Studies on Distribution of Cerebral Blood Flow with Thorium B-Labeled Erythrocytes
(Preliminary Report)

By Gustav Nylin, M.D. and Hans Blömer, M.D.

This paper is a preliminary report describing adaptation of the technic used for determination of blood volume and cardiac output by thorium B-labeled red cells to estimation of cerebral blood flow and its distribution.

In recent years there have been a number of attempts to study the cerebral blood flow. Kety and Schmidt between 1945 and 1948 introduced a nitrous oxide method, and for the first time measured quantitatively the minute volume of the brain. This was the first occasion on which the total oxygen consumption of the brain was measured through simultaneous determination of the arterial venous oxygen difference of the brain. In Germany, this method was first introduced between 1951 and 1952 in the clinic in Düsseldorf by Bodechtel and the method was modified and improved by Bernsmeier and Siemons.

In the present paper the method by Nylin and Celander for determination of the cardiac output by means of radioactive labelled erythrocytes has been applied on studies of the brain circulation.

PRINCIPLES

The following is a short review of the method for determination of cardiac output with labelled red cells. The activity values of successive blood samples drawn uninterruptedly from arterial blood after intravenous injection of a fixed amount of labelled blood are plotted against time in seconds. This procedure gives a so-called dilution curve similar to those obtained by the dye method. The amount of injected dye and the hematocrit reading make it possible to calculate the minute volume of the heart according to the formula:

\[ X = \frac{h_1 \cdot v_1 \cdot c_1}{h \cdot \int_0^t c \cdot dt} \]

Where \( X \) = minute volume of the heart, \( v_1 \) = amount of injected blood, \( c_1 \) = concentration of activity of injected blood, \( h \) = hematocrit readings of injected and patients blood, \( \int_0^t c \cdot dt \) = area of the dilution curve with the extrapolated part and the time axis.

The so-called pool volume of the chest (heart and lungs) is calculated according to the formula:

\[ V = X \cdot \Delta t \]

where \( V \) = pool volume, \( X \) = minute volume of the heart and \( t \) = the time difference between the injection and the maximum of the dilution curve. The total volume of circulating blood is calculated according to the following formula:

\[ V_r = \frac{\gamma c \cdot v_1}{c_1 \cdot h} \]

where \( V_r \) = total blood volume of the body, \( \gamma \) = hematocrit of injected blood, \( v_1 \) = amount of injected labelled blood, \( c_1 \) = concentration of activity of injected blood, \( c_r \) = concentration of activity of blood samples at the 5th and 10th minute, \( h \) = hematocrit reading.

The method is applicable also for circumscribed fields of the circulation if the injected indicator only mixes with the blood in that field and its concentration can be determined in the venous blood that corresponds strictly to the circumscribed field. This premise is fulfilled by the brain circulation. If the labelled blood is injected directly into a brain artery and the blood samples are taken from the jugular bulb, one can expect the mixing and dilution to be similar to that found when determining the minute volume of the heart. While the mixing conditions in the brain circulation will not be so complete as that in the heart cavities, it is probably better in the venous sinuses.

METHOD

In order to get dilution curves of the cerebral blood flow, labelled blood was injected into the internal carotid artery and blood samples were taken either successively from one or simultaneously from both jugular bulbs. This blood holds only about 2.6 per cent extra cerebral blood.

Received for publication: September 13, 1954.
From the Cardiovascular Clinic, South-hospital, Stockholm, Sweden and the II University Medical Clinic, Munich, Germany.
from the superior jugular bulb and not from the jugular vein which derives a great amount of blood from the facial vein.

On 12 patients 14 experiments were made in which 3-5 cc. of labelled blood with thorium B was injected into the internal carotid artery or in the arm vein, and thereafter continuous samples were drawn from one or both bulbi jugulares and too, in some experiments, simultaneous samples were drawn from the brachial artery. The technic of Gibbs and his co-workers for puncturing the jugular bulb was followed. After puncture, the cannulas were connected with thin rubber tubes, joined to two-way stopcock, and fixed to a holder. The system was washed with saline solution. The injection of the labelled blood was made rapidly within half a second, and synchronised with a metronome which gave a signal every second second. Immediately after the injection with the help of the metronome, simultaneous blood samples were drawn during 40 seconds from one jugular bulb and brachial artery or simultaneously from both jugular bulbs. At the end of the sampling, two further samples were drawn, one five minutes and the other ten minutes after the end of the first series of samples.

Furthermore, before the injection a blood sample was drawn from the brachial artery or carotid artery and one from jugular bulbs for blood gas analysis according to the technique of van Slyke and Neill and thus the arterial venous oxygen difference and carbon dioxide difference were determined.

The labelling of the blood with radioactive Thorium.

—The labelling was done with thorium B according to the Hevesy-Nylin method as modified by Nylin. If total blood is activated by thorium B, the plasma activity is extremely low, one fourth to one-half per cent. Through this method, the blood is labelled and retains a constant activity about 2 hours, and it is not necessary to centrifuge the blood. Therefore, it is possible to inject the labelled whole blood. The half lifetime of thorium B is only 10.6 hours which is an advantage, for the body is not radiated for a longer time and it is possible to repeat injections at short intervals. Moreover, the method of labelling with thorium B takes less time than the labelling with P² and K安定. The method has been thoroughly described in earlier publications.

The following is a brief description:

At the bottom of a glass container shielded with lead (left in figure 1) are placed 30 mc of radioactive thorium from Harwell with a lifetime period of 1.9 years. An oxygen stream is led over the radio-thorium which takes the Thorium gas from the preparation and leads it into a blood sample in a sterilised blood container to which a small amount of heparin has been added to prevent clotting. The blood is activated in this way in 30 to 45 minutes, and the oxygen stream causes about 60 bubbles per minute. Thereafter the labelled blood is shaken in a water bath for 30 minutes at 37 C.

Measuring of samples.—The drawn blood samples are collected in small heparinised glass tubes. A small amount of saponin is added for hemolysing the blood. One to one-half cc. samples are pipetted on to blotting paper at the bottom of previously weighed metal dishes. Thereafter the weight is again determined exactly. All samples are then dried and their activity measured with the Geiger counter. This method of preparation and measuring is simplified to a high degree. The activity of every sample is measured twice, and if the difference between the two is over 4 per cent a third determination is made. Thereafter the number of impulses per minute is calculated, and a correction made for loss of activity.

RESULTS

Typical dilution curves obtained from synchronously drawn blood samples from both jugular bulbs after intraarterial injection into the internal carotid artery is shown in Fig. 2. The patient (Case No. 10) had a suspected carcinoma metastasis in the brain. Cerebral arteriography revealed only normal contrast filling, but very rapid filling of the brain vessels.

Cardiological examination was negative. The dilution curves gave the surprising result that almost the total radioactivity came from the right jugular bulb, that is, on the same side as the injection, as early as four seconds after the injection and rapidly reached a maximum in 8
Fig. 2. Simultaneous dilution curves from right (solid line) and left jugular bulb (dash line) after injecting thorium B-labelled red cells into right internal carotid (Case No. 10).

Ordinate, radioactivity per gr/min; Abscissa, time in seconds and minutes after injection.

seconds, with a count of 75,000 impulses per gr. a minute. Thereafter there was a rapid fall of activity until the 12th second. Recirculation began after 20 seconds. Blood from the left jugular bulb showed very small activity; the maximum was reached after 14 seconds with a value of 3500 impulses per minute or about 4.6 per cent of the value for the right jugular bulb. Comparison of the areas for the two dilution curves, shows the same relation. This indicates that the brain circulation was unilateral and that broadly speaking the total activity was given chiefly by blood from only one hemisphere. These results contradicted those obtained by cerebral angiography where during normal conditions the arteriogram is unilaterally represented but the phlebogram shows bilateral contrast filling. The results obtained by the isotope technique are surprising, if we remember the confluence of the veins from both hemispheres in a common sinus. It may be that even here laminar flow is maintained.

In this case recirculation set in after 20 seconds and through this second injection the brain got blood into both carotid arteries. As a consequence, the dilution curves of blood from the two bulbi jugulares run parallel, a result which supports the view that there is an equal cerebral blood flow of both hemispheres. From this single observation it is possible to calculate the blood flow, the minute volume of the brain, through one hemisphere. The calculations of the minute volume of the brain in this case (10) and in another (1) can be seen in table 1.

Quite different conditions were found in a case of severe cardiac decompensation with a large, dilated heart and pronounced congestion. A 69 year old man, case no. 11, with decompensated hypertension was suspected of suffering from a sinus thrombosis. Angiography of the common carotid artery and the internal carotid artery revealed no thrombosis; the circulatory conditions were equal on both sides, but the circulatory velocity was retarded. The severe congestion as well as the intense bleeding when the jugular bulb was punctured pointed to a great increase of venous pressure. Three cc of labelled blood were injected into the right internal carotid artery and blood samples were drawn from both jugular bulbs in the usual way.

The dilution curves of blood drawn from the side of injection and from the opposite side are shown in fig. 3. The former shows a pronounced retardation; it rises slowly for 6 to 8 seconds then steeply reaching its maximum in 14 seconds with an activity of 65,000 impulses per minute. The decrease of activity is less rapid and reaches its minimum after 30 seconds. In this case no recirculation could be traced owing to the pronounced retardation. The mixing of the blood was complete at one, five and ten minutes.

Contrary to results depicted in fig. 2, the blood samples drawn from the left jugular bulb showed a much stronger activity comprising about one-third of the curve. The curve rises after 8 seconds and reaches its maximum also after 12 seconds with 20,000 impulses per minute; it then decreases to its minimum after 24 seconds. No recirculation is indicated. Calculation of the minute volume of the brain circulation and oxygen consumption of the brain are given in table 1, case 11.

In calculating cerebral minute volume it is of...
primary importance to know whether labelled erythrocytes injected into one carotid artery are diluted by the blood from one hemisphere only and if, as a consequence, the dilution curve from the homolateral jugular bulb represents the brain circulation through that hemisphere only. During such circumstances, one should get activity only from the bulbular vein on the same side of the intraarterial injection and no activity from that of the contralateral side. On the other hand, if the injected blood is mixed with blood from both hemispheres, one should get activity in both jugular veins. If the blood from both hemispheres mixes equally with the injected labelled blood, the dilution curves from both bulbi jugulares should be quite similar. Consequently, dilution curve from only one jugular bulb should be representative for the total brain circulation. If the dilution curves from both jugular veins are different and one gets higher activity from that on the injected side, the calculated mean of both dilution curves should represent the total brain circulation.

In case 10, fig. 2, where practically all injected activity was found in the jugular bulb from the side of injection, the dilution curve of this vein is representative for the brain circulation through one hemisphere.

In case 11, fig. 3, the injected blood is mixed not only with the blood from one hemisphere but with some part of that from the left hemisphere. Therefore, with the assumption of symmetric distribution of blood in the two hemispheres, the activity received from the vein on the injected side is reduced by that amount which is contributed by the contralateral side. The sum of the surface of both dilution curves represents then the unilateral brain circulation. Probably the high venous
pressure and retarded speed of circulation explains the more complete mixing of the blood from both hemispheres in this case.

When comparison is made between these results of the minute volume of both hemispheres and the values from Kety and Schmidt\(^2\) and Bernsmeyer and Siemons\(^4\), our values are at the upper limits of their values in case 1 (1.0 l/min.) and case 11 (0.8 l/min.). On the other hand, case 10 shows much higher values (2.0 l/min.). They agree with angiographic interpretations of rapid circulation and high values of the minute volume. The same holds for case 11; a retarded filling in angiography corresponded to our finding of a low minute volume.

One consequence of the rather high values of the minute volume of the brain in our investigation is that the total oxygen consumption of the brain was great. On the other hand we must be careful in evaluating our results; there were only 3 cases and the patients were probably not representative of normal cases.

To the clinician it is also important, from a practical point of view, to be able to state whether there is any difference in the cerebral blood flow between the two hemispheres. We have tried to examine empirically, whether it is possible to discover this by means of the radioactive isotope technique. As an example, a 67 year old heart patient, who had no signs of disturbances in the cerebral blood flow from a clinical point of view was studied (case no. 12). Three cc. of labelled blood were injected intravenously into an arm vein and thereafter simultaneous successive blood samples were drawn every 3rd second from both jugular bulbs. As shown in figure 4, the dilution curves from the two sides run astonishingly parallel. The curves begin to rise 18 seconds after injection and reach a maximum between 27 to 30 seconds. The top of one curve is only a little lower than the other. The declining slopes run parallel and reach a minimum 46 seconds after injection. In this case, similar to case 3, the brain receives blood with labelled erythrocytes from both carotid arteries when re-circulation sets in. Since the dilution curves were the same on both sides the blood flow from the two hemispheres was the same.

If there were some difference between the two hemispheres in brain circulation, there ought to be different types of dilution curves from the two bulbi jugulares. Consequently, to get quantitative information as to whether

![Fig. 4. Simultaneous dilution curves from both jugular bulbs after intravenous injection of thorium B-labelled red cells. (Case No. 12). Lines as in Fig. 2. Discussion in text.](image-url)
DISTRIBUTION OF CEREBRAL BLOOD FLOW

Fig. 5. Simultaneous dilution curves from right jugular bulb (solid line) and brachial artery (broken line) after intravenous injection of thorium B-labelled red cells. (Case No. 5). Discussion in text.

Differences exist in the brain circulation through the two hemispheres successive bilateral arterial injections must be given and simultaneous blood samples taken from both bulbi jugulares. Four dilution curves can be determined in that way. The brain circulation through the two hemispheres could be calculated quantitatively and compared with each other and with the total brain circulation.

The results presented in fig. 5 (case 5) are of special interest. The unusual type of the dilution curve seems to prove that the dilution of the injected blood forms the basis for calculation of the brain circulation. The results obtained in this case support such an assumption. Five cc. of labelled blood were injected intravenously into an arm vein, blood samples were drawn simultaneously from the right jugular bulb and brachial artery, and dilution curves were plotted. In the arterial dilution curve a further second maximum appears at the 22nd second simulating a new injection, a circumstance which we cannot explain. Furthermore, this second maximum rises a little higher than the first one. A similar result has been achieved only once before. It has been described by Nylin10 but no explanation has been given. The assumption that in our case no. 5 the second maximum might be an expression of an arterio-venous shunt was not confirmed.

For the moment, however, we must move on from discussion of the origin of this second maximum to look at the results obtained from jugular bulb—the solid line—in relation to the arterial dilution curve. Without question, the brain received two injections from the arterial system. The venous curve shows two maxima that tardily follow the two maxima of the arterial curve. The activity appears in the venous blood samples after that in the arterial blood, but 10 to 12 seconds later. The relation between the maxima of the arterial and venous dilution curves is calculated at 1.79. The second increase of the venous curves is simultaneous, i.e. the venous curve imitates the arterial curve with a difference of 10 seconds and the maxima are also reached with a difference of 10 to 12 seconds. This time the relation between the two maxima is calculated to 1.80. These results clearly show that there is a constant relation between the venous and the arterial dilution curves both in the time delay and in the dilution, which is shown in the decrease in the activity of the venous blood in relation to the arterial blood. If the dilution in the brain had fluctuated, it would not have been possible to find this marked correspondence in both instances. The relation between arterial and venous dilution curves is reproduced.

SUMMARY AND CONCLUSION

This preliminary report describes adaptation of a blood-dilution method to quantitative
measurement of cerebral blood flow. Erythrocytes labeled with thorium B were injected into the internal carotid artery and the radioactivity of blood drawn from both superior jugular bulbs was determined. A technic for the study of separate flows through the two hemispheres is discussed.

The procedure has been tried 14 times on 12 patients and the abnormalities discovered in representative cases are analyzed.

ACKNOWLEDGMENT

The authors wish to express their sincere thanks above all to the chief of the II Roentgenological department of Sodersjukhuset, Dr. Stig Löfstedt, who made the intraarterial injections into the internal carotid artery. We also thank Dr. Sven Hedlund, Dr. Johan Karnell and Dr. H. E. Hansson of the Heart Clinic for all their help and assistance. Last, but not least, we thank Mrs. Marianne Björklund and Miss Randi Baden for their technical assistance. We are also very grateful to Dr. Rylander who has worked out the mathematical calculations.

REFERENCES

Studies on Distribution of Cerebral Blood Flow with Thorium B-Labeled Erythrocytes: (Preliminary Report)
GUSTAV NYLIN and HANS BLÖMER

Circ Res. 1955;3:79-85
doi: 10.1161/01.RES.3.1.79

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1955 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/3/1/79