

**SEATO Medical Research Studies in Neurology**

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**General Introduction** As a result of a thirteen-week preliminary investigation of malaria and its clinical effects on the nervous system<sup>1</sup>. it was evident that investigations of cerebral hemodynamics and metabolism were warranted not only in malaria but in other systemic infections. The following report describes the experience and results obtained during the application of a cerebral blood flow technique.

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## STUDY REPORT

Title: Malaria and the Nervous System: Cerebral Hemodynamics and Metabolism in Patients with Malaria and Central Nervous System Symptoms

### Part I. Cerebral Hemodynamics in Young Thai Males

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In 1948 Kety and Schmidt introduced the nitrous oxide technique for the determination of cerebral blood flow and metabolism and established normal values in fourteen healthy young men.<sup>2</sup> Since then a considerable amount of information has been accumulated on the effect of various drugs and disease states on cerebral hemodynamics and metabolism. During the past twenty years technological innovations, particularly the use of isotopes, have refined the determination of cerebral blood flow; nevertheless, the original Kety and Schmidt inert gas procedure and the principle on which it is based remain the standards against which other techniques are compared.

This report describes the first measurements of cerebral blood flow in Thailand, discusses the use of the Scheinberg and Stead simplification<sup>3</sup> of the Kety and Schmidt nitrous oxide technique, and then compares the results with those obtained by previous investigators.

Introduction. The inert gas technique is based on the Fick Principle. Applied to the measurement of cerebral blood flow, the Fick Principle postulates that the flow is equal to the ratio of the brain uptake of inert gas per unit time and the arteriovenous difference of this gas during the same period. Kety & Schmidt used 15% nitrous oxide as the physiologically inert gas and administered it to supine patients for ten minutes. During the ten minutes saturation period, multiple simultaneous superior jugular bulb and femoral artery samples were obtained, their arteriovenous differences integrated, and the resultant value placed in the denominator of the Fick equation. The numerator of the equation, representing the nitrous oxide concentration of the brain at saturation, was derived from the concentration of the inert gas in the jugular bulb at the end of ten minutes.<sup>2</sup>

### The Fick Equation

$$* \text{ CBF} = \frac{100 \text{ C}_{v10} \cdot S}{\int (C_a - C_v) dt}$$

- Where
- CBF = Cerebral blood in ml./min./100 grams of brain
  - C<sub>v10</sub> = The concentration of nitrous oxide in the jugular bulb at the end of ten minutes
  - S = The brain: blood coefficient; this factor represents the ratio of nitrous oxide solubility in blood and brain for varying hematocrits
  - $\int (C_a - C_v) dt$  = The arteriovenous nitrous oxide difference integrated over 10 minutes.

This technique which measures only the mean blood flow requires that the concentration of the inert gas and its rate of administration remain constant throughout the ten minute saturation period, and that arterial pCO<sub>2</sub> not change appreciably ( $\pm 4.5$  mm Hg)<sup>5</sup> during the procedure. Kety<sup>2</sup> and Lassen<sup>6</sup> have discussed the theoretical bases for the experimental assumptions which are made in this method.

Scheinberg and Stead simplified the Kety-Schmidt procedure by drastically reducing the number of nitrous oxide determinations.<sup>3</sup> The denominator of the Fick equation was obtained by mechanically integrating arterial and jugular bulb samples over ten minutes and the drawing a rapid jugular bulb sample whose nitrous oxide content represented the nitrous oxide content of the brain at the end of ten minutes.\*

Method. Healthy males between 21 and 30 who volunteer for this study are seen by at least one of the investigators (U.K. and/or M.C. and W.B.) the day before the procedure. An explanation of the procedure is given to each patient. Pertinent history is obtained, and physical examination, chest films, urinalyses, and EKG's are then done. If no abnormalities are found the patient returns the next morning for cerebral blood flow examinations.

Before beginning the procedure each patient is placed on a stretcher cart where he rests for at least 10-15 minutes. The right mastoid tip and the left antecubital areas are then washed with Methyolate. The cutaneous and subcutaneous areas below the mastoid process and around the antecubital fossa are then infiltrated with 1% Xylocaine. A 19 gauge, 13/4 inch siliconated needle attached to a 5-ml syringe is inserted just below and anterior to the tip of the mastoid process and directed anteriorly and superiorly in the direction of the internal auditory meatus. The needle passes just beneath the base of the skull and enters the superior bulb of the internal jugular vein shortly after it exits from the jugular foramen. Figure 1 illustrates the course of the needle. An 18 gauge Courmand needle is placed in brachial artery. The needles are attached through suitable adapters to the 5 stop-cock sampling manifolds which are fitted with flushing syringes and lightly glycerinated and heparinized sampling syringes. A drip containing 500ml. of 5% dextrose and water mixed with 5 mgms of Heparin keeps the jugular bulb needle patent. A dampened aneroid manometer<sup>7</sup> attached to the arterial manifold monitors mean arterial blood pressure (MAP). When mean arterial pressure becomes stable the manifolds are filled with blood, a 6-ml control sample is drawn from the jugular bulb, and simultaneous arterial and venous samples are drawn for pH, pCO<sub>2</sub> and hematocrit.

\* Adapted from McHenry<sup>4</sup>.

\* The brain: blood coefficient for nitrous oxide at normal hematocrits is unity.

Immediately after re-checking the mean arterial pressure the patient begins to breath a gas mixture of 15% nitrous oxide, 25% oxygen and 60% nitrogen through a Ruebens non-rebreathing valve. As soon as gas inhalation starts the simultaneous venous and arterial blood samples are drawn at the rate of 2 ml. per minute for 10 minutes. At the end of 10 minutes the stop-cocks to the integrated samples are closed and while the patient continues to breath the gas mixture 6-mls. of venous and arterial blood are drawn in 20 seconds. The mask is then removed, the mean arterial pressure checked, and samples for pH and  $pCO_2$  are rapidly drawn. The mechanically integrated blood samples are analyzed for nitrous oxide by the Kety modification of the Orcutt-Waters-Van Slyke procedure<sup>2</sup> and for oxygen and carbon dioxide contents by the Van Slyke-Neill manometric technique.<sup>8</sup> pH and  $pCO_2$  are measured with the Astrup Radiometer apparatus and nomograms.<sup>9</sup>

Figure 2 illustrates the Scheinberg and Stead method for calculating mean cerebral blood flow (CBF), cerebral vascular resistance (CVR), and cerebral oxygen consumption ( $CMRO_2$ ).

Results and Discussion Table I demonstrates the results obtained in 26 normal, young, male volunteers. Using the Scheinberg and Stead modification of the Kety-Schmidt nitrous oxide method we obtained a mean cerebral blood flow of 57.0 ml./min./100 grams of brain, a mean cerebral vascular resistance of 1.5 mm Hg/ml./min./100 grams of brain, and a mean cerebral oxygen consumption of 3.8 ml./min./100 grams of brain. Significant changes of  $pCO_2$  pH and mean arterial pressure did not occur during the procedures. These results and their standard deviations are similar to those obtained by earlier investigators who used the same method (Table 2). Our results also closely approximate those obtained by Lassen and Munck.<sup>13</sup> (CBF=51.9ml./min./100 grams of brain with a S.D. of 8.6) and McHenry<sup>14</sup>. (CBF=56.5ml./min./100 grams of brain with a S.D. of 7.7) both of whom used the more accurate Krypton<sup>85</sup> saturation and desaturation methods.

No complications occurred in the 26 patients described in this report. In an earlier group of 53 patients we had three minor complications: two vasovagal reactions which quickly responded to raising the foot of the stretcher cart and one case which developed a five minute paresis of the muscles on the right side of the face secondary to Xylocaine infiltration of the peripieral branches of the facial nerve. Fazakas has reported similar complications.<sup>12</sup>

Summary: The measurement of cerebral hemodynamics and oxygen metabolism in 26 young normal Thai males is described.

The bases of the Kety-Schmidt inert gas technique are discussed and the data obtained in our patients with this method are compared with those of other investigators.

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**Figure 1. Basal view of the skull demonstrating the method for puncturing the superior bulb of the internal jugular vein.**

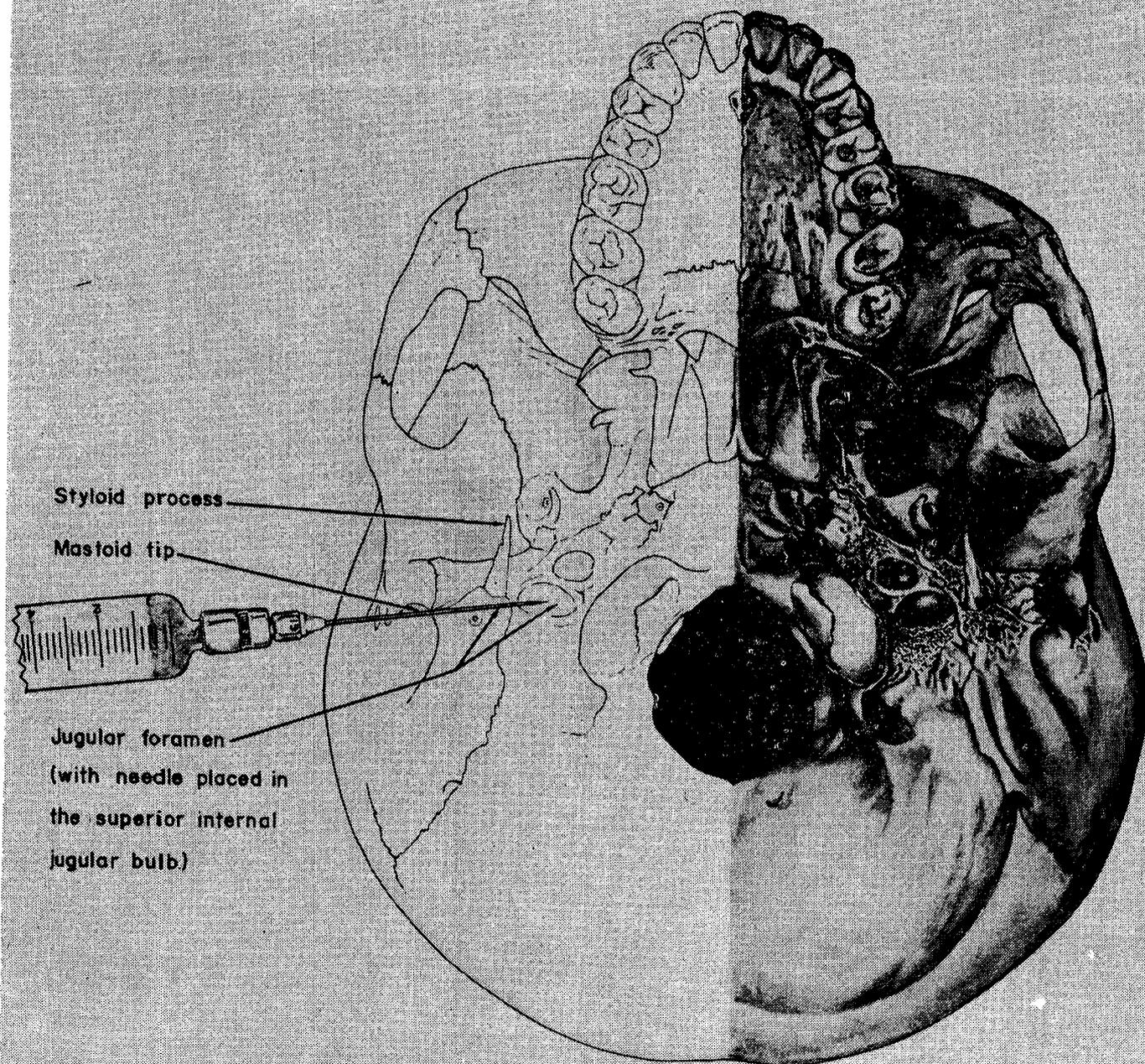


Figure 2

\* An Illustration of the Scheinberg—Stead Method for Calculating Mean Cerebral Blood Flow (CBF), Cerebral Vascular Resistance (CVR) and Cerebral Oxygen Consumption (CMRO<sub>2</sub>)

		Subject #17		
		Nitrous Oxide Analyses (in Vol%)		
		1st Analysis	2nd Analysis	Mean
** Control		1.18	1.18	1.18
RJB <sub>F</sub>		5.32	5.34	5.33
LBA <sub>F</sub>		5.31	5.34	5.33
∫ LBA		5.20	5.17	5.19
∫ RJB		4.48	4.50	4.49
A-V <sub>N<sub>2</sub>O</sub>				0.70

$$1. \text{ CBF} = \frac{(\text{RJB}_F - \text{Control}) \times 100}{\text{A-V}_{\text{N}_2\text{O}} \times 10} = \frac{(5.33 - 1.18) \times 100}{0.70 \times 10} = 59.3 \text{ ml/min/100 grams of brain}$$

$$2. \text{ CVR} = \frac{\text{MAP (Mean Arterial Pressure)}}{\text{CBF}} = \frac{84}{59.3} = 1.4 \text{ mm Hg/ml/min/100 grams of brain}$$

$$3. \text{ CMRO}_2 = \text{CBF} \times \frac{\text{Arteriovenous O}_2 \text{ difference}}{100} = 59.3 \times \frac{6.5}{100} = 3.9 \text{ ml/min/100 grams of brain}$$

∫ LBA = integrated artery sample  
 ∫ RJB = integrated jugular bulb sample  
 A-V<sub>N<sub>2</sub>O</sub> = integrated arteriovenous nitrous oxide difference

\* All analyses are done in duplicate and then averaged  
 \*\* RJB<sub>F</sub> = Jugular bulb sample at saturation  
 LBA<sub>F</sub> = Brachial artery sample at saturation (this sample is obtained as a control and should be no more than 0.4 Vol% more than RJB<sub>F</sub>)

**Table I**  
**Cerebral Blood Flow, Cerebral Oxygen Consumption**  
**Cerebral Vascular Resistance and Blood Gases in 26 Normal Young Thai Males**

Subject	Age	CBF	CMRO <sub>2</sub>	CVR	MAP	O <sub>2</sub> Content		CO <sub>2</sub> Content		Arteriovenous O <sub>2</sub> Differences	Control pH		Control pCO <sub>2</sub>		Hct %
						BA	JB	BA	JB		BA	JB	BA	JB	
1	29	51.3	3.5	1.9	97	17.4	10.5	49.6	54.6	6.9	7.40	7.29	41.0	52.8	38
2	22	53.9	3.8	1.8	97	16.8	9.7	48.3	55.6	7.1	7.33	7.30	49.0	50.0	39
3	25	64.2	6.3	1.1	88	17.0	9.2	50.6	58.3	7.8	7.39	7.37	41.0	45.0	36
4	24	63.6	3.8	1.5	95	19.1	13.2	47.5	52.9	5.9	7.39	7.37	41.5	60.0	44
5	22	56.4	4.1	1.5	86	18.8	11.5	48.8	53.7	7.3	7.34	7.28	40.0	57.0	42
6	24	66.7	4.8	0.9	90	20.3	13.1	52.5	58.9	7.2	7.35	7.29	43.5	56.0	49
7	26	66.1	4.0	1.2	82	18.5	12.5	49.1	55.1	6.0	7.36	7.29	40.0	53.0	44
8	30	53.0	3.2	1.6	83	16.5	10.4	51.8	56.9	6.1	7.33	7.31	47.0	53.5	39
9	26	49.7	3.4	1.8	89	17.7	10.9	51.0	57.4	6.8	7.35	7.30	42.0	54.0	41
10	21	70.0	4.9	1.3	90	19.0	12.0	47.9	55.0	7.0	7.40	7.33	41.0	56.2	47
11	24	62.3	4.2	1.5	91	18.0	11.3	47.4	53.7	6.7	7.39	7.32	40.5	52.0	41
12	22	48.0	2.4	0.9	90	17.2	12.1	55.0	60.0	5.1	7.39	7.32	48.0	49.0	40
13	22	59.3	3.9	1.4	84	15.9	9.4	50.5	56.7	6.5	7.39	7.32	40.0	57.0	39
14	30	45.8	2.7	1.7	80	17.3	11.4	49.9	56.2	5.9	7.40	7.36	41.5	43.5	41
15	26	49.4	3.5	1.7	84	19.2	12.2	49.5	55.7	7.0	7.40	7.35	38.5	54.0	45
16	22	48.8	3.4	1.7	83	18.0	11.1	52.0	58.3	6.9	7.37	7.34	44.0	50.0	45
17	22	65.9	3.8	1.2	76	19.8	14.0	53.7	59.4	5.8	7.45	7.40	40.5	51.0	47
18	28	47.3	3.3	1.6	76	18.2	11.2	51.6	58.7	7.0	7.36	7.33	40.5	52.5	42
19	23	44.4	3.0	2.0	87	17.2	10.9	49.9	55.3	6.7	7.32	7.27	44.0	56.0	38
20	24	71.6	5.1	1.2	86	18.5	11.3	54.3	61.5	7.2	7.36	7.29	47.0	62.0	41
21	23	48.4	3.0	1.6	79	19.5	13.2	48.0	54.3	6.3	7.38	7.33	-	-	45
22	24	59.9	4.2	1.3	79	17.5	10.5	48.8	55.1	7.0	-	-	-	-	40
23	28	64.4	3.4	1.4	87	15.5	10.2	50.7	55.4	5.3	-	-	-	-	34
24	22	53.9	3.0	1.5	81	19.1	12.8	51.6	58.0	6.3	-	-	-	-	43
25	25	58.3	3.7	1.6	91	18.5	12.2	53.4	59.3	6.3	-	-	-	-	40
26	24	60.3	3.5	1.4	83	16.6	10.8	48.6	54.1	5.8	-	-	-	-	38
Mean															
25	57.0	3.8	1.5	86	18.0	11.4	50.5	56.6	6.5	7.37	7.32	42.5	53.7	41.5	
Standard Deviation															
8.1	0.8	0.3	5.5	1.2	1.2	2.1	2.2	0.7	0.03	0.03	3.0	3.9	3.6		
Number of Determinations															
26	21	21	20	20	20	20	20	20	20	20	20	20	20	20	20

Table 2

Normal Mean Blood Flows Obtained by Investigators Using the Nitrous Oxide Technique

Investigators	No. of Observations	Mean Age	CBF	S.D.	CMRO <sub>2</sub>	S.D.	CVR	S.D.	MAP	S.D.	Arteriovenous O <sub>2</sub> Differences	S.D.
Kety & Schmidt <sup>2</sup>	34	25	54.0	±12.0	3.3	±0.4	1.6	±0.4	86	±7.0	6.3	±1.2
Scheinberg & Stead <sup>3</sup>	33	25	64.7	±12.1	3.8	±0.6	1.3	±0.2	83	±8.3	6.0	±0.8
Bernsmeier & Siemons <sup>10</sup>	30	37	58.3	±6.6	3.7	±0.4	1.5	±0.3	95	±11.0	6.4	±0.8
Fazekas et al <sup>11</sup>	12	32	57.5	—	3.2	—	1.7	—	94	—	—	—
Chipman et al <sup>*</sup>	26	25	57.0	±8.1	3.8	±0.8	1.5	±0.3	86	±5.5	6.5	±0.7

\* Data presented in this report