THE NITROUS OXIDE METHOD FOR MEASUREMENT OF CEREBRAL BLOOD FLOW AND CEREBRAL GASEOUS METABOLISM IN DOGS*

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Quantitative estimation of cerebral blood flow has been made possible by the recent introduction of the nitrous oxide method of Kety and Schmidt[7] and the dye method of Gibbs.[4] These indirect methods are particularly suited to the dog. The fallibility of direct methods and anatomical peculiarities of the dog have been discussed in detail elsewhere.[16] A corollary to the measurement of cerebral blood flow is the measurement of cerebral gaseous metabolism. This will be considered more fully later.

The following investigation was undertaken in the course of experiments devised to determine the effect of intracranial injury upon both cerebral blood flow and cerebral gaseous metabolism.[3] The present paper provides the technical background to this study, and also gives in detail the control observations made prior to intracranial injury.

The nitrous oxide method was used in preference to the dye method as the former had been published in more detail, had been applied to more varied situations, and sources of error had been better evaluated. The details of the technique are as nearly as possible those employed by Kety and Schmidt,[7, 8, 10] although they have not published the minutiae as applied to the dog. A few modifications which do not alter the validity of the method were made.†

General principles

The theory of the nitrous oxide method for determination of the cerebral blood flow has been described by Kety and Schmidt[7] and subjected to critical analysis, more recently by Kety.[9] In brief, it depends upon the fact that this gas is physiologically inert in the low concentrations employed.

Samples of blood are withdrawn simultaneously from the arterial and cerebral venous circulation at intervals after the animal begins breathing the gas. The levels of nitrous oxide measured in these samples are plotted against the time of their withdrawal. An arterial and venous curve of nitrous oxide content can be interpolated and the area between these curves

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is a function of the cerebral blood flow during the time of sampling. This relation may be expressed by the equation:

$$CBF = \frac{100\ V_t \quad S}{\int_0^t (A - V)\ dt}$$

where CBF is cerebral blood flow, as cc./100 gm. of brain/min.; V_t is the nitrous oxide content of the cerebral venous blood in volumes per cent when it is in equilibrium with brain tissue; S is the distribution ratio of nitrous oxide between blood and brain; $\int_0^t (A - V)\ dt$ is the integral of the arteriovenous difference of nitrous oxide in volumes per cent from the onset of nitrous oxide inhalation, 0, to equilibrium time, t. Equilibrium time is approximately 10 minutes, when the distribution of nitrous oxide between blood and brain is equal, hence S equals one.[10]

To supplement the determination of cerebral blood flow, an estimate is obtained of the average arteriovenous difference of oxygen and carbon dioxide during the period of the cerebral blood flow measurement. The necessary calculations depend upon the Fick principle. Applied to the cerebral circulation, this states that the cerebral oxygen consumption in cc. of oxygen is equal to the cerebral blood flow through the brain multiplied by the cubic centimeters of oxygen taken out of each cubic centimeter of this blood, or 100 CMR = CBF x $(A - V)_{O_2}$, where CMR is cerebral metabolic rate or the cerebral oxygen consumption.

Since $(A - V)_{O_2}$ is expressed in volumes per cent and CBF as cc./100 gm. min., the CMR is expressed as cc. of O_2/100 gm. of brain/min.

Method

The principal observations concerned cerebral blood flow and oxygen consumption in the lightly anesthetized dog. Subsidiary and often concomitant observations were made of other physiological functions. These included: pulse rate, respiratory rate, mean femoral arterial blood pressure, total body oxygen consumption, tidal air, respiratory minute volume, rectal, stomach, and skin temperatures. Room temperature was also recorded.

Material. Twenty-two mongrel dogs* of both sexes were operated upon in the morning after an evening fast (Table 3). Intravenous pentobarbital, 30 mgms./kg., supplemented when necessary by 5-15 mgm./kg. doses, was used to maintain relatively steady light anesthesia. The manipulations were made with a minimum of operative trauma and were unsterile.† Operative blood loss was not accurately determined

* Analysis of results in 17 experiments are presented.

† The temporal muscle was reflected prior to the first measurement in preparation for the observations to be made after intracranial injury.

though it possibly amounted to 25-100 cc. An additional 80 cc. of blood were required for each cerebral blood flow determination and ancillary measurements of oxygen and carbon dioxide. Large dogs between 10.8 and 26 kg. were used in order to avoid serious depletion of the circulating blood volume.

Technique of blood sampling. The mechanical arrangement of the apparatus is indicated in Figure 1A. Arterial blood was obtained from a cannula in a femoral artery. Cerebral venous blood was obtained through a cannula screwed into the

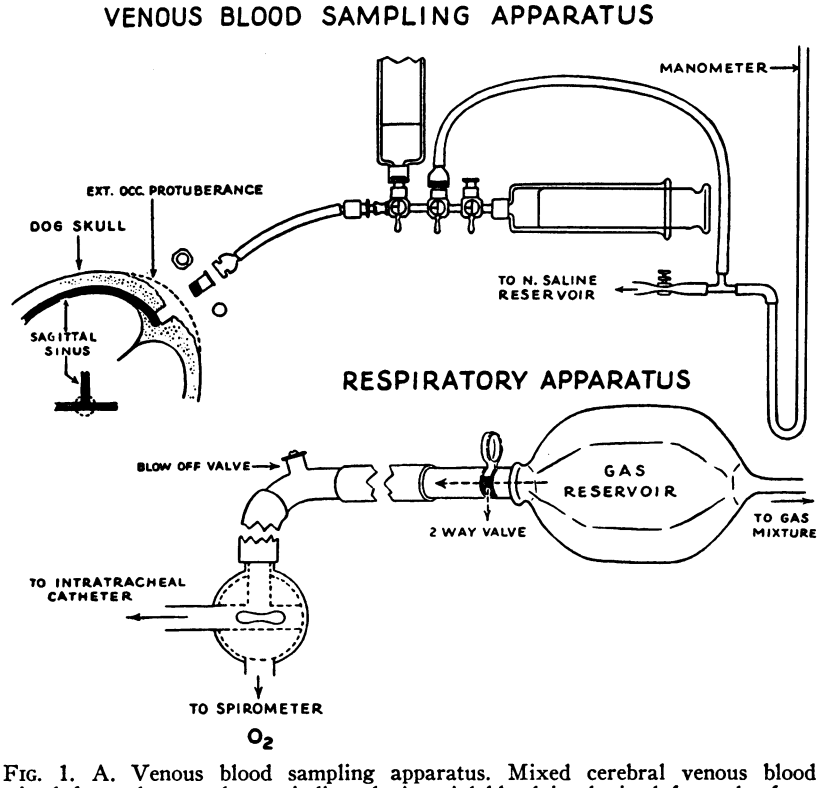

FIG. 1. A. Venous blood sampling apparatus. Mixed cerebral venous blood is obtained from the torcular as indicated. Arterial blood is obtained from the femoral artery with a slightly modified cannula for the artery and a Hg manometer. See text.
B. Respiratory apparatus. Nitrous oxide mixtures supplied from either a large spirometer, a closed system, or from the rubber-bag reservoir as indicated for an open system, provide the necessary inert blood gas. See text.

posterior portion of the skull in the midline, entering the sagittal sinus of the torcular. A series of three-way stopcocks was attached to the cannulae.

No systemic anticoagulant was used, although cannulae were rinsed with dilute heparin solution in normal saline or 5% chlorazole-pink.

Each sample of blood was between 3-5 cc. A few drops of 5% chlorazole-pink or heparin were used in 10 cc. syringes to prevent coagulation. The interior of each syringe was coated with mineral oil. Syringes filled with blood were capped with metal caps, shaken briskly and stored in ice and water. One cc. of mercury was added to each syringe after all samples were drawn.

A sample of arterial and one of venous blood were collected immediately before inhalation of the gas mixture was begun. After gas inhalation was begun, a series of five pairs of samples of arterial and venous blood were taken at 0-1 minutes, 1′ 15″, 3′, 5′, and 10′ respectively. Each of the last four samples was drawn in about 15″.

Technique of gas administration. The mechanical arrangement of the apparatus is indicated in Figure 1B. An intratracheal catheter with inflatable bag afforded a gas-tight airway. To this was attached a system of valves leading either to a gas mixture contained in a closed spirometer with soda-lime carbon dioxide adsorbent or to a rubber bag (an open system as indicated in Fig. 1B) which was filled with the gas mixture to be inhaled and also supplied with a blow-off valve for exhalation into the ambient air.

The closed system was used with a mixture of 25% nitrous oxide and 75% oxygen. Preliminary inhalation of 100% oxygen for about 30 minutes was needed partially to denitrogenate the blood to permit accurate analyses of nitrous oxide. The three-way valve, indicated, enabled immediate transition from breathing 100% oxygen provided in one spirometer to the gas mixture in a second spirometer. Both spirometers were fitted with soda-lime carbon dioxide adsorbent.

The alternate, open system, was more physiological. It required no preliminary denitrogenation or carbon dioxide adsorption, and used nitrous oxide and nitrogen mixed with 21% oxygen. Either 13% or 34% nitrous oxide was used.*

Technique of blood gas analysis. Blood gas analyses followed the techniques used by Kety, with the modification that 1 cc. volumes of blood were used instead of 2 cc. volumes satisfactory in man. The details not available are outlined.

When the simple nitrous oxide-oxygen mixture was used, the corrected partial pressure due to residual nitrogen in the preliminary sample was determined using factors for nitrogen as given by Van Slyke and Neil.[18] Then, the partial pressure of the nitrogen in the preliminary arterial sample was subtracted from the total inert gases in the other arterial samples and the partial pressure due to nitrogen of the preliminary venous sample was subtracted from the total inert gases in the other venous samples. These doubly corrected partial pressures were calculated as volumes per cent of nitrous oxide using the factors calculated by Orcutt and Waters.[13]

When a mixture of nitrous oxide, nitrogen, and oxygen was used, no preliminary inhalation oxygen was necessary and only a preliminary venous sample was needed. To eliminate the fraction due to nitrogen, Kety[7] has applied a correction which may be stated as follows: $V_{N_2O} = 1.03\ V_o - 1.1$ where V_o is the partial pressure of inert gases corrected for the partial pressure of reagents and water vapor (columns 7 and 8, Table 1).†

The manipulations used to determine nitrous oxide content described by Orcutt and Waters, and suggested in part by Kety, to expedite the analysis are as follows. For 1 cc. volume of blood: A standard Van Slyke-Neil apparatus was used to evacuate 7.5 cc. of distilled water and 2 drops of capryllic alcohol in the vacuum chamber at the 50 cc. level under mercury seal. After shaking for 1.5 minutes, 6 cc. of this emulsion were expelled into the cup above the chamber and used as a seal for the introduction of 1 cc. of whole blood into the chamber without contact with air. One cc. of emulsion in the cup was then reintroduced, washing the blood completely into the chamber. Two cc. of gas-free potassium hydroxide, hydrosulphite, anthraquinone beta-sulphonate solution were then added to adsorb all oxygen as well as carbon dioxide. A mercury seal was secured and the mixture was again evacuated at the 50 cc. level and shaken for

* Gas mixtures were obtained from the Thomas A. Edison Gas Co. of New Jersey.

† This has been recalculated for the percentages of gases employed and has been found to be unchanged.

3 minutes. A reading of the pressure of the evacuated gases and water vapor, P, (columns 2 and 3, Table 1) was obtained, and the temperature, tw, (column 1, Table 1) recorded as in example #15. Each observation, P, was also corrected for the partial pressure due to water vapor, $P_1 = P - P_{H_2O}$ (column 4, Table 1). Duplicate blank analyses, P_b, were made in exactly the same manner upon the reagents. Using a nomogram for convenience, the readings were corrected for the partial pressure of water at the temperature of observation, tw, e.g., $P_o = P_b - P_{H_2O}$. The corrected values were in turn corrected for the partial pressure due to the reagents in P_b, by

TABLE 1

DATA FROM GRAPH, EXPERIMENT #15

			$P_1 =$					*Time of drawing samples*		
t_W	S	P	$P-P_{H_2O}$	P_1-P_o	V_o	$1.03V_o$	V_{N_2O}	*Initial*	*Final*	*Mean*
°C.		*mm. Hg*			*vol. %*					
21.1	P_b	130.0	110.6	Blank on Reagents						
21.3	"	130.0	110.4	Mean 110.5 = P_o						
20.0	A1	172.3	154.8	44.3	11.81	12.18	11.1			
20.5	V1	142.0	123.9	13.4	3.57	3.68	2.6	0′ 30″	0′ 59″	.74′
20.6	A2	177.0	158.8	48.3	12.88	13.26	12.2			
21.0	V2	149.0	130.3	19.8	5.28	5.45	4.4	1′ 4″	1′ 16″	1.17′
21.3	A3	186.0	167.0	56.5	15.00	15.45	14.4			
21.3	V3	165.3	146.3	35.8	9.50	9.80	8.7	3′ 1″	3′ 9″	3.08′
21.0	A4	188.0	169.3	58.8	15.63	16.10	15.0			
21.0	V4	175.0	156.3	45.8	12.20	12.58	11.5	5′ 1″	5′ 10″	5.09′
21.0	A5	190.5	171.8	61.3	16.30	16.80	15.7			
21.0	V5	185.5	166.8	56.3	14.95	15.40	14.3	10′ 0″	10′ 10″	10.08′

Legend:
t_W Temperature of observation.
S Sample.
P Observed residual partial pressure.
P_{H_2O} Vapor pressure of water.
V_o Inert gas content of sample.
V_{N_2O} Nitrous oxide content of sample.

subtracting the mean P_o from all the observations, e.g., $P_1 - P_o$ (column 5, Table 1). These partial pressures, due to nitrous oxide alone, or nitrous oxide plus a small amount of nitrogen, were computed as content in volumes per cent with factors derived for nitrous oxide by Orcutt and Waters[12] (column 6, Table 1). A nomogram may be used here also for rapid calculation (Chart 1). Duplicate checks of nitrous oxide within 0.2 volumes per cent were consistently obtainable.

Calculations. The values of nitrous oxide content were plotted against the mid-time of drawing the samples. The area between the curves (Fig. 2) representing arterial and venous nitrous oxide content was determined graphically. The areas of trapezoids one minute in width and a length taken as the average ordinate in the period considered, were summed as illustrated in Figure 2 and Table 2. The area thus obtained was introduced into the equation for cerebral blood flow, together with the appropriate venous nitrous oxide content, and the cerebral blood flow computed.

The average arterio-venous oxygen and carbon dioxide differences during the course of the experiment were obtained by pooling simultaneous 5 cc. arterial and venous samples drawn before and after gas mixture inhalation. These were analysed in duplicate.

Nomograms for N_2O Content in Blood

$$p_{N_2O} + p_{Sol} - P_b = p_{N_2O}^{[p_{N_2O} + p_{Sol} + p_{H_2O}]} - p_{H_2O} = p_{N_2O} + p_{Sol}$$

$$p_{N_2O} \times F = \text{Vol}\%\, N_2O$$

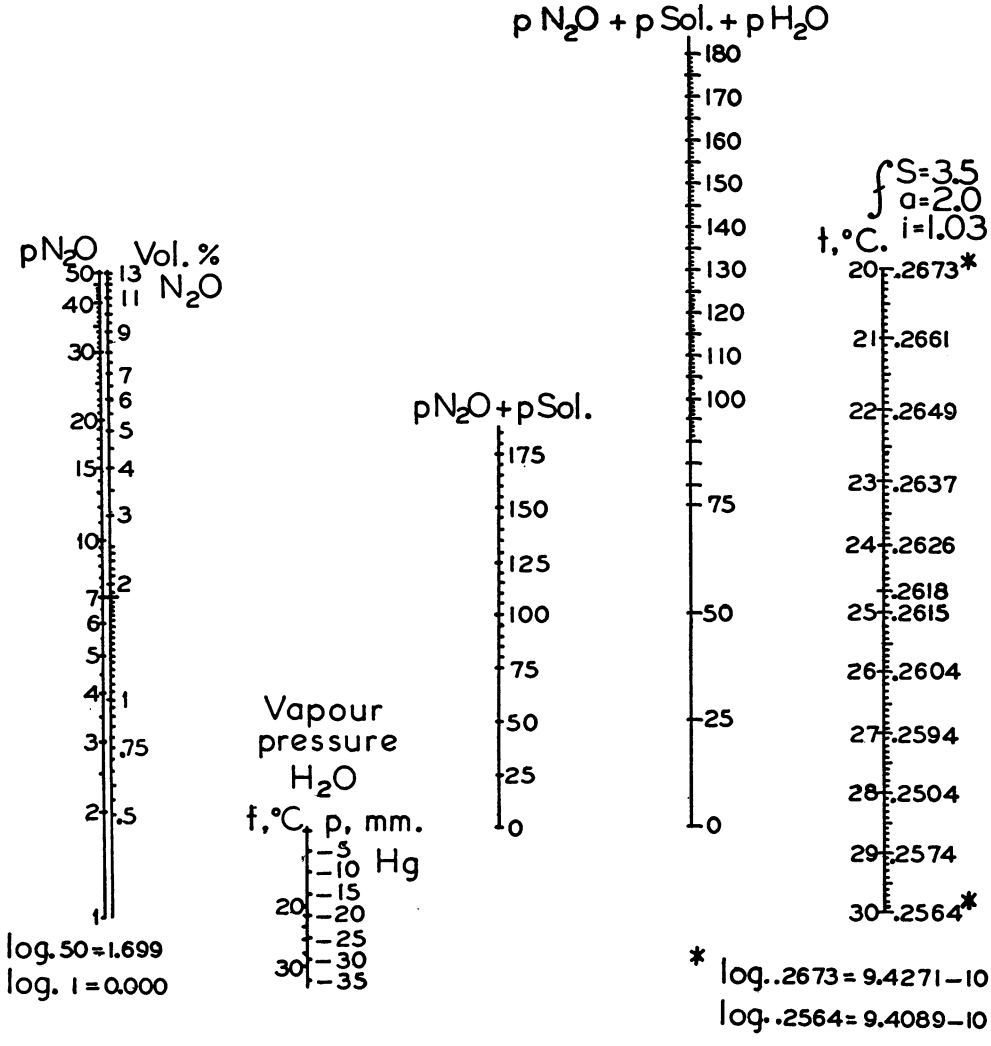

Chart 1. The nomograms presented are approximately one-half the size of the originals used. A straight edge is required to connect appropriate points. In the enlarged form calculations can be made with accuracy greater than that of the basic observations.

Technique of subsidiary observations. Rectal temperatures were recorded with a long, chemical thermometer. Stomach, skin, and room temperatures were recorded continuously with thermocouples.

A spirometer with carbon dioxide adsorbent and filled with 100% oxygen was used to measure respiratory rate, tidal air, respiratory minute volume, and total body oxygen consumption.

Possible sources of error. Possible intrinsic error in the technique has been discussed by Kety.[7,10] It is concerned particularly with the assumptions that the specific gas employed is devoid of physiological effects in the concentration used, and that torcular blood represents a mixed sample of cerebral venous blood. In the dog, these assumptions are valid with the possible reservation that contamination of torcular blood by extracerebral venous blood may occur to a very small degree. It is of negligible significance since the form of the curves obtained indicated that equilibrium between blood and brain nitrous oxide is reached approximately as expected.

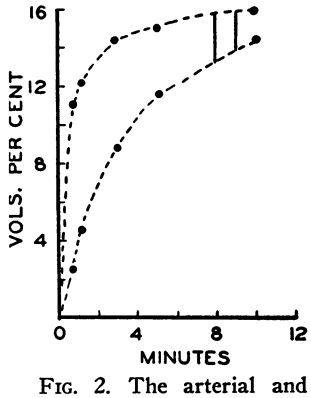

FIG. 2. The arterial and cerebral venous contents of nitrous oxide are plotted against time of inhalation of this gas. The areas of successive trapezoids one minute in width are estimated as follows: Expt. #15. The mean ordinates for ½ minute are, A = 8.0, V = 1.8; ½ minute arteriovenous difference = 6.2 which is the area of the first trapezoid from 0 to 1 minute. The mean ordinates of the trapezoid indicated from 8 to 9 minutes were $A = \frac{2.4}{2}$, $V = \frac{1.9}{2}$; $8\frac{1}{2}' (A - V) = 2.15$. The data for each minute interval are given in Table 2. See text.

Results and comment

At the time of cerebral blood flow measurement, observations were made of suitable variables to establish the experimental situation. The data, given in Table 3, are those expected for lightly pentobarbitalized dogs. The mean values obtained included: pulse rate, 162 beats per minute; mean femoral blood pressure, 133 mm. Hg; respiratory rate, 20 breaths per minute; pulmonary minute volume, 6.0 liters; arterial oxygen content, 19.2 volumes per cent; arterial carbon dioxide content, 39.5 volumes per cent; and body temperature, 38.3° C.

Cerebral blood flow. The mean of 17 measurements of CBF made in dogs was 40 ± 3.4* cc./100 gm. of brain/min. This mean is lower than either the mean of 54 cc./100 gm./min. obtained in men[10] or the 47 cc./100 gm./min. of monkeys.[14] This may be presumed to be a physiological difference. It cannot be explained by blood loss since the animals never lost more than 9% and frequently only about 5% of their blood volume, while the blood pressure never differed appreciably from its initial level at the time of the CBF measurement. Anesthesia apparently is of little significance in the range employed, compared with other variables.

Between different animals, the correlations between CBF and the factors usually implicated in changes in cerebral blood flow were calculated: arterial

* Standard error of the mean.

CO_2 content, r = .29; arterial O_2 content, r = .03; and mean femoral blood pressure, r = .31. As none of these correlations is statistically significant, the variables were probably restricted within limits too narrow to evaluate their relationships, considering the random errors involved.

Cerebral vascular resistance. The resistance to flow has been stated by Kety[10] as the pressure required to drive one cubic centimeter of blood through 100 grams of brain in one minute. The mean cerebral vascular resistance in dogs was found to be 3.6 mm. of Hg/cc./100 gm. of brain/min. This is somewhat greater than the value for men of approximately 1.7, cal-

TABLE 2

DATA FROM GRAPH, EXPERIMENT #15

t	Art. N_2O	Ven.	$(A-V)_{N_2O}$	$\int_{t-1}^{t}(A-V)dt$	$\int_{o}^{t}(A-V)dt$	$CBF = 100V_t S/\int_{o}^{t}(A-V)dt$
min.	*vol. %*					*cc./100 gm./min.*
1	...	...	..	6.20	6.20	
2	13.3	6.8	6.5	7.30	13.50	
3	14.1	8.5	5.6	6.05	19.55	
4	14.6	9.8	4.8	5.20	24.75	
5	14.8	10.8	4.1	4.45	29.20	
6	15.1	11.6	3.5	3.80	33.00	
7	15.3	12.4	2.9	3.20	36.20	
8	15.5	13.1	2.4	2.65	38.85	
9	15.6	13.7	1.9	2.15	41.00	
10	15.7	14.2	1.5	1.70	42.70	$33.3 = 100 \cdot 14.3/42.7$ $V_t = 14.3$

Legend:

$(A - V)_{N_2O}$ = Cerebral arteriovenous nitrous oxide difference.

$\int_{t-1}^{t}(A - V)dt$ = Area between curves A and V in Figure 2 from t — 1 to t.

$\int_{o}^{t}(A - V)dt$ = Summed areas between the same curves from o to t.

V_t = Cerebral venous nitrous oxide content at time t.

S = 1.0.

culated from data collected by Kety and Schmidt using a mean femoral blood pressure of 90 mm. Hg and a CBF of 54 cc./100 gm./min. It reflects in part the lower relative CBF in the dog, but principally the relatively high mean arterial blood pressure in this species.

Since intracerebral changes in vasomotor tone are reflected in a quantitative manner in cerebral vascular resistance, the relation between the latter and the arterial carbon dioxide content was evaluated. A non-significant correlation coefficient, r = —.37 was found, although this appears to be an improvement over the relation observed between arterial carbon dioxide content and cerebral blood flow. Conflicting influences in each animal undoubtedly prevented a more clear relation from being apparent.

TABLE 3

Expt. no.	Pulse rate	Resp. rate	Pulm. vent.	Blood pressure	CBF	CVR	CMR	A-V diff. O_2	A-V diff. CO_2	Brain R.Q.	O_2 content Art.	O_2 content Torc.	CO_2 content Art.	CO_2 content Torc.	O_2 consumed Total body	O_2 consumed Brain	Weight Total	Weight Brain	Body temp.	Sex
	per min.		L./min.	mm. Hg	*	BP/CBF	*	vol. %			vol. %				cc./min.	*	%	kg.	gm.	°C.	
75-100% Oxygen																				
4	195	10	...	130	34	3.8	1.2	3.5	3.4	.97	19.9	16.4	44.2	47.6	....	...	..	11.3	...	...	F
5a	195	20	...	135	59	2.3	1.7	2.8	4.0	1.42	17.3	14.5	48.2	52.2	....	...	..	12.1	84	...	M
5b	195	22	3.7	135	45	3.0	2.9	6.5	4.0	.62	21.0	14.5	46.5	50.5	110.8	.92	2.2	12.1	84	...	M
7a	140	16	3.3	135	31	4.4	1.2	3.8	3.5	.92	15.9	12.1	44.9	48.4	99.4	.70	1.1	14.3	91	...	M
7b	146	7	6.2	120	33	3.6	1.8	5.6	5.6	1.00	19.9	14.3	39.3	44.9	94.9	.66	1.7	14.3	91	...	M
9	202	25	5.2	140	24	5.8	1.9	7.9	7.3	.92	18.4	10.6	35.3	42.6	93.1	.78	1.7	12.0	85	...	F
10	183	30	11.2	140	66	2.1	1.1	1.7	2.8	1.65	19.3	17.6	43.5	46.3	119.7	1.11	.7	10.8	76	39.1	F
11	162	31	6.4	140	52	2.7	3.1	5.8	4.8	.83	16.4	10.6	32.1	36.9	95.2	.81	2.8	11.8	86	39.0	M
Mean	177	20	6.0	134	43	3.5	1.9	4.7	4.4	1.04	18.5	13.8	41.8	46.2	102.2	.83	1.7	12.3	85	39.1	
21% Oxygen																				
14	150	25	...	140	24	5.8	1.6	6.8	4.3	.63	21.7	14.9	36.7	41.0	198.1	.76	.8	26.0	99	39.1	M
15	144	14	...	132	33	4.0	2.7	8.2	3.4	.42	16.9	8.7	44.9	48.3	...	...	...	17.7	107	36.7	M
17	156	14	5.8	143	56	2.6	3.1	5.5	5.5	1.00	19.6	14.1	40.1	45.6	121.6	.64	2.2	19.1	85	37.2	M
18	114	19	8.3	155	32	4.8	2.8	8.9	9.0	1.01	19.6	10.7	39.5	48.5	157.9	.71	1.8	22.4	102	38.3	M
19	...	20	5.8	150	60	2.5	2.9	4.9	6.6	1.35	18.7	13.8	34.9	41.5	200.0	.96	1.3	20.9	93	38.6	F
20	130	37	6.9	105	42	2.5	3.3	7.8	7.0	.90	18.2	10.4	43.1	50.1	95.0	.75	2.8	12.7	80	38.4	M
21	166	13	5.4	120	21	5.7	2.4	11.4	10.2	.90	21.4	10.0	33.2	43.3	109.3	.64	1.8	17.1	80	36.4	F
22	...	9	3.3	110	34	3.1	3.0	8.9	8.8	.99	20.8	11.9	39.3	48.1	108.8	.79	2.6	13.8	96	36.9	M
Mean	143	19	5.9	132	38	3.9	2.7	7.8	6.9	.90	19.6	11.8	39.0	45.8	141.5	.75	1.9	18.7	93	37.7	
†12a	188	33	...	125	40	3.1	4.9	12.3	13.0	1.06	22.4	10.1	25.7	36.8	125.9	1.00	3.3	12.1	85	41.8	M
Grand mean	**162**	**20**	**6.0**	**133**	**40**	**3.7**	**2.5**	**6.6**	**6.1**	**.98**	**19.2**	**12.6**	**39.5**	**45.5**	**118.4**	**.80**	**1.9**	**15.3**	**89**	**38.3**	

* cc./100 gms./min.

† This animal breathed 75-100% oxygen.

Cerebral oxygen consumption. The relation between blood flow, A-V oxygen difference, and oxygen consumption in the brain, as described by the Fick principle, is expressed in a three coordinate logarithmic grid in Figure 3,* where the basic data of the experiments are plotted.

Eight measurements were made with animals breathing 21% oxygen. The mean cerebral oxygen consumption was 2.7 ± 0.2 cc./100 gm./min. Eight other measurements were made with animals breathing 75-100% oxygen for about 30 minutes, with a mean of 1.9 ± 0.3 cc./100 gm./min. The difference between these means was 0.9 ± 0.3 cc./100 gm./min.† This reduction is similar to the *in vitro* diminution of oxygen consumption in cerebral tissue in an atmosphere of 100% oxygen which has been reported by Elliott.[1] This may be the fundamental cerebral change in the phenomenon of oxygen poisoning which becomes most evident at two atmospheres.[6] Because of its possible clinical implications, this warrants further investigation in man, both at normal and abnormal atmospheric pressures.

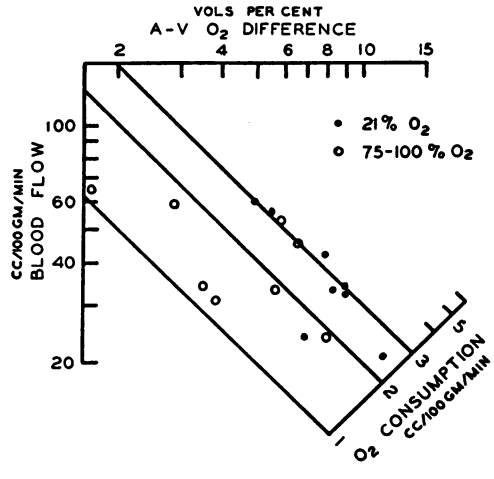

FIG. 3. Cerebral oxygen consumption is plotted as the resultant of the observation pairs of cerebral blood flow and $(A - V)_{O_2}$ difference on a logarithmic grid. The depression of cerebral oxygen uptake by high concentrations of oxygen is indicated by the comparison made between animals breathing 21% and 75-100% oxygen at the time of the cerebral blood flow measurement.

A preliminary survey in dogs indicates that a rise in body temperature is accompanied by an increase in both cerebral and the corresponding total body oxygen consumption (Fig. 4). The observations plotted were limited to those with a cerebral R.Q. within 20% of 1.00, for which a temperature measurement was available. Two of the seven observation groups were in animals breathing high concentration oxygen. The relation observed is in keeping with the known effect of temperature upon chemical reactions, and specifically the effect of temperature from 0° to 40° C. on oxygen uptake by brain tissue *in vitro* found by Field.[2]

Anesthesia is known to lower the cerebral oxygen consumption in both monkeys[14] and men.[5] Light anesthesia in dogs probably produced a slight depression below the waking state. While the exact amount is uncertain, the regular increase in both cerebral and the corresponding body oxygen con-

* Take any point, e.g., $(A - V)_{O_2} = 4$ and CBF = 80; then CMR = 3.2.
† Statistically highly significant, i.e., $P < 0.01$.

sumption noted with increased body temperature suggests that any effect is quite constant.

The mean Q_{O_2} for dogs breathing 21% O_2 was 8.1 microliters of O_2 per mgm. of dry tissue per hour, which is lower than that found for various species from studies of brain slices and homogenates, i.e., 10-15.5.[14] It is closer to the mean of 11.1 found *in vivo* in the monkey[14] and the mean of 9.9 found in man.[10] The relatively lower values found in animals and men in a near normal state, might be explained by an increase in O_2 consumption due to trauma necessarily introduced by *in vitro* study, bringing into action abnormal processes.

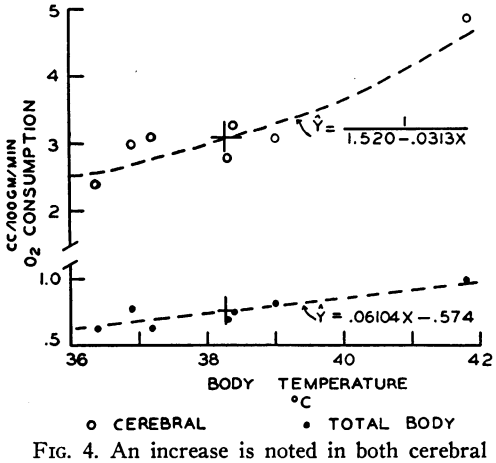

FIG. 4. An increase is noted in both cerebral and the concomitant total body oxygen consumption with increasing temperature. The calculated curves of regression give values of t = 4.36** for cerebral and t = 4.38** for total body oxygen consumption. In spite of the statistical validity of the curves, extrapolation in the range above 39° C. is not intended.

Cerebral $(A\text{-}V)_{O_2}$. Using the arteriovenous O_2 difference as a criterion, numerous attempts have been made to evaluate qualitative variations in either CBF or CMR, assuming one or the other to be constant.[16] In these experiments the $(A\text{-}V)_{O_2}$ reflects changes in both variables as is shown by the correlations: CBF, r = —.60** and CMR, r = .71.** A corollary shows that CBF alone does not determine the CMR, nor vice versa. It is apparent that it is necessary to determine both CBF and $(A\text{-}V)_{O_2}$ in order to compare individuals in different states.

Cerebral R.Q. The cerebral respiratory quotient had a mean value of 0.98. The variability was somewhat greater than is usually found, but these observations were of secondary importance to this investigation. For accurate measurements of this function, pooled blood samples are probably not ideal.

Summary and conclusions

1. The nitrous oxide method for quantitative measurement of cerebral blood flow in man developed by Kety and Schmidt has been applied to the measurement of cerebral blood flow and cerebral oxygen consumption in dogs. The details of the technique are described fully and possible sources of error are indicated.

2. Simultaneous control observations were made of suitable variables to establish the experimental conditions which were as nearly normal as possible.

3. Seventeen experiments were analyzed from a study of 22 dogs lightly anesthetized with intravenous pentobarbital. The mean cerebral blood flow was about 40 cc./100 gm./min., with a standard error of ±8.6%. The mean cerebral oxygen consumption, with dogs breathing 21% oxygen, was about 2.7 cc./100 gm./min., with a standard error of ±7%.

4. Cerebral blood flow in the dog appeared to be less than in either monkey or man, in this order, for the same quantity of brain.

5. Cerebral vascular resistance was considerably higher for dogs than for men.

6. Dogs breathing 75-100% oxygen showed no difference in cerebral blood flow from those breathing 21% oxygen, but the cerebral oxygen consumption was lower in the group breathing the higher oxygen concentration. This may be the fundamental cerebral change in oxygen poisoning.

7. Both cerebral oxygen consumption and the corresponding total body oxygen consumption were directly proportional to the body temperature.

8. Cerebral oxygen consumption in living dogs appeared to be lower than values found among various species from *in vitro* studies but was similar to the recent observations in living monkeys and men.

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