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Research Article

THE NITROUS OXIDE METHOD FOR THE QUANTITATIVE DETERMINATION OF CEREBRAL BLOOD FLOW IN MAN: THEORY, PROCEDURE AND NORMAL VALUES [1]

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In 1945 the authors reported the determination of cerebral blood flow in man by the use of nitrous oxide in low concentration, a technique which permitted for the first time quantitative clinical measurement of this important physiologic function (1). Since that time numerous modifications have been made in the procedure (2) and the underlying theory has been subjected to extensive experimental evaluation. The present report constitutes a description of the technique as we have now employed it in over 300 determinations, an examination of its underlying theory and validity, and values obtained with its use in 34 studies on 14 normal young men.

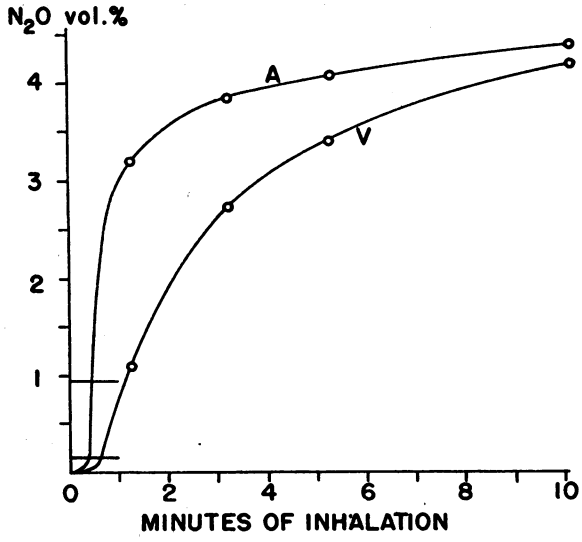

FIG. 1. TYPICAL ARTERIAL (A) AND INTERNAL JUGULAR (V) CURVES OF N_2O CONCENTRATION DURING A TEN-MINUTE PERIOD OF INHALATION OF 15 PER CENT N_2O

THEORY

If the nitrous oxide concentration be determined in arterial and cerebral venous blood for a ten-minute period from the beginning of the inhalation of a low concentration of this gas, curves will be obtained similar to the typical ones in Figure 1. The venous concentration curve is a fairly complex function of the arterial curve and the cerebral blood flow (3) but from these curves the cerebral blood flow can be calculated by the application of the familiar Fick principle. This postulates in its simplest form that the quantity of any substance taken up in a given time by an organ from the blood which perfuses it is equal to the total amount of the substance carried to the organ by the arterial inflow less the amount removed by the venous drainage during the same time period. For the case of the brain uptake of N_2O:

Let $(Q_B)_u$ = quantity of N_2O taken up by the whole brain in time u measured from the start of inhalation,
$(Q_A)_u$ = quantity brought to the brain by the arterial blood in time u,
$(Q_V)_u$ = quantity carried away by cerebral venous blood in time u,
A = arterial N_2O concentration,
V = venous N_2O concentration,
W = weight of brain,
TF = total cerebral blood flow per minute,
CBF = cerebral blood flow per unit weight of brain per minute.

From the Fick principle:

$$(Q_B)_u = (Q_A)_u - (Q_V)_u$$

but, since both A and V are variables with respect to time,

$$(Q_A)_u = TF \int_0^u A\,dt$$

and

$$(Q_V)_u = TF \int_0^u V\,dt,$$

whence

$$(Q_B)_u = TF \int_0^u (A-V)\,dt$$

or

$$TF = \frac{(Q_B)_u}{\int_0^u (A-V)\,dt} \qquad (1)^2$$

[1] The expenses of these investigations were defrayed by grants from the Office of Scientific Research and Development and the Committee on Research in Dementia Precox founded by the Supreme Council, 33° Scottish Rite, Northern Masonic Jurisdiction, U. S. A.

[2] This is a general formula for the Fick principle applying to any organ or the whole body and to any substance. In the special case of its use for determination of cardiac output using O_2 or CO_2 the denominator

or, in terms of unit weight of brain,

$$CBF = \frac{(Q_B)_u/W}{\int_0^u (A-V)dt}, \qquad (2)$$

The denominator is readily obtained from the respective arterial and cerebral venous curves.[3] The numerator, or the cerebral concentration of nitrous oxide, is not obtainable directly in man. If the time u is sufficiently long, however, equilibrium will have occurred between brain and the blood leaving the brain with respect to nitrous oxide tension. At that time:

$$\frac{(Q_B)_u}{W} = V_u S, \qquad (3)$$

where S represents a partition coefficient for nitrous oxide between brain and blood. By substituting appropriately and multiplying through by 100, one obtains a value for cerebral blood flow in convenient units:

$$CBF = \frac{100 V_u \cdot S}{\int_0^u (A-V)dt}, \qquad (4)$$

where CBF is expressed as cc. of blood flow per 100 g. of brain per minute.

DISCUSSION

Before this technique can be regarded as capable of yielding valid measurements of cerebral blood flow the assumptions on which it is based must be subjected to experimental verification. This was recognized in our original description of the method (1) and evidence was adduced to validate the assumptions. Since that time it has been possible to make a more exhaustive evaluation of these assumptions and to determine more precisely the value of the constant S.

Blood from one internal jugular bulb as representative of mixed cerebral venous blood

The method yields values for mean cerebral blood flow only insofar as the venous blood samples obtained from one internal jugular are representative of mixed cerebral venous blood. Three studies of oxygen content in samples taken simultaneously or in rapid succession from both right and left internal jugular have revealed significant differences between the two sides in as many as one third of the subjects (4 to 6). Himwich and associates (7) recently reported what they interpreted as significant differences between the two sides with respect to cerebral blood flow and oxygen consumption determined by the nitrous oxide method in a number of patients. They conclude that one internal jugular is predominantly representative of cortical drainage while the other largely drains the basal ganglia, and find anatomical justification for this conclusion in the statement that "except in the small proportion of human subjects who have torculars, the two internal jugular veins do not drain symmetrical portions of the brain." Some doubt arises both as to the validity of this statement and the conclusion based upon it. According to the results of Edwards (8), Manno (9), and Riggs (10) who studied a total of 125 specimens, there is a real confluence of the sinuses in approximately two thirds of the population. But even in that minority of patients where a confluence does not exist or is markedly lopsided one cannot neglect the fact that the torcular is only one of many means whereby mixing may occur. According to Cobb (11), the venules which emerge from the cortex are continuous with those which pass through the subcortical regions to drain into the internal venous system; there is thus no clear-cut differentiation of cortical from subcortical blood even at their origin. An examination of the larger veins of the brain (12) reveals many opportunities for mixing exclusive of the torcular. Thus in a patient where the superior sagittal sinus drained almost completely to the right lateral sinus and the straight sinus to the left, the left internal jugular would also receive "cortical" blood from the entire left inferior surface of the cerebrum, from the anastomotic veins of Trolard and L'abbe and from the left half of the cerebellum, while the right internal jugular would receive in addition to blood from the superior sagittal sinus, "subcortical" blood from the cavernous sinus, the cerebellum, pons and medulla. In other words, from the smaller architectural units through the major dural sinuses there is little evidence for segregation of cortical venous outflow from the drainage of subcortical tissue.

In an effort to obtain a more definitive answer

becomes simply $(A-V)t$ since the arteriovenous differences of these gases are presumed to be constant.

[3] In our original report the integral was approximated by a single exponential function. Although this was fairly accurate there is no need for fitting the arteriovenous difference into any rigid formula, since whatever its nature its integral can be found graphically or by the trapezoid rule.

TABLE I

An evaluation of the anatomical and experimental errors of the method

Simultaneous measurements on right and left internal jugular blood									Successive measurements on the same side								
Patient	$(V\text{-}A)CO_2$		$(A\text{-}V)O_2$		Cerebral				Patient	$(V\text{-}A)CO_2$		$(A\text{-}V)O_2$		Cerebral			
					Blood flow		O_2 consumption							Blood flow		O_2 consumption	
	Right	Left	Right	Left	Right	Left	Right	Left		I	II	I	II	I	II	I	II
	vol. %	*vol. %*	*vol. %*	*vol. %*	*cc./100 g./min.*	*cc./100 g./min.*	*cc./100 g./min.*	*cc./100 g./min.*		*vol. %*	*vol. %*	*vol. %*	*vol. %*	*cc./100 g./min.*	*cc./100 g./min.*	*cc./100 g./min.*	*cc./100 g./min.*
E. B.	6.1	6.7	6.1	6.4	45	42	2.7	2.7									
S. S.	6.7	6.7	5.4	5.6	64	64	3.5	3.6	J. Mc.	6.2	7.1	7.0	6.8	48	42	3.4	2.9
*M. M.	1.3	1.3	2.0	2.3	149	136	3.0	3.1	V. Z.	5.3	6.3	5.5	6.1	50	46	2.8	2.8
U. P.	10.6	11.7	8.0	8.2	50	53	4.0	4.3	R. B.	5.9	6.1	6.7	7.0	57	57	3.8	4.0
W. R.	5.6	5.3	5.7	5.5	46	56	2.6	3.1	W. R.	5.1	6.1	5.3	6.0	59	57	3.1	3.4
J. S.	5.0	5.3	5.9	5.7	61	75	3.6	4.3	J. Sk.	5.1	5.0	5.5	5.6	57	60	3.1	3.4
W. L.	6.5	6.4	6.8	6.6	58	53	3.9	3.5	G. A.	5.1	5.2	5.1	5.8	62	55	3.2	3.2
R. B.	6.1	5.8	6.4	6.2	65	57	4.2	3.5	U. P.	7.2	6.1	8.3	5.9	36	50	3.0	3.0
*F. B.	1.1	2.4	1.7	2.1	201	169	3.4	3.6	W. L.	6.1	6.6	6.0	6.1	61	56	3.7	3.4
M. T.	6.9	6.5	7.2	7.1	48	47	3.5	3.3									
Mean	5.59	5.81	5.52	5.57	78.7	75.2	3.44	3.50	Mean	5.75	6.06	6.18	6.16	53.8	52.9	3.26	3.26
Standard deviation of the differences within an individual							±0.281		Standard deviation of the differences within an individual							±0.187	

* These two patients had large unilateral cerebral hemangiomata.

to this question we made measurements of cerebral blood flow by means of the nitrous oxide technique, and of arteriovenous oxygen and carbon dioxide differences, simultaneously on both internal jugular bulbs in a series of ten patients. These included two patients with unilateral cerebral hemangiomata, the resultant arteriovenous shunt producing a tremendous increase in cerebral blood flow locally and straining to its utmost the mixing capacity of the cerebral venous drainage. The results are presented in Table I. The agreement between bilateral measurements in any one patient is quite good, the standard deviation of the individual differences for cerebral oxygen consumption is ± 0.28 cc. O_2/100 g./min. This includes not only the anatomical variation in drainage but also all the sampling and analytical errors inherent in the estimations of CBF and $(A\text{–}V)_{O_2}$. These errors of the method may be estimated from the set of duplicate determinations on the same side in another series of patients before and after a procedure which produced no variance *per se* (13). Here the standard deviation of the differences between duplicates was ± 0.19 cc. O_2/100 g./min., which is not significantly less than 0.28. Thus the differences found between the right and left internal jugular measurements are within the experimental error of the method, which is also quite small. It would be essential to know similarly the experimental error of the nitrous oxide method as employed by Himwich and associates (7) in evaluating the differences which they found between the two sides.

The extent of contamination of internal jugular blood at the level of the superior bulb, with blood of extracerebral origin

Evidence that one internal jugular contains blood which is adequately representative of both does not exclude the possibility that both may be equally contaminated with blood which arises outside the brain. Examination of the cerebral venous drainage (12) reveals several emissary veins or communications between the cerebral and extracerebral drainage systems. Although their size in comparison with the total of cerebral veins would indicate that such contamination could hardly be important, it was nevertheless necessary to arrive at a measurement of the fraction of internal jugular blood at its superior bulb having extracerebral origin. This has been done in a series of eight patients in whom the carotids on one side were ex-

posed in preparation for cerebral angiography (12). In these patients a dye (T-1824) could be injected into an external carotid artery while samples were slowly taken from the internal jugular bulbs and the external jugular vein. By comparing the dye concentration in the internal jugular with that in the external jugular, it was possible to arrive at a fairly quantitative measure of the extent of this contamination.[4] It averaged 2.6% with a maximum value of 6.5%. It is interesting to note that when the procedure was reversed and the dye injected into the internal carotid, significant amounts appeared in the external jugular indicating that on the average about 20% of external jugular blood is of cerebral origin. The older anatomists who named these communications *emissary* veins anticipated these results. A possible source of significant contamination is the common facial vein which joins the internal jugular several centimeters below the superior bulb. For this reason it is important that the needle be placed high in the superior bulb and that blood samples be taken from this needle at a rate slow enough to insure against the possibility of drawing blood in a retrograde direction from the lower parts of the vein.

From the results of these two studies, necessarily limited in number by the obvious technical difficulties involved, it is possible to conclude that in the great majority of individuals blood from one internal jugular at the level of the superior bulb is fairly representative of mixed cerebral venous blood not significantly contaminated with blood from extracerebral sources. Exceptions may occur, but are unlikely to constitute a significant fraction of the population. This is also borne out by the comparatively small spread of our data on cerebral oxygen consumption, in a series of 34 observations on normals (Table III) and 30 studies on schizophrenics (13). Although the possibility of gross anatomical variation in any individual case still remains, it is not great and does not compromise the validity of results obtained or conclusions drawn from a statistically significant series of cases.

[4] This would not include, however, that part of the venous return from the eye supplied by the internal carotid and draining into the cavernous sinus.

Equilibration between brain and cerebral venous blood

Although it is obvious that there must be a time during the inhalation of a constant tension of inert gas when the brain is in equilibrium with the blood leaving it with respect to this gas, this time interval must be evaluated. In our original report we presented indirect evidence that after ten minutes practical equilibrium between brain and cerebral venous blood had been achieved. Since that time we have been able to make direct analyses of the nitrous oxide contents of brain and cerebral venous blood in dogs exposed to nitrous oxide for varying times (14). These studies have demonstrated that ten minutes is sufficient for the attainment of equilibrium between brain and cerebral venous blood with respect to nitrous oxide tension. The value for u in Equation 4 may therefore be taken as ten minutes.

The partition coefficient (S) of N_2O between brain and blood

The same experiments yield a value for S which is very close to unity (0.98). These *in vivo* results compare very well with the partition coefficients obtained *in vitro* for dog (1.03) and human (1.06) brains (14).[5]

Although the nitrous oxide curves are capable of yielding a value for flow per unit N_2O capacity:

$$CBF/S = \frac{V_u}{\int_0^u (A-V)dt},$$

regardless of the absolute value of S, flow in terms of unit weight of brain is dependent on the constancy of the partition coefficient among different individuals and in the same individual at different

[5] On the basis of these more accurate studies it appears that our previous tentative value of 1.3 for this factor was in error. This value had been derived from N_2O curves on monkeys obtained simultaneously with direct measurement of cerebral blood flow using the bubble-transfer flowmeter (1). Re-examination of these experiments revealed the source of error: the length of time which the arterial blood spent in the meter before reaching the brain. This rendered the samples taken from the artery and internal jugular vein not really simultaneous. Recalculation of these curves to correct this error yields a mean value for the factor S of 1.07, more comparable with that obtained by the other methods.

TABLE II

Comparison between the nitrous oxide method and simultaneous direct measurement of CBF

Rhesus or Spider Monkeys

Experiment	Bubble meter flow	N_2O flow
	cc./100 g./min.	*cc./100 g./min.*
24	37	31
27	42	33
28	17	20
30 I	46	37
30 II	60	54
30 III	31	34
31 I	38	34
31 II	76	71
31 III	32	37

times. This coefficient, however, depending on gross physico-chemical constitution would be expected to change significantly only with such changes in brain or blood composition as would be incompatible with life (14).

Final corroboration of the validity of the nitrous oxide method is to be found in comparison between it and the direct flow measurement by means of the bubble flowmeter performed simultaneously in monkeys (Table II). These experiments have been reported previously (1); now, however, the systematic error due to the interposition of the bubble meter has been removed. The nitrous oxide technique employed had not been refined to its present state, but the recently determined value of 1 for the partition coefficient has been used in the calculations. It is seen that the agreement between the two methods is quite satisfactory.

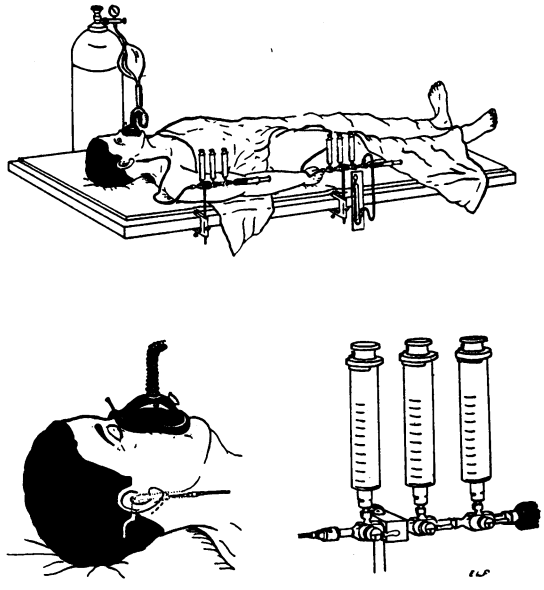

FIG. 2. EXPERIMENTAL SET-UP FOR CEREBRAL BLOOD FLOW DETERMINATION

Position of needles in internal jugular is shown as well as plastic tubing, manifolds, sampling and flushing syringes, and inhalation system. Mean arterial blood pressure is read from a mercury manometer attached to the arterial manifold. Only the expiratory valve on the mask is shown, the inspiratory valve is between the fluted tubing and the mask.

(Drawings by Dr. E. L. Foltz)

METHODS

Blood sampling

For taking the accurately timed serial blood samples from artery and internal jugular vein, manifolds of three-way stopcocks[6] (Figure 2) have been found very convenient (2). The syringes (10-cc. Luer-Lok) are prepared beforehand by lightly oiling the plunger with mineral oil, filling the dead space with heparin solution and sealing with the closed hubs of discarded hypodermic needles. Transparent plastic tubing of small bore[7] connects the manifold to the needle (19 G 3″ spinal) through suitable adaptors. The needle is placed in the superior bulb of the internal jugular after procaine infiltration according to the technique of Myerson, Halloran and Hirsch (15) as recently modified by Gibbs, Lennox and Gibbs (4). We have found this technique readily tolerated and very dependable; there have been only two failures in the last 200 attempts. For arterial blood we have used the femoral or brachial arteries. After the needle is in place it is carefully connected to the plastic tubing which has been filled with sterile heparin solution (10 mg./cc.) by means of the end syringe containing 3 cc. of heparin (Figure 2). Just before each sample is taken 3 cc. of blood are drawn into this syringe to clear the system and at the conclusion of each sample 3 cc. of the blood-heparin mixture in this syringe are pushed back to prevent clotting.

The following samples of 6–8 cc. each are taken: *X*, a blank taken from the vein just before the beginning of N_2O inhalation; 1*A* and 1*V* taken at a constant rate (1 cc. every ten sec.) from the onset of N_2O inhalation over the first minute; 2*A* and 2*V* from 1′5″ to 1′30″; 3*A* and 3*V* from 2′45″ to 3′15″; 4*A* and 4*V* from 4′45″ to 5′15″; 5*A* and 5*V* from 9′45″ to 10′15″. Of course the actual times are a matter of indifference so long as they are accurately noted and fairly evenly spaced. Samples are sealed and iced until analysis. The N_2O mixture consists of 15% N_2O, 21% O_2, and 64% N_2, kept in large cylinders under pressure.

The gas is administered in an open system through an anesthesia bag and tightly fitting mask equipped with

[6] These were constructed for us by Mr. D. W. T. Cochrane of this laboratory.

[7] "Transflex," 14 gauge, made by Irvington Insulator Co., Irvington, N. J.

inspiratory and expiratory valves. It is very important that these valves be competent and the mask fit perfectly. Unless the patient breathes a constant tension of N_2O throughout the flow the arterial and venous curves will not be smooth functions and cannot accurately be drawn from only five pairs of samples.

It is possible to perform a second measurement on the same patient while the needles are still in place. It is important when this is done that at least 20 minutes elapse between *CBF* determinations for cerebral N_2O desaturation to occur and of course a blank blood sample is taken just before the second determination.

Analysis of blood samples for N_2O

Because of the number of analyses necessary for each blood flow determination it has been necessary to modify the original method of Orcutt and Waters (16) making it simpler, more accurate and more rapid (2): Two drops of caprylic alcohol and 9 cc. of distilled water are de-aerated in the Van Slyke-Neill manometric apparatus, then run up to the 5 cc. mark of the cup. Two cc. of blood, shaken in the syringe by means of a droplet of mercury and transferred directly to an Ostwald-Van Slyke pipette, are run into the chamber and washed in with 1 cc. of de-aerated water. The cup is cleared with gentle suction and 3 cc. of the usual alkaline O_2 absorber (sodium hyposulfite, sodium anthraquinone-beta-sulfonate, potassium hydroxide), previously de-aerated and stored anaerobically, are added to the cup and the lower 2 cc. run into the chamber. No air bubbles should be present in the chamber at this time. The chamber is sealed with mercury and the mixture extracted for three minutes, then allowed to rise smoothly to the 2 cc. mark. Readings are made of pressure (r_a) and temperature to 0.1 mm. and 0.1 degree. The mixture is now expelled and the next analysis begun without washing the chamber. A single blank analysis using 2 cc. of de-aerated water instead of blood yields a reading which, after correction for difference in water vapor tension resulting from a temperature change between the blank and each analysis, may be used as the r_0 for each analysis. A blood blank (X) is also necessary to correct for other gases (largely N_2) or N_2O remaining from a previous flow.

$$\text{vol. \% } N_2O = f'_{N_2O}(r_a - r_0) - X,$$
$$X = f'_{N_2O}(r_x - r_0).$$

The manometric factor (f'_{N_2O}) for 15% N_2O and 64% N_2 varies linearly from a value of 0.1456 at 20° C. to 0.1383 at 30° C. The procedure above corrects not only for nitrogen but also for its inverse relationship to nitrous oxide during the period of gas administration.[8] Under these circumstances the value for X should be close to 1.15 vol. % unless a previous flow measurement has been performed. If 20 minutes is permitted to elapse between successive flows, nitrous oxide desaturation will be nearly complete and X will be found to be only 0.1 or 0.2 vol. % higher than 1.15. With ordinary care duplicate analyses for blood N_2O should agree within 0.05 vol. %. After sufficient skill has been acquired it is possible to forego duplicate analyses, using the smoothness of the resultant curves as a check on the individual analyses.[9]

Calculation of cerebral blood flow

When the nitrous oxide analyses are completed the values are plotted against time. The time of each sample is taken as the mid-time of the interval over which the sample was taken except for the first pair, taken at a constant rate over the first minute (and therefore already integrated) which are plotted as lines. Smooth curves are then drawn through the arterial and venous points and so constructed over the first minute that the average samples obtained ($1\bar{A}$ and $1\bar{V}$) approximate the respective integrals of the curves (Figure 1). From these smooth curves values for A, V, and $A-V$, are recorded at the end of each minute over the ten-minute period. $\int_0^1 (A-V)dt$ is obtained directly as the difference between the first pair of samples (taken at a constant rate and hence automatically integrated); the remaining integrals are calculated by means of the trapezoid rule, *i.e.*, $\int_1^2 (A-V)dt = \frac{(A-V)_1 + (A-V)_2}{2}$; $\int_2^3 (A-V)dt = \frac{(A-V)_2 + (A-V)_3}{2}$, etc. It is then possible by serial addition to calculate values of $\int_0^u (A-V)dt$ and thence $\frac{100 V_u}{\int_0^u (A-V)dt}$ for serial values of u from one to ten minutes (2). The latter function, in a typical study, decreases rapidly over the first five or six minutes but in the last several minutes tends to level off. This tendency serves as an internal check on the final result since equilibration between brain and venous blood should be complete inside of ten minutes.[10] In most cases this function is not perfectly constant at that time indicating the small amount of contamination from extracerebral sources. Occasionally one obtains a study in which this function is falling rapidly even at ten minutes; this is evidence that contamination is significant and the study should be discarded. We have observed this only twice in our last 100 studies. Since the partition coefficient (S) is unity and the equilibration time is ten minutes, the value of this function at u = ten minutes represents the cerebral blood flow expressed as cc. per 100 g. of brain/min.

[8] Since the solubility of N_2O in blood is more than 32 times that of N_2 the error due to nitrogen even if uncorrected is small; with proper correction it vanishes.

[9] A modification is necessary in the Van Slyke-Neill manometric technique for CO_2 and O_2 to prevent an error due to the solubility of nitrous oxide in the respective absorbing reagents: These are added at the appropriate times but instead of a slow addition this may be made quite rapidly, after which the upper cock is sealed with mercury, the mixture extracted at the 50 cc. mark for two minutes, raised smoothly and read at the 2 cc. volume.

[10] For this reason we prefer to make the calculation as described rather than calculate the entire ten-minute integral at once. The additional work involved is negligible.

With the value for cerebral blood flow it is now possible to arrive at a measurement of some extremely important functions. The utilization or production by the brain of any substance capable of accurate analysis in arterial and cerebral venous blood is estimated quantitatively by substitution in the transposed Fick formula. Thus for the cerebral utilization of oxygen (CMR_{O_2}):

$$CMR_{O_2}\text{ (cc. } O_2\text{/100 g. brain/min.)} = CBF\ X\ \frac{(A-V)_{O_2}}{100}$$

if $(A-V)_{O_2}$ is expressed as vol. %. A value for cerebrovascular resistance (CVR) is calculable from the mean carotid blood pressure, the internal jugular pressure, and CBF:

$$CVR = \frac{\text{(mean carotid } BP - \text{mean jugular } BP\text{) mm. Hg}}{CBF\text{ (cc./100 g./min.)}}.$$

CVR is obtained in convenient units representing the pressure necessary to force 1 cc. of blood per minute through 100 g. of brain. This may be converted to absolute units by means of an appropriate factor. In practice a satisfactory approximation is derived using the femoral arterial mean pressure for the carotid pressure and neglecting the jugular venous pressure.

NORMAL VALUES

In the course of our studies on the effects of altered carbon dioxide and oxygen tensions on cerebral blood flow (17, 18) we have obtained a series of 34 measurements of cerebral blood flow and cerebral oxygen consumption in addition to several other observations in 14 healthy young men lying at rest. Mean values and standard deviations are given in Table III. These subjects

TABLE III

Blood flow and oxygen consumption of the human brain (34 observations on 14 healthy young men)

	Mean	σ*
Cerebral blood flow (cc./100 g./min.)	54	±12
Cerebral O_2 consumption (cc./100 g./min.)	3.3	± 0.4
Cerebrovascular resistance (mm.Hg/cc. blood/100 g. brain/min.)	1.6	± 0.4
Cerebral arteriovenous O_2 difference (vol. %)	6.3	± 1.2
Cerebral respiratory quotient	0.99	± 0.09
Mean femoral arterial B.P. (mm. Hg)	86	± 7

* σ refers to the deviation among individuals.

were all cooperative, well motivated and intelligent; disturbing factors such as fear and apprehensiveness were at a minimum. Although they do not represent a complete cross section of the population these data constitute the only quantitative study yet reported of blood flow and metabolism in the normal human brain.

These values for cerebral oxygen consumption are comparable to values found in the rhesus monkey by a more direct method (19), although the human values are about 15% lower than those for the monkey. The ever present but slight factor of contamination by the extracerebral circulation would work in opposite directions in the two methods used, possibly causing the nitrous oxide method to underestimate the true value by several per cent and the bubble flowmeter to overestimate the figure to a like degree. This factor alone would explain the small discrepancy although species differences would certainly be expected to exist.

SUMMARY

1. The nitrous oxide method for measurement of cerebral blood flow in unanesthetized man is described and its errors estimated.

2. The fundamental assumptions on which the method is based have been subjected to experimental verification.

3. Comparison between the nitrous oxide technique and direct measurement of flow by means of the bubble flowmeter in monkeys shows excellent agreement between the two methods.

4. In a group of normal young men the mean value for cerebral blood flow was 54 ($\sigma = \pm 12$) cc./100 g./min. The mean value for cerebral oxygen consumption was 3.3 ($\sigma = \pm 0.4$) cc. O_2/100 g./min.

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