac{Q_D}{S_P K} - T_H \quad \text{and} \quad T_B = \frac{Q_{net}}{S_P K} + T_C
\]

Combining the 2 equations:

\[
T_B - T_C = \frac{Q_{net}}{S_P K} + \frac{Q_D}{S_P K} = 0
\]

\[\therefore T_H - T_C = \frac{Q_{net} + Q_D}{S_P K} \]

\[
S_P K (T_H - T_C) = Q_{net} + Q_D
\]

\[\therefore K = \frac{Q_{net} + Q_D}{SF(T_H - T_C)}\]

---

**Table**

<table>
<thead>
<tr>
<th>( F_f )</th>
<th>( F_w )</th>
<th>( W_f )</th>
<th>( W_w )</th>
<th>( \Delta V_o - \Delta V )</th>
<th>( \pm )</th>
<th>( \text{CBF} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>3.7</td>
<td>40.8</td>
<td>59.2</td>
<td>19</td>
<td>106,213.5*</td>
<td>8.8</td>
</tr>
<tr>
<td>23</td>
<td>3.6</td>
<td>31.9</td>
<td>68.1</td>
<td>22</td>
<td>115,000.0*</td>
<td>10.3</td>
</tr>
<tr>
<td>28</td>
<td>3.25</td>
<td>30.5</td>
<td>69.5</td>
<td>30</td>
<td>93,333.3*</td>
<td>14.5</td>
</tr>
<tr>
<td>30</td>
<td>4.4</td>
<td>36</td>
<td>64</td>
<td>37</td>
<td>75,000.0*</td>
<td>18.4</td>
</tr>
<tr>
<td>31</td>
<td>10.9</td>
<td>35</td>
<td>65</td>
<td>62</td>
<td>44,285.7*</td>
<td>33.6</td>
</tr>
<tr>
<td>33</td>
<td>5.1</td>
<td>35.3</td>
<td>64.7</td>
<td>42</td>
<td>82,500.0*</td>
<td>21.2</td>
</tr>
<tr>
<td>43</td>
<td>10.4</td>
<td>31.2</td>
<td>68.8</td>
<td>69</td>
<td>57,333.3</td>
<td>38.4</td>
</tr>
<tr>
<td>45</td>
<td>10.9</td>
<td>37</td>
<td>63</td>
<td>83</td>
<td>50,000.0</td>
<td>48.7</td>
</tr>
<tr>
<td>48</td>
<td>14.9</td>
<td>32</td>
<td>68</td>
<td>75</td>
<td>60,000.0</td>
<td>42.7</td>
</tr>
<tr>
<td>49</td>
<td>10.0</td>
<td>32.9</td>
<td>67.1</td>
<td>78</td>
<td>54,444.4</td>
<td>44.9</td>
</tr>
<tr>
<td>49</td>
<td>11.7</td>
<td>30</td>
<td>70</td>
<td>86</td>
<td>49,000.0</td>
<td>51.1</td>
</tr>
<tr>
<td>51</td>
<td>5.9</td>
<td>21</td>
<td>79</td>
<td>92</td>
<td>46,363.6</td>
<td>56.0</td>
</tr>
<tr>
<td>67</td>
<td>8.6</td>
<td>30.1</td>
<td>69.9</td>
<td>110</td>
<td>47,857.1</td>
<td>72.1</td>
</tr>
<tr>
<td>71</td>
<td>16.3</td>
<td>44</td>
<td>56</td>
<td>100</td>
<td>59,166.7</td>
<td>62.8</td>
</tr>
<tr>
<td>71</td>
<td>11.1</td>
<td>23</td>
<td>77</td>
<td>102</td>
<td>56,800.0</td>
<td>64.6</td>
</tr>
<tr>
<td>73</td>
<td>10.8</td>
<td>25</td>
<td>75</td>
<td>120</td>
<td>45,925.0</td>
<td>82.2</td>
</tr>
<tr>
<td>85</td>
<td>19.1</td>
<td>57.1</td>
<td>42.1</td>
<td>114</td>
<td>56,666.7</td>
<td>76.1</td>
</tr>
<tr>
<td>85</td>
<td>7.1</td>
<td>27</td>
<td>23</td>
<td>119</td>
<td>53,125.0</td>
<td>81.2</td>
</tr>
<tr>
<td>93</td>
<td>19.1</td>
<td>54</td>
<td>46</td>
<td>121</td>
<td>58,125.0</td>
<td>83.3</td>
</tr>
<tr>
<td>122</td>
<td>19.0</td>
<td>41</td>
<td>59</td>
<td>153</td>
<td>50,833.3</td>
<td>123.1</td>
</tr>
<tr>
<td>125</td>
<td>10.4</td>
<td>46.5</td>
<td>53.5</td>
<td>160</td>
<td>48,076.9</td>
<td>133.7</td>
</tr>
<tr>
<td>135</td>
<td>14.0</td>
<td>44.2</td>
<td>55.8</td>
<td>166</td>
<td>48,913.0</td>
<td>143.5</td>
</tr>
<tr>
<td>147</td>
<td>14.0</td>
<td>32.4</td>
<td>67.6</td>
<td>174</td>
<td>49,000.0</td>
<td>157.5</td>
</tr>
</tbody>
</table>

Mean: 10.6 ± 5, 35.5 ± 9.1, 64.4 ± 9.2, 52,431.2 ± 4796.32

*Deleted
The thermal conductivity (K) is inversely proportional to the temperature difference (T_H - T_c) or ΔT. As pointed out by Grayson to demonstrate the relationship between flow and temperature difference (ΔT) let K_o = the thermal conductivity of dead brain, α = transfer coefficient, F = blood flow in ml/100 g/min and K = K_o + α F at any level of cortical blood flow.

\[ K_o + \alpha F = \frac{Q_{net} + Q_D}{S_p \Delta T} \]

Let ΔT_1, ΔT_2, ΔT_3, ..., represent the temperature difference for the corresponding F_1, F_2, F_3, ...

\[ \frac{Q_{net} + Q_D}{S_p \Delta T_1} = K_o + \alpha F_1 \]
\[ \frac{Q_{net} + Q_D}{S_p \Delta T_2} = K_o + \alpha F_2 \]

by subtracting the 2 equations

\[ \frac{Q_{net} + Q_D}{S_p \Delta T_1} - \frac{Q_{net} + Q_D}{S_p \Delta T_2} = \alpha (F_1 - F_2) \]
\[ \frac{Q_{net} + Q_D}{S_p} \left( \frac{1}{\Delta T_1} - \frac{1}{\Delta T_2} \right) = \alpha (F_1 - F_2) \]

\[ F_1 - F_2 = \frac{Q_{net} + Q_D}{S_p} \left( \frac{1}{\Delta T_1} - \frac{1}{\Delta T_2} \right) \]

To relate any flow to CBF_p = 0

\[ F = \frac{Q_{net} + Q_D}{S_p} \left( \frac{1}{\Delta T_1} - \frac{1}{\Delta T_0} \right) \]

where ΔT_0 = temperature difference at CBF_p = 0.

Over a limited range as occurs with this model the temperature is linearly related to voltage of the thermocouples. The temperature difference is related to the voltage difference of the thermocouples (ΔV) by the equation ΔT = γΔV.

\[ \Delta T = \frac{Q_{net} + Q_D}{S_p} \left( \frac{1}{\Delta V_1} - \frac{1}{\Delta V_2} \right) \]

Since the power input to the stack is held constant and the brain is a large heat sink compared to the gold plates, Q_{net} + Q_D does not vary significantly. S_p is the surface coefficient of the stack which does not change as long as the plates remain in contact with the cortex. α is a constant transfer factor for relating thermal conductivity to flow as used by Grayson and γ is the thermocouple constant that describes the relationship of voltage and temperature.

Let Φ = \frac{Q_{net} + Q_D}{S_p} \left( \frac{1}{\Delta V_1} - \frac{1}{\Delta V_2} \right)

\[ \Delta V = \Phi \left( \frac{1}{\Delta V_1} - \frac{1}{\Delta V_2} \right) \]

From this equation zero flow values do not need to be determined. A probe can be calibrated by knowing any 2 points on the curve.

If F_2 is 0 flow then ΔV_2 has been experimentally determined to be 342.8 μV.

\[ \Delta V_2 = \Phi \left( \frac{1}{342.8} \right) \]

Since F and ΔV have been experimentally determined for 23 points Φ was calculated for these points. (See table).

Six Φ values were greatly different from the remaining figures. Since these were at flows of less than 35...
ml/100 g/min, as determined by Xe133 clearance, these were most likely in error, as pointed out by Risberg et al.8

Olesen, Paulson and Lassen noted that bicompartamental analysis of intra-arterially injected Xe133 is not valid at low flows.9 Iliff et al. stated that with reduced flows the resolution of clearance curves into two compartments is difficult and to some extent arbitrary.10

A mean of 52,431.2 ± 4796.3 was found by deleting these six values. Figure 4 demonstrates the plot of

$$\text{CBF}_p = 52,431.2 \left( \frac{1}{\Delta V} - \frac{1}{342.8} \right)$$

The average deviation of the calculated curve from the 17 experimental data points was ± 6.3.

Discussion

Gibbs originally demonstrated that changes in cerebral blood flow could be detected using thermal techniques.11 In 1952 Grayson found that changes in thermal conductivity are linearly related to blood flow, thus permitting quantitative evaluation.4 Assessment of flow with thermal diffusion techniques in myocardium was demonstrated by Benzing12 and in skin by Van De Staak, et al.13 Betz et al. and Levy et al. have pointed out the dependence of thermal techniques on local vascular geometry;14 however, this problem can be surmounted by the use of a larger contact surface, thus producing an averaging effect over the capillary bed and placing the probe on the cortex in a manner avoiding major vascular channels. Since the absolute temperature of the tissue being evaluated may change, Brawley used a Peltier stack to produce a temperature gradient which theoretically should not change significantly with gradual alteration in tissue temperature.18 In 1973 Carter and Atkinson reported that indeed this does remain constant within the physiologic temperature range and the temperature gradient is linearly related to the fast component of Xe133 clearance in the exposed cerebral cortex of cats up to 90 ml/100 g/min.1

Xe133 clearance in the exposed cortex was chosen as the experimental model for calibration because this is an accepted method of determining cortical blood flow (Fg). This technique differs from our previous study1 by using a more sophisticated detector system and higher count rates, thus increasing the accuracy of the Xe133 clearance curves. Obviously the accuracy of the calibration depends upon the reliability of the Xe133 clearance curves which have an estimated 7% error.18 At lower flow rates the accuracy of isotope clearance falls off due to less tracer entering the tissue initially. Olesen et al. and Iliff et al. have pointed out the difficulties of obtaining accurate flow values with intra-arterial injected Xe133 at low flows.8,9 Bicompartamental analysis will overestimate Fg at lower flows as pointed out by Risberg et al.8 This occurs because in separating the compartments some slower Ff values are included in Fw, therefore overestimating Fg as is demonstrated in Fig. 4. We confirmed this in the present study by constructing an equation to describe the relationship between F and ΔV. Below 35 cc/100 g/min F changed markedly.

Φ should be the same for each flow probe at the same input to the Peltier stack. It depends upon the power transferred from the hot plate to the brain, the power transferred from the brain to the cold plate, and the characteristics of the stack, plates and thermocouples. Obviously, if the plates lose contact with the cortex or the Peltier stack, or plates are altered, Φ will change.

Figure 5 demonstrates our previously reported calibration curve of M, probe.1 This probe was physically different than the M8B probe which was used in this study. The gold plates were of different size and shape, the Peltier stack was different and the power input was not the same; therefore Φ would describe a different curve. Probe M8A is of similar construction to M8B but was calibrated by comparing to M1. The M8A and M8B have similar slopes which differ from the M1 slope.

One may question our placement of the probe on one hemisphere while measuring isotope clearance in the other; however, we believed this was preferable to looking at different lobes of the same hemisphere. Ideally one would record thermal and isotope...
THERMAL DIFFUSION IN CORTICAL BLOOD FLOW/Carter et al.

from brain resection and autopsy cases is now being studied to delineate further the thermal conductivity of nonperfused human cortex.

Previously described thermal probes have been based on heated and neutral plates.26 The Peltier flow probe with an actively cooled surface has 3 advantages over such a probe:

1) The temperature gradient can be greater without heating the hot plate over 42°C which could cause tissue damage.

2) Changes in cortical temperature affect a neutral plate directly while the cooled plate is not as directly affected. The temperature gradient is maintained despite alteration of the temperature of the brain.

3) A neutral plate may be affected by the heated plate's thermal field. This is less likely to occur with active cooling.

The thermal flow probe has some advantages over other techniques of measuring cortical blood flow such as isotope or hydrogen clearance. The thermal flow probe is theoretically more accurate at lower flows, and can demonstrate abrupt changes in flow. There is no need to perforate the pial membrane and the thermal flow probe is easy to use. These advantages make the technique useful for studying cerebral ischemia models and observing pharmacological effects in the laboratory. The probe has been of help in the operating theater and may provide some information in monitoring postoperative patients.

References


14. Betz E, Ingvar DH, Lassen NA, Schmahl FW: Regional blood
FIBROMUSCULAR HYPERPLASIA involving the cervical portion of the internal carotid artery has been reported to be a cause of cerebrovascular insufficiency.\(^{1,2}\) Demonstration of this lesion, however, has been limited to arteriography. We report a patient with fibromuscular hyperplasia demonstrated with gray scale digital sonography. The advantages of sonographic evaluation of the carotid arteries as a non-invasive screening procedure are discussed.

**Report of a Patient**

A 44-year-old normotensive white female was found to have loud, high-pitched bilateral carotid bruits during a routine physical examination. She was referred for neurological evaluation and follow up. Initial clinical examination revealed a rather intense, nervous lady with a blood pressure of 126/68; no cardiac murmurs were found on auscultation. No signs or symptoms suggestive of peripheral arterial disease were detected. She had bilateral loud pansystolic bruits over both areas of carotid bifurcation. Neurological examination was normal. Non-invasive cerebrovascular tests were performed. Carotid phonoangiogram confirmed the bruits to be of carotid origin and her oculophthysmography (OPG) was found to be normal bilaterally. Carotid sonography, utilizing a commercially available Rohe digital gray scale ultrasound unit, model 5580, equipped with a 5 mHz short focus transducer, was used. Several areas of segmental stenosis were demonstrated revealing multiple areas of shadowing (figs. 1A, 1B) similar to a sonogram demonstrating atherosclerotic disease with calcific plaques of the carotid arteries. Subsequently a bilateral internal carotid angiogram showed typical findings of bilateral internal carotid artery fibromuscular hyperplasia (figs. 2A, 2B). Because the natural history of fibromuscular hyperplasia of the carotid artery is still unclear, it was decided to follow the patient clinically. In the past 16 months, the patient continued asymptomatic.

**Discussion**

Fibromuscular hyperplasia is an arterial dysplasia of unknown etiology which usually involves the renal arteries.\(^{11}\) It has also been reported to involve the internal carotid arteries often producing transient cerebrovascular insufficiency.\(^{1,2}\) Arteriography is usually the procedure of choice in evaluating the extracranial portion of the internal carotid artery. However, carotid arteriography, either by direct puncture of the carotid artery or catheterization of the femoral artery, is a traumatic and invasive procedure which requires ionizing radiation. Ultrasound, on the other hand, is atraumatic and non-invasive. It has recently gained considerable popularity in evaluating carotid artery disease. More sophisticated Doppler-flow units, as well as ocular pneumoplethysmography, have been reported to be valuable for the detection of carotid artery stenosis.\(^{2,4}\) More recently, high resolution real-time ultrasound has produced scans of considerable detail in visualizing the area of the carotid bifurcation.\(^{2,4}\)
Cortical blood flow: thermal diffusion vs isotope clearance.
L P Carter, R Erspamer and W J Bro

doi: 10.1161/01.STR.12.4.513

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/12/4/513

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/