Contributions to the Study of Blood Brain Flux Using Radioactive Tracers

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Abstract

In this paper, we present an original radiocirculographic method for investigates of cerebral blood flow, which has proven to be very useful, simple, and efficient for studies of brain hemodynamics. Physical considerations on injected radioactive tracer in cardiovascular system, allowed us to state a relationship for the blood flux, \( F \), valued as the amount of fluid-blood that traverses a vascular segment in unit time. All these theoretical facts, along with a host of remarkable clinical results, are presented in a doctoral thesis entitled “The cerebral Hemodynamics in Essential Hypertension and Arteriosclerosis” of the eminent doctor Ioan Mureșan, who died in 1984, at only 50 years old. Using tracers marked with radioactive chrome \(^{51}\)Cr and iodine \(^{131}\)I, it was studied, for patients with various vascular diseases the blood circulation in other territories as an echo of cerebral blood flow. Outstanding results, relating to physiology, diagnosis, and therapy of some diseases, have been obtained. Through intensive collaborations, this method has been operationalized at the University Clinics of Cluj. Here, thousands of patients have been investigated, obtaining quantifiable information which highlighted the patient’s condition by emergent and incident blood flows in the global circulatory process and related to other vascular segments.

Keywords: Cerebral circulation, clinical indices, radiocirculographic technique, weighing blood flux

Introduction

The use of radioactive tracers, in the study of stationary fluid’s flow through a tubular network, is a widely used technique, very useful, in determining the static and dynamic parameters of the fluxes. In neuropathological studies of brain blood circulation, the radiocirculography was sporadically applied, only parameters, quantitatively expressed, during boom creating in cerebral circulation, is the time, in seconds, whose values do not depend on the injected dose of radioactive substance.

Starting from the phenomenological aspects, and theoretical considerations, reflected in a the radiocirculogram (RCG) and from the premise this method would bring in solving of many internal medicine and cardiology problems, Dr. I. Mureșan done an extensive research under technical implementation, analysis, interpretation, and enhancement of clinical results. RCG, as recorded curve, is a plotting temporal graph of radioactive tracer intensity proportional to blood flux. All this have been analyzed in terms of technique, reproducibility, morphology, and meaning of blood circulation by qualitative-quantitative clinical values in their pathological limits of normal and abnormal in terms of cerebral hemodynamic of cardiovascular diseases. All this was taking into account the experience in making and interpreting of 583 recorded RCG to 487 cardiovascular patients and 94 healthy controls, lots statistically significant. Information obtained has confronted and compared with data provided by other existing investigative
techniques and then interpreted, in terms of clinical censorship. Hence, exploring cerebral circulation in arteriosclerosis has obtained measurable nuanced information on the circulatory global process and specific phenomenon in each vascular segment that could be correlated to fluxes incidents and emerging through dynamic parameters specific flows network such as perfusion pressure and vascular resistance, flow and speed of movement.

**Principles and Technique of Brain Blood Flow Radiocirculography**

Radiocirculography involves graphical transposition of temporal radioactivity of sanguine flux, in a section of a vascular segment, after minimum infecting blood flow through arterial injected radioactive tracer. From cerebral RCG curve form of tracer passage in the segment of carotid-confluens sinum, we obtain some direct relations on blood flow speed and the transcerebral vascular resistance. In principle, we have implemented this method of investigation, as a new technical variant used by Eichhorn\(^1\) and Oldendorf and Kitano.\(^2\) Using injectable doses of \(^{51}\)Cr or radioactive tracer \(^{131}\)I serum albumin (RISA) marked with \(^{131}\)I, however, we have standardized body weight. Tracer is injected into the cubital vein, into a split second, so radioactive blood bowl touch heart and brain, flowing to more compact. Gamma ray detector strictly centered needs external occipital protuberance on to be precisely collimated to remove inaccuracies.

The injected tracer reaches the left ventricle where the next systole will distribute partly to cerebral circulation in the arterial segment of tract, running through the neck and then the arteriocapillary and venous. The injected doses were reduced to a minimal value of 18.5 kBq/body’s kg, so harm irradiation drops to a value lower than those counts in the course of X-ray radioscopy, without significant changes of globular blood. For vigorous young people, the obtained radiocirculographic curves have normal forms such as those shown in Figures 1 and 2. The regular curves contour, with crest caused by wave fronts of the regular systolic pulses, suggests conspicuous differences on vascular resistance and sanguine fluid velocity. Nominalized in the same figure, the observing parameters of RCG curve can be correlated with the hemodynamic state.

The temporal radioactivity variation, shaped like a triangle with the top angle, less or more sharp, shows the brain function as vascular permeability. The deviations from the normal form of RCG and their standard parameters represent anomalies of cerebral sanguine circulation or damage of fluid blood passing through the brain.

Besides to arm-brain travel time and cerebral circulations time, used before by other authors, our factual analysis of brain RCG allow us to introduce and determine some quantitative key parameters of the vital sanguine movement. Therefore, correlated with precise meanings of cerebral sanguine circulation, we define the following parameters:

- The RCG maximum amplitude \( A_{\text{max}} \) (imp/s)
- Average ascending slope \((c-e)\)
  \[ p_{\text{asc}} = \frac{e-c}{2} \text{(imp/s)} \]
- Average descending slope \((e-g)\)
  \[ p_{\text{desc}} = \frac{e-g}{2} \text{(imp/s)} \]

\( p_{\text{asc}} \) and \( p_{\text{desc}} \) parameters are two synthetic indicators which characterize arterial and venous, cerebral circulation, each revealing the rates of cerebral blood flux input respective output in the brain segment.

**Determination of Cerebral Sanguine Flux by Radiocirculography**

Through administration of standardized tracer doses, intravenously injected, based on the dilution RCG curves, conform to Stewart- Hamilton principle, measuring of total blood volume and cardiac output, allows us a quantitative evaluation of cerebral blood flux. Phenomenological analysis of dilution processes, based on radioactivity conservation for short periods, and taking into account that actually RCG is a reflection of the temporal variations of flows sanguine radioactivity, marked by the tracer bowl, we established a formula of intensity flux (flow) of fluid.

![Figure 1: Cerebral radiocirculographic parameters.](image-url)
that is pumped through the cerebral sanguine vascular circulation.

The calculation of circulating blood volumes
Using dilution principle, it is possible to evaluate the volume of filed compartments with a radioactive labeled liquid. Thus, if in a sanguine circuit of volume \( V_s \) is injected a small dose of radioactive tracer with volume, \( v \), and with high radioactive concentrations \( C \), after a number of re-circulation, it will dilute homogeneously in the blood flow without significantly changing the blood volume \( V_s \), but becoming contaminated with a small radioactive tracers’ concentration \( c \).

By choosing a not metabolizable radioactive substance, with a long enough half-lives time, after a short time of their dilution in circulant blood, conformed to conservation principle, the radioactivity, at two levels, is inversely proportional to the volume in which was homogeneous dilute the amount \( Q \) of a radioactive isotope. I mean:

\[
C = \frac{Q}{v}; C = \frac{Q}{v} \leftrightarrow \frac{C}{v} = \frac{C}{v} \leftrightarrow \frac{V_s}{v} = v \frac{C}{c}
\]

Therefore, in our case, knowing radioactive concentration \( C \), the volume \( v \) of RISA serum albumin injected intravenously and the concentration \( c \) allows calculus of sanguine plasma volume \( V_s \), which is difficult otherwise. From the foregoing considerations, by this simple method, the total sanguine volume evaluation becomes very simple after the relationship:

\[
V_s = \frac{v}{c} \frac{C}{v}
\]

Principle of sanguine flux determination through radioactive tracers
The use of radioactive isotopes in the study of sanguine flow relies on the radioactivity preservation and recording the real-time dilution curves of blood pumped into closed circuit by the heart. Phenomenological considerations on to tracer radioactivity in cardiovascular system allow to deduce a formula for the blood flux, \( F \), valued as the amount of fluid that traverses a vascular segment unit time.

As the electric current intensity through a conductor is proportional with the carrier’s electric charge drift velocity, so, with respect to Stewart-Hamilton principle, the infected blood cells flux \( F \), during infinitesimal \( dt \), will carry through a vascular segment of \( dV \) volume, \( S \) section and length \( dx \) an infinitesimal radioactivity \( dQ \) of atoms tracers:

\[
dQ = dcV = cSdx = cSvdt = c \left( t \right) Fdt
\]

where \( c = c \left( t \right) \) is the momentary concentration of tracer radioactive atoms carried by the blood flux \( F=vS \) of sanguine flow through unit cross section of the vessel segment in question.

Integrating for a sufficiently long period compared with the time passage of the radioactive isotopes bowl, we obtain the deemed amount,

\[
Q = \int_0^Q \frac{dQ}{F} = \frac{c}{k} \left( t \right) dt
\]

It follows a mathematical relationship that expresses the Stewart-Hamilton’s principle in a radioactive liquid flow of infected blood:

\[
F = \frac{Q}{\int_0^1 c(t)dt}
\]

The measurement of radioactive concentration for a series of samples, sequentially taken through arterial puncture, could allow the construction of the curve and thus the blood flux calculation. However, it encounters technical difficulties. External registration of temporal emissivity variation proportional to \( c \left( t \right) \) concentration of gamma radiation emitters, allows flow calculation without collection of blood samples. Registering with a particle counter, in a given angular field, the variation in time \( R \left( t \right) \) of infected blood flow radioactivity, will be, during registration, proportional to the concentration, namely:

\[
R = k c \left( t \right)
\]

Moreover, the flow rate:

\[
F = \frac{Q}{k \int_0^1 R \left( t \right) dt} = k \frac{Q}{A}
\]
After enough successive recirculations, experimental brain’s RCG is readily registered [Figure 2]. Analyzing this graph will determine final homogeneous concentration of blood radioactivity $C_f$, reporting to the local natural background’s radioactivity, and area $A$ comprised between the curve $R(t)$ and the horizontal exponential extrapolated $R(f)$. So having $R_f = kC_f$ by eliminating constant, flow calculation formula is:

$$F = \frac{Q}{C_f A}$$

With this relationship, knowing experimental area value, the cerebral blood flux can be calculated.

Promoters of radiocirculography method did not mention any test for determining cerebral blood flow in their work. Even reproduction of radiocardiographic blood routes through electronic analog simulators is limited to the determination of pulmonary circulation, time of transit and filling/emptying of the left ventricle.

### Experimental Procedures and Calculus of Cerebral Sanguine Flux

Starting from above physical and mathematical considerations, we propose two possible methods for determining cerebral blood-flux based on radiocirculographic data.

#### Intracarotidian injection method

Using specified techniques, the serum containing a measured amount of radioisotope $^{51}$Cr is intracarotidian injected and simultaneously RCG is started for registering. Knowing that all injected substance $Q$ passes through the brain and then is collected in venous crossroads HEROPHILE pool and then is registered, via a solid angle, by a particle counter fixed on the external occipital protruding it can obtain all the data to use the expression of Stewart-Hamilton principle. So for flux calculation, we use:

$$F = \frac{R_f Q}{C_f A}$$

From Figure 2, it can see that area $A$, can be, planimetric, measured and the final concentration $C_f$ can be evaluated by dosimetry on blood samples extracted after the number of pulses remains approximately constant, that is, after 10–14 min.

The method is encumbered by the necessity of carotid puncture, thus simple, but not enough for broad clinical application. It has, however, a sufficient degree of accuracy.

#### Intravenous injection method

This investigation technique can be clinically used more simple and intensively. After injecting in cubital vein a minimum $^{51}$Cr quantity of 18.5 kBq/kg score, the cerebral RCG is registered by a common technique.

The direct application of the principle of Stewart-Hamilton using intravenous injection is not possible to determine cardiac output; it would seem it is not possible because only part of the blood flow and radioactive material will be distributed through the brain. Analyzing hydrodynamic processes in brain blood network, after intravenous injection, we have established a way of determining radiocirculographic cerebral flow. The cerebral fraction $Q_1$ of radioactive substance intravenous injected can be expressed in terms of final concentration $C_i$ and volume of mixture $V_m$ above occipital venous confluence which is detected:

$$Q_1 = C_i V_m$$

How the two volumes, apparently mixing $V_m$ and sanguine circulating volume $V_s$ are proportional to the corresponding radioactivity:

$$V_m = \frac{R_f}{R_m} V_s$$

The brain blood flow rate or cerebral sanguine flux will be:

$$F = \frac{Q_1}{C_f} = \frac{V_s R^2_f}{A R_m}$$

This relationship allows the calculation of cerebral sanguine flux $F$ simply because $V_s$ can be determined as in the “Intracarotidian injection method” section, and $R_f$ and $R_m$ are measured as ordinate reported to the natural radioactivity value $R_o$, and finally $A$, as area placed upon registered circulograme [Figure 2], is planimetric measured.

Flux values determined through this technique defined and used by us are distributed between 480 and 480 ml/min, depending on sex and age table physiological or pathological conditions of cases where investigations were conducted. Our results are in good agreement with those found by other authors through other flowmeters techniques.

#### Determination of cerebral/cardiac sanguine flux fraction

It is known that cerebral flow is dependent only to a small extent by changes in cardiac output; even when large variations appear, only small variations in cerebral flow
are detectable. It is not parallelism between decreasing of two flows rate even in controlled hypotension. The situation is similar in the case of cardiac output increasing. These relationships are also valid for sudden changes of cardiac sanguine flux. For the first time, to determine correlations between cardiac output, in real time and the brain flux in the cases of chronic diseases, we used enrollment simultaneously RCG of heart and brain to bring the two curves in their areas.

Radiocardiography
To evaluate the cerebral fraction of cardiac blood flow, first it is necessary to obtain temporal dilution curve of a radioactive tracer injected intravenously through external chest detection and then to identify the morphological qualitative and quantitative parameters of it. These recordings were made using the RISA injecting a dose of 0.74–0.95 MBq right arm cubital vein. The detection was made by a scintillation counter placed precordial and a gamaspectrometer recorded by magnetic memory. In the heart RCG [Figure 3], injection timing is \( t_0 \) and \( R_0 \) corresponds to natural background radiation. After a period of 1–2 s, radioactive tracer reaches the right heart chambers causing a rapid increase up to a maximum radioactivity \( R_m \) corresponding to the peak reached at the \( t_d \) time. After several cardiac revolutions visualized by small hooks, tracer is expelled from the right ventricle into the pulmonary circulation, marking the start of a depression corresponding tracer output of the meter field detection. It then finds a new path upward curve that reaches a second peak (\( S \)) corresponding to the maximum concentration of the indicator right in the heart at time \( t_s \).

Right and left ventricular blood radioactivity decay follows the form of the \( e^{-s} \), respectively, \( e^{-d} \) exponential curve, that can be interpolated logarithmically system, so being able to assess the rate of expulsion of blood from the two wells. Then achieved a balance of blood and radioactivity curve tracer height stabilizes at a value \( R_f \). The information you can provide regarding hemodynamic cardiac blood circulation RCG in the heart and lungs is the assessment of traffic parameters such as timings filling and emptying of the left ventricle, pulmonary circulation time and minimum environmental and pulmonary transit time. The decay rates of the blood radioactivity ejected from the left ventricle determine the index of this ventricle efficiency. Some authors calculated left ventricular ejection coefficients (KS) and evaluated as exponential curves of the two ventricular drain.\[^9,10^\]

Dilution principle allows the calculation of volume and flow sanguine. Overall concentrations are calculated to the height curves, and their surface allows assess the volumes and reporting them according to defined time cardiac output.

Like in other direct determination of hydrodynamic flows, using radioactive isotopes, for calculating cardiac output by Stewart-Hamilton’s principle, we obtain the following relationship:

\[
F = \frac{R_iQ}{C_fA}
\]

where: 
- \( F \) = Cardiac output
- \( Q \) = Amount of injected radioactive substance
- \( C_f \) = Final radioactive concentration (dosimetric determined)
- \( A \) = Area, planimetric determined
- \( R_i \) = Radioactivity corresponding to final concentration \( C_f \).

Relationship between the cerebral and cardiac blood output
Knowing the faction of cerebral circulation, flow returns ventricle is one of the major issues addressed in this paper. To determine this report, we used the simultaneous registration of radiocardiogramme and brain RCG [Figure 4], which allowed us both calculating flow rates and their relationship.

Thus, from Figure 4 curve I, representing cardiac circulogramme, named radiocirculogramme, we can identify the size of \( R_i \), \( C_i \) and \( A \), which allowed us to calculate cardiac output after the above relation. Cerebral blood flux can be calculated using the relationship:

\[
F = \frac{V_i}{A R_m} R_i^2 R_f
\]

Required parameters amounts are given in brain RCG [curve II in Figure 4].
The femoral neck blood flux can also be calculated from curve III (the femoral RCG) represented in the same [Figure 4]. The femoral neck blood flux can also be calculated. It follows that simultaneous recording and reporting of brain RCG and radiocirculogram of heart and possibly femoral circulogram is not only a technical process economically and efficiently requiring a single injectable dose and determination, but also a method of study and determining the ratio between cardiac and brain output, eventually femoral ones.

The knowledge of relative indexes of cerebral circulation in normal and pathological conditions cerebral flux is one of the major questions of healthy state. There is not enough to determine absolute cerebral flux, it is necessary to evaluate how it depends on the work efficiency of the heart. Hence, the above-described method is an ideal tool to analyze the degree of dependency between cerebral circulatory troubles and cardiac hemodynamic deterioration.

Conclusions on the Clinical Value of Brain Radiocirculography

Clinical significance and truthfulness in this investigation has been established on the basis of the analysis of a large number of investigations carried out in the conditions laid down and through the confrontation of information obtained from RCG curves with other clinical and laboratory data. Concerning to the status of this study for the patients, their investigations bring prompt and reliable details on the degree of impairment of the functioning of the brain.

General morphology of the cerebral RCG, in all cases, is so characteristic that the clinician can appreciate at a glance if a curve is normal or pathological. If the cerebral hemodynamic disorders exist, the RCG shape and parameters indicate the type and severity of them. Carotid radiocirculography associated with cerebral angiography, in addition to detection and localization of obliteration, offers much other direct information on the affected flux, vascular resistance, and other cerebral hemodynamic indices.

In Figure 5 you can follow radiocirculographic paths and variability of parameters specific to the cerebral circulation in three subjects of close ages with cerebral diffuse atherosclerosis diagnosed: (a) neurastheniform Syndrome and obstructive Emphysema (b) Parkinsonism: ischemic decompensated cardiomyopathy (c) Senile dementia; chronic pulmonary uncompensated heart. Status of cerebral blood circulation is illustrated in many dozens of charts presented in this thesis; the curved shape of the three RCG clearly indicates how much altered cerebral blood circulation of the three patients is.

The high degree of trust was proved by repeated registering. Radiocirculographic routes are reproducible, as in normal and pathological states. In the case of some patients, if hemodynamic parameters are dubitable, getting RCG repeated recorded curves, after certain periods with or without treatment by comparative quantitative assessment is particularly eloquent and useful. At set intervals, their temporal variance allows objectification of spontaneous or therapeutic effects and action mechanism of various medications and some vasoactive therapy of cerebral palsy as are vasodilators, medical gymnastics, oxigenoterapy, physical work and mobility.

The facts presented in this article have been addressed and used clinically in his doctoral thesis entitled “the Cerebral Hemodynamics in Essential Hypertension and Arteriosclerosis” that in 1970, have been public presented at the Institute of medicine and pharmacy of Cluj, in administrative headquarters. The thesis was graduating “magna cum laude” and chiefly doctor Ioan G. Muresan was awarded the title of doctor in medical sciences. Taking into account the scientific and clinical value of high academic and pioneering research held, we consider that book deserves to be drafted with computerized complete fulfillment, translated and put into service by electronic means.

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**Conflicts of interest**

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Figure 5: Specific brain's radiocirculogram for diseases of old age: (a) Emphysema, (b) parkinsonism, (c) senile dementia