REVIEW ARTICLE

Cerebral blood flow monitoring

Manikandan Sethuraman

Abstract

Brain is a unique organ of the body that receives highest amount of cardiac output and totally depend on the blood supply for its survival and no reserve of blood flow making it vulnerable for ischaemia. Other important properties of cerebral circulation include autoregulation of blood flow, high oxygen extraction, and selective increase in blood flow to specific brain areas during various functional activities. It is important to understand that systemic and local factors affect the cerebral blood flow and the brain functions. Moreover the alterations in cerebral blood flow (acute or chronic) can be responsible for various symptoms as well as diseases pertaining to the brain. Hence it is important to measure the cerebral blood flow for the diagnostic as well as therapeutic purpose. This review focusses on the various techniques available for monitoring the cerebral blood flow.

Key words: Cerebral blood flow, monitoring techniques, global and regional

INTRODUCTION

Cerebral blood flow (CBF) is unique compared to other organs in the body. Even though the brain is only 2% of the body weight, it receives approximately 15% of the total cardiac output. Moreover, brain has highest metabolic activity without any storage of glucose or reserve of blood flow. Hence, a continuous supply of blood and nutrients is essential for its functioning. In addition the CBF is not constant as the flow increases in increased activity of the brain a phenomenon called cerebral autoregulation. Cerebral autoregulation is an important protective mechanism wherein the brain adjusts its blood supply depending on its needs. A lower CBF can lead to cerebral ischaemia and a high blood flow can lead to hyperaemia. In addition to local factors various systemic factors such as cardiac output, arterial blood gases, and temperature also affect the CBF. Many diseases are caused by alteration in CBF like ischemic stroke, whereas in some brain conditions the CBF is altered as in head injury. It is important to understand the pathophysiology of brain pathological conditions for which knowledge of global and regional CBF (rCBF) is important. This chapter describes various techniques and their principles for measuring the CBF.

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HISTORY OF CEREBRAL BLOOD FLOW MEASUREMENT

The interests in the cerebral circulation date back to Andreas Vesalius in 15th century.[1] The anatomy and the CBF in the circle of Willis were explained by Thomas Willis (1621–1675) a physician after William Harvey's described the physiology of circulation of blood. The interest in the measurement of CBF starts since the description of Monro-Kellie doctrine describing the relationship between the contents of cranium, namely brain, cerebrospinal fluid and blood. Initial attempts to measure CBF involved direct cannulation of jugular

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veins of experimental animals' in 1887, and measuring the venous blood return; however the values were inaccurate due to contamination by extracranial blood.[2] Later methods involved direct cannulation of the internal carotid artery. It was not until Adolf Fick in 1870 described a mathematical principle for meaning the cardiac output using differences in oxygen content of arterial and venous blood, an alternate method was followed to measure blood flow to an organ. The measurement of CBF using Fick's principle was described after seven decades by Kety in 1960.[3] Following his work, various techniques have been developed using diffusible tracers for the measurement of global and regional blood flow. The drawbacks of these techniques were the need for radioactive substance, lack of widespread availability and cannot be used in clinical situations. Current refinements in radiological techniques have allowed us to measure the CBF in different pathological situations with more reliability.[4] This article reviews some of the techniques that are available for measurement of CBF.

METHODS BASED ON RADIOACTIVE AGENTS

Kety-Schmidt method

Kety and Schmidt were the first to attempt to measure global CBF in 1945. They used nitrous oxide to determine the global CBF based on the Fick's principle.[5] It is based on the principle that the rate at which the cerebral venous blood content of an inert gas approaches the arterial blood content depends on the volume of blood flowing through the brain. The subjects were allowed to inhale 21% of oxygen, 15% of N_2O and 64% of nitrogen and blood samples of N_2O content were obtained from the femoral artery and right internal jugular vein over 10 min period. The N_2O content for artery and vein were plotted [Figure 1] and the CBF was estimated using the formula;

CBF = 100 Qt/∫o t [A-V] dt

Qt = quantity of N2O taken up by brain form beginning at time 't'

A-V = arteriovenous difference in content of N_2O at time 't'

The derived value was found to correlate with the directly measured global CBF. The same method can be performed using Kr^{85}.

Intravenous radioactive tracers

The Kety-Schmidt inhalational technique was found be cumbersome and required repeated blood sampling. Moreover, it overestimated the CBF due to recirculation and diffusion to the brain. Attempts were made to use intravenous (IV) agents. Lassen and Hoedt-Rasmussen used IV radioactive agents dissolved in saline and used external counters placed over skull which detects the radioactivity.[6] Initial methods used the beta, later techniques used gamma counting for detection of radioactivity. The radioactivity doses employed in each study were about 2 mc of Kr^{35} and about 0.5 mc of Xe^{133}, doses that, with the counting equipment used, gave maximal counting rates of 100,000–200,000 counts/min over the brain. The agents were injected into internal carotid arteries to reduce contamination by extracranial tissues. The radioactive decay is plotted over time. The estimation of the CBF was based on two types of calculations:

Stochastic method

In this method, the radioactive counts are plotted against time [Figure 2]. It is a mono exponential curve.

The CBF is calculated using the formula CBF = ƛ X A/HX100 (ml/100 g/min),

A = area under the curve, H = peak height of the curve that corresponds to the maximum activity of the tracer, ƛ = blood partition coefficient. The disadvantage of this method is that the formula does not take into account of recirculation and areas with slow blood flow. The tracer must have single pass metabolism, and the counter should measure the activity very fast without lag in such cases. Even though the area under the curve (A) can be

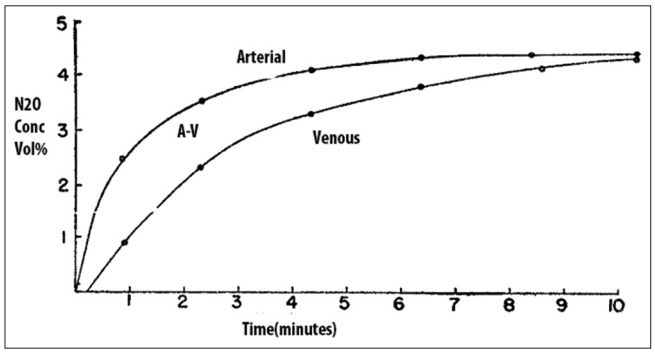

Figure 1: Kety-Schmidt method of arterial and venous nitrous oxide concentration for calculating cerebral blood flow

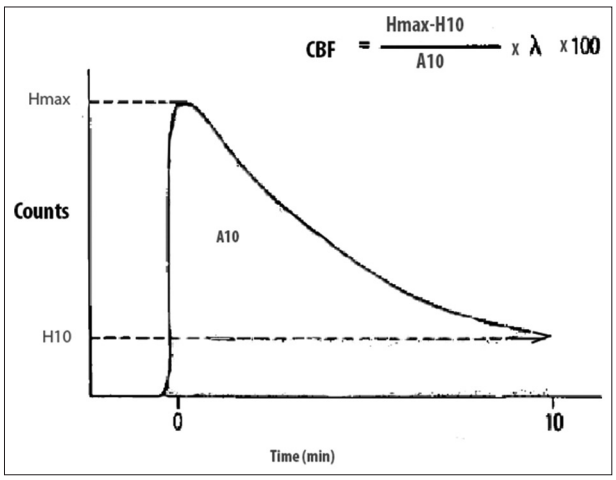

Figure 2: The stochastic method of calculating cerebral blood flow

traced up to infinity, as with Kety-Schmidt method, the area is calculated within 10 min limit period. Hence, the calculated value may overestimate CBF.

Two compartmental models

In order to correct the drawbacks of the above technique, a two compartmental model is derived. The assumptions are (1) diffusion equilibrium in each separate tissue, and (2) the existence of only two quantitatively important compartments viz. grey (g) and white (w) cerebral matter with different blood flow. The curves are derived for gray and white matter separately [Figure 3].

The mean flow 'F' is derived using the formula:

$$F = \frac{H}{Ig / fg + Iw / fw}$$

Ig, Iw = zero intercepts for gray and white matter, fg, fw = flow of gray and white matter

Ig = D × Wg × fg (D = radioactivity of the tracer, w = weight of the tissue, f = flow into the tissue), Iw = Dx Ww Xfw.

Hydrogen clearance method

Inhalational or IV hydrogen has been used to assess the CBF with Kety-Schmidt method using the hydrogen clearance technique. The basic principle consists of hydrogen ions will produce changes in the current in the electrode placed in the body and the changes in the current strength between the arterial and brain electrodes can be measured the CBF.[7] It is an invasive method where platinum electrodes are placed stereotactically in the cortical areas of the brain. 7% of hydrogen is usually added to the inspired gas whereas $PaCO_2$ is maintained constant. Once the hydrogen concentration increases in the arterial blood, a platinum electrode placed inside the aorta via femoral artery will record the current changes and after a period the current strength changes in the electrodes placed in the brain due to diffusion of hydrogen inside the brain. This technique can be used to measure both global and regional blood flow.

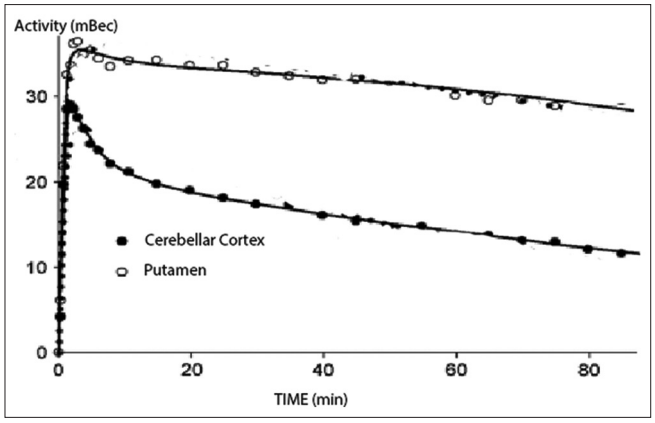

Figure 3: The compartmental model for calculating the cerebral blood flow

Microspheres technique

Microsphere techniques have been popular since the introduction of the techniques by Rudolph and Heymann in 1967 for examining the regional blood flow in sheep foetuses in utero.[8] They are easier to use and give a higher resolution than methods using molecular tracer washout. They can measure regional as well as global blood flow. Microsphere techniques have been thought to reduce the disadvantage of Xe clearance where the extracranial flows are not excluded.[9] Microsphere techniques consists of injecting the radioactive tracers delivered into the left side of the heart usually left atrium via catheter and the radioactive decay counts are calculated from the brain as well as arterial blood. Microspheres labelled with radionuclides ^{141}Ce, ^{51}Cr, ^{85}Sr, and ^{46}Sc and with sizes of 15 ± 0.8/tm mixed with saline are injected into the left atrium.[10] Simultaneous serial arterial samples at a constant rate were sampled before injection and after injection of microspheres and the counts from brain and radioactivity of the arterial blood is calculated. The CBF is calculated using the following formula:

CBF = Cb × 100 × RBF/Cr,

Where BF = blood flow in ml/min × 100 g, Cb = counts per gram of brain, RBF = reference blood flow in ml/min (rate of withdrawal from the reference arteries), and Cr = total counts in the reference blood. The counts in the paired reference blood samples were averaged.

Fluorescent microspheres technique

A fluorescent microsphere is a newer technique which has an advantage of simple to use.[11] It does not require the use of radioactive microspheres which are difficult to obtain in many centres. Moreover, it reduces the risk of exposure to radiation. The fluorescent microsphere technique resembles that of radioactive microspheres. Microspheres capable of editing fluorescent light at particular wavelength are injected into the left atrium and the tissues are screened for the fluorescent light using a fluorescent reader. Absolute CBF (ml/min/100 g) was calculated in each tissue region for each colour as:

CBF = ts × rf × 100/rs × V × ρ

where ts is the number of tissue microspheres, rs is the number of reference blood withdrawal microspheres, rf is the rate of the reference blood withdrawal (0.97 ml/min), V is the volume of the tissue region in cm^3 (calculated as described above) and ρ is the density of mixed gray-white matter brain tissue (1.04 g/cm^3).

COMPUTED TOMOGRAPHY SCAN BASED TECHNIQUES

Xenon enhanced computed tomography

With the advent of computed tomography (CT) scans,

methods have been developed for measurement of CBF using CT scans since CT scans are less time consuming, better availability, better delineation of morphology. Measurement of the CBF using a contrast agent is an attractive method for measuring CBF; however, the water soluble contrast does not penetrate the blood-brain barrier (BBB).

Xenon (Xe) is an inert gas with a molecular weight of 54. Xenon has the advantage of rapidly diffusing across the BBB and into the gray and white matter of the brain. Its distribution follows the CBF and volume. Xe is a simple method.[12] Non-labelled xenon readily enhances the brain substance by freely diffusing across the blood-brain barrier; CT scanning provides a simple and reliable method for monitoring this enhancement. The presence and rate of clearance of xenon from small regions of gray and white matter may be monitored by knowing the anatomy of the brain as defined by the CT scan. Compartmental analysis enables the separation of the brain washout curve into three basic compartments using inhalation methodology; fast (predominant grey matter washout), slow (predominantly white matter washout), and slower (predominantly extra- cerebral sources).

The technique of xenon enhanced CT consists of; an initial plain CT scan of the brain is done. The subjects are allowed to inhale 100% of oxygen until the expired gas contains at least 95% of oxygen to remove the nitrogen. Then, the subjects are asked to inhale non-enhanced Xe to reaches a concentration of 80% and an immediate CT scan (maximum Xe) is obtained. The xenon inhalation is abruptly stopped with 100% of O_2 inhalation and serial CT scan (every 2 min up to 10 min) for washout period is obtained (To identify different compartments of brain as well as to construct washout curve).

CBF (ml/100 g/min) was then analysed by two methods (compartmental model or stochastic) (λ) is the partition coefficient of xenon.

Xenon-enhanced CT scanning can help in three basic applications: (1) Evaluation of capillary-brain tissue integrity, (2) evaluation of gross comparative cerebral perfusion, and (3) evaluation of CBF.

Computed tomography perfusion techniques

With the availability of CT scanners, CT perfusion techniques have been used to assess the CBF. Perfusion CT was introduced as a means to rapidly and easily evaluate cerebral perfusion in patients presenting with acute stroke symptoms. Perfusion CT can be performed quickly with any standard spiral CT scanner, and the perfusion maps can be generated in a short time at a workstation equipped with the appropriate software. The basic principle used in the perfusion CT is the central volume principle. In the central volume principle, the CBF, cerebral blood volume (CBV) is related by the formula CBF = CBV/MTT, where MTT is the mean transit time. Perfusion CT is performed by injection of a bolus of iodinated contrast agent intravenously and monitoring the attenuation of signals using CT imaging of a particular area continuously. The contrast causes attenuation of the signals in the CT scan. There are two phases in the scan. Initial rapid attenuation is considered to be the arterial phase, and the washout of attenuation is considered to be the venous phase [Figure 4]. Contrast agent time-concentration curves are generated in an arterial region of interest (ROI), a venous ROI, and in each pixel. Deconvolution of arterial and tissue enhancement curves (deconvolution is an algorithm-based process used to reverse the effects of convolution on recorded data), a complex mathematic process, gives the MTT. CBV is calculated as the area under the curve in a parenchymal pixel divided by the area under the curve in an arterial pixel. The central volume equation can then be solved for CBF.[13]

Technique: Initial non-contrast CT scan is usually done. Four adjacent 5 mm slice of CT in the region of basal ganglia is taken which gives a reference foe all three vascular territories (anterior, middle, posterior cerebral arteries). Usually, a 50 ml IV contrast is given at a rate of 4 ml/s. At 5 s after initiation of the injection, a cine (continuous) CT scan (every 1 s) is initiated. The recorded image is reconstructed in the imaging console. Arterial (anterior or middle cerebral) and venous (torcula) ROI is placed and the attenuation curves with respect to time are constructed to calculate CBV and MTT. If the rCBF is needed then the ROI is placed in the brain parenchyma to obtain tissue attenuation curves.

The overall effective dose required for dynamic CT (2.0–3.4 mSv) is only slightly higher than that required for routine head CT (1.5–2.5 mSv). This dose equivalent is less than the dose equivalent obtained with positron emission tomography (PET) or single photon emission computed tomography (SPECT) and is comparable to that of a single-level xenon CT examination.

Single photon emission computed tomography

SPECT is a tomographic scintigraphy technique in which a computer-generated image of local radioactive tracer distribution in tissues is produced through the detection of single-photon emissions from radionuclides introduced into the body. Brain perfusion SPECT imaging is a functional nuclear imaging technique performed to evaluate regional cerebral perfusion. A lipophilic, pH-neutral radiopharmaceutical (most commonly technetium-99m-hexamethyl propylene amine oxime [Tc-99m-HMPAO] and 99m Tc-ethylene cysteine diethylester [ECD], with a half-life of 6.02 h) is

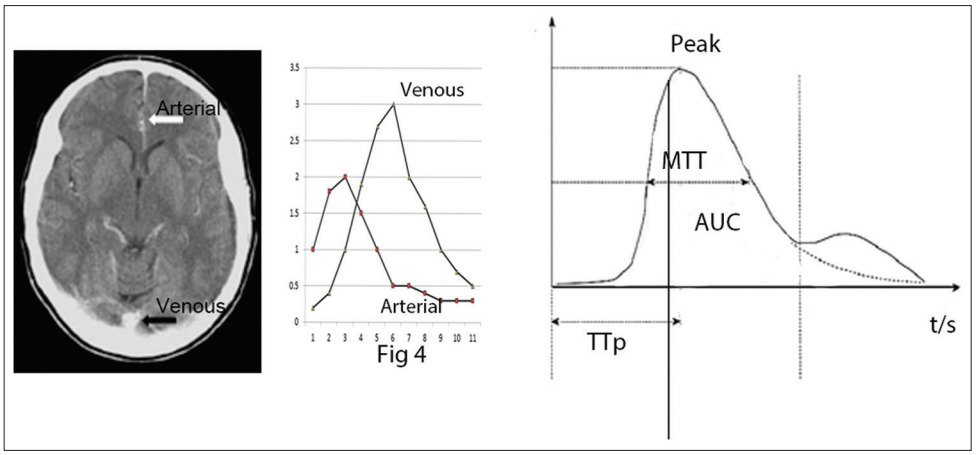

Figure 4: The computed tomography perfusion technique of calculating the mean transit time

injected intravenously into the patient, which crosses the blood-brain barrier and continues to emit gamma rays. A three-dimensional (3D) representation of CBF can be generated using gamma detectors, allowing for interpretation. Brain SPECT can be complemented with pharmaceutical agents that enhance rCBF, such as acetazolamide (carbonic anhydrase inhibitor). Acetazolamide increases local PCO_2 and causes arteriolar dilation, allowing for assessment of cerebrovascular reserve. SPECT/CT is a newer mode of SPECT which has the advantage of anatomical imaging as well as blood flow quantification. In SPECT/CT combination of high-resolution CT imaging with the additional rim of gamma cameras to detect single photons is used. Combined SPECT/CT devices provide both the functional information from SPECT and the anatomic information from CT in a single examination. Some studies have demonstrated that the information obtained by SPECT/CT is more accurate in evaluating patients than that obtained from either SPECT or CT alone.[14]

Three accumulative tracers, iodine-123-labeled N-isopropyl-p-iodoamphetamine, Tc-99m-HMPAO, and Tc-99m-labeled ethyl cysteinate dimer (Tc-99m-ECD) are widely used to measure CBF in SPECT. Diffusible tracers, such as H215O or 133Xe, can be used in SPECT for rCBF measurement. They all have first pass metabolism. CBF is quantified using the fluid microsphere model proposed by Kuhl *et al.*,[15] in which CBF = (R × Cb)/O and R = constant withdrawal rate of arterialised venous blood in millilitres per minute (usually 1 ml/min), Cb = local tracer concentration in microcuries per 100 g trapped by the brain in the first 5 min, and O = octanol extraction of the (true) tracer concentration in the withdrawn blood in microcuries. The advantage of SPECT is it is non-invasive and produces accurate values of global as well as rCBF. The disadvantages are it is not a bedside investigation and continuous measurement not possible due to the long half-life of tracers and is expensive. It is not widely available due to the lack of availability of tracers.[16]

MAGNETIC RESONANCE IMAGING BASED TECHNIQUES

Advancement in the software as well as quality of magnetic resonance imaging (MRI) had dramatically improved the techniques for measurement of CBF. They are non-invasive, relatively rapid and accurate. Both global and rCBF can be measured. Some of the techniques for measuring CBF using MRI are given below.

Phase contrast magnetic resonance imaging

Phase-contrast MRI (PC-MRI) is a non-invasive technique to visualise blood vessels and measure blood flow velocity. It utilises the phase of an image to encode the velocity of flowing spins. The most significant advantages of PC-MRI are its simplicity and accuracy in absolute CBF quantification as well as the relatively short scan duration.

Moran analysed the phase effects on stationary and moving spins subjected to a pair of bipolar gradients as shown in Figure 5. A stationary spin, when subjected to a bipolar gradient pair, will experience no net phase shift, but a moving spin will have a net phase shift proportional to its velocity. Two spins flowing at the same speed but in opposite directions will have equal but opposite phase shifts. By measuring changes in phase, therefore, velocity can be computed.[17]

In phase difference images, the signal is linearly proportional to the velocity of the spins - faster moving spins give rise to a larger signal, and spins moving in one direction are assigned a bright (white) signal, whereas spins moving in the opposite direction are assigned a dark (black) signal. Thus, the vascular anatomy can be assessed, and the speed and direction of the blood flow can be qualitatively determined, by observing the phase difference images. In addition, quantitative information regarding the velocity and volume flow rate of the blood can be derived from the phase difference

images. To assess flow information, the images must demonstrate the cross section of the vessel so the area can be determined. The product of the area and the average velocity over the vessel yield the volume flow rate.

The amplitude, duration, and spacing of the bipolar gradients determine the degree of sensitivity to slow or fast flows. This is controlled by an operator-selectable parameter known as velocity encoding (VENC) which must be prescribed prior to any PC-MRI/magnetic resonance angiogram (MRA) study. Proper setting of VENC is critical to the performance of the study. By applying bipolar gradients sequentially along the cardinal directions [*x*-, *y*-, and *z*-] and measuring phase shifts, velocity components of flow along each direction [*vx*, *vy*, and *vz*] can be computed.

Dynamic susceptibility weighted imaging

Gadolinium chelates can be used as 'tracer' to estimate the CBF. They stay intravascularly in the areas with intact BBB.[18] The contrast is administered using a wide bore IV cannula at faster rate (>4 ml/s) and the first pass of the agent is imaged using cine mode at a rate faster than the bolus enters the tissue. Images are first acquired to determine the baseline signal intensity of each voxel. When the bolus passes through the voxel, the signal intensity drops. This drop occurs because the contrast agent is confined to the vascular space, which creates microscopic variation in the local magnetic field, which in turn leads to decreased signal intensity on gradient echo (GRE) images. The intravascular contrast also creates magnetic field gradients around the vessel, which cause a signal-intensity loss when protons diffuse in these gradients. The CBF is calculated based on the central volume principle (CBF = CBV/MTT) MTT = mean transit time, CBV = cerebral blood volume (proportional to A-V concentration of the contrast).[19]

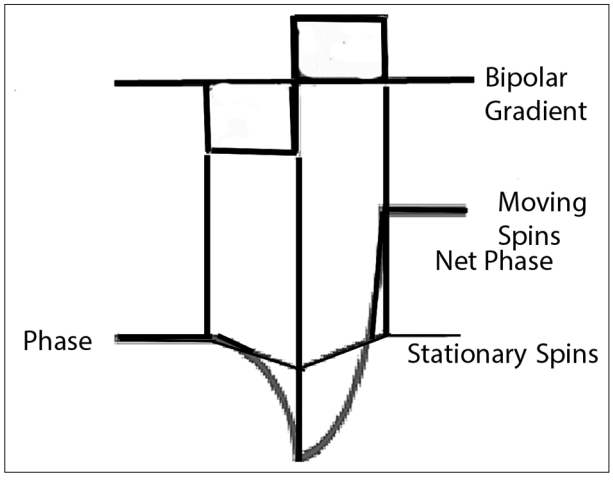

Figure 5: The phase contrast magnetic resonance imaging technique of measuring the cerebral blood flow

Arterial spin labelling

The principle of arterial spin labelling (ASL) is similar to radio labelled water using PET scan. However instead of radiolabeling the water molecules are labelled using magnetisation.[20] In ASL, arterial blood water is magnetically labelled then imaged. First, arterial blood water is magnetically labelled just below the region (slice) of interest by applying a 180° radiofrequency inversion pulse. The result of this pulse is inversion of the net magnetisation of the blood water. After a period of time (called the transit time), this 'paramagnetic tracer' flows into slice of interest where it exchanges with tissue water due to the property of free diffusion of water. Thus, the inflowing inverted spins within the blood water alter total tissue magnetisation, reducing it and, consequently, the MR signal and image intensity. During this time, an MRI is taken (called the tag image). After a period of time, another T1-weighted image is acquired at the sane slice which is without magnetisation (called control image). Control image has higher signal intensity compared to tag image. Subtraction of the tag from control gives the perfusion of the ROI and the whole brain perfusion can be calculated using the software [Figure 6]. The difference of the control and tag images magnetisation (M) yields an image delta (§) M = M control - M tag that is proportional to CBF. The major disadvantage of ASL is the low signal-to-noise ratio (SNR), which requires 5–10 min of MRI time at clinical field strengths of 1.5T and erroneous low CBF measurements and artifacts in regions with delayed blood arrival.

Magnetic resonance angiography

Haemodynamic assessment by quantitative MRA (qMRA) has been used to identify patients at high risk for stroke and to guide treatment decisions. qMRA has been used to determine the total CBF, the effect of age and sex on the total CBF, distribution of CBF in the circle of Willis, and cerebral autoregulation, as well as to evaluate various cerebrovascular disorders.[21] The technique of qMRA consists of acquiring 2D or 3D train of flight MRA images of the brain and neck

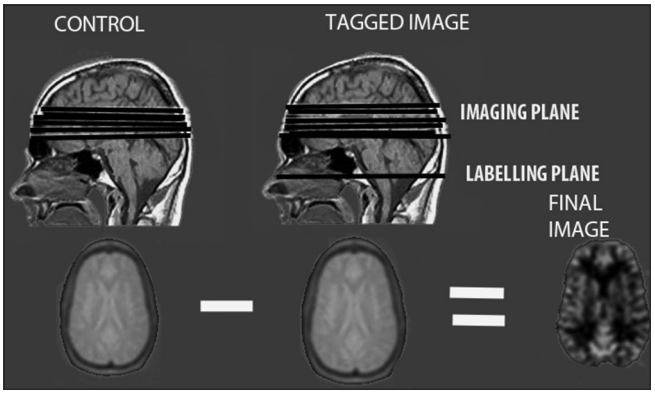

Figure 6: Arterial spin labelling method for measurement of cerebral blood flow

in 1.5 or 3T MRI scanners. After acquiring the images are processed usually in the console. Accurate flow measurements required precise orientation of the imaging plane transverse to the long axis of the target vessel. Following selection of the measurement plane, we acquired a phase contrast GRE sequence with peripheral triggering and VENC of 80 cm/s. This approach generated a (fast field echo-M, the anatomical data), phase contrast angiography-m (modulus data for vessel morphology), and phase contrast angiography-p (velocity-encoded data for processing flow information). A ROI was automatically placed on the phase-contrast images and was also displayed in the 3D surface-rendered image for vessel verification. The vessel borders over a cardiac cycle were automatically extracted and displayed on the color-coded and magnified ROI image for vessel border verification. The velocities at all of the pixels inside the vessel border were then integrated to calculate the flow in millilitres per minute. The flows were averaged over a cardiac cycle to obtain the mean flow for each vessel.

OTHER RADIOLOGICAL TECHNIQUES

Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is a non-invasive method which uses inert radioactive materials to determine the CBF. ^{19}F NMR is the technique commonly used.[22] The technique consists of inhalation of ^{19}F radioactive gas added to inspiratory gas mixture for 15 min. The gas freely diffuses in the brain. After 15 min the NMR computes the washout of the radioactive tracer from the brain and the washout curves are constructed. The CBF is determined using Kety-Schmidt method.

Positron emission tomography

PET is accepted as the current standard of reference for the *in vivo* assessment of CBF and brain metabolism. However, high cost and limited accessibility have restricted the widespread clinical use of PET. Contrast material used in CT perfusion imaging acts as a non-diffusible, intravascular tracer, whereas PET and SPECT use diffusible tracers. Therefore, blood flow measured with CT perfusion imaging reflects intravascular blood flow; however, PET or SPECT do not measure intravascular blood. PET is capable of providing *in vivo* quantitative measures of CBF and has evolved to be considered the gold standard for studying cerebral haemodynamic. Another major advantage of PET is the measurement of regional and global cerebral metabolism using radiolabeled glucose utilisation; however, PET imaging involves the injection of radioactive tracers, which limits its repeatability and application in healthy volunteers. Among other limitations are low temporal and spatial resolution, low SNR, as well as the requirement for a cyclotron.

Technique: PET uses on [^{15}O] H_2O for measurement of CBF and (^{18}F)-2-fluoro-2-deoxy-D-glucose for quantitative determination of the cerebral metabolic rate of glucose utilisation. Catheters are inserted in the antecubital vein for injection of tracers and radial artery for sampling. Patients are positioned on the high resolution research tomograph scanner bed. Following the injection of the desired amount of tracers emission scans are repeated for radioactivity usually until 10 min and the images are acquired. Sampling of the arterial blood is taken at intervals to measure the radioactivity. The global and rCBF as well as the glucose utilisation are measured by reconstruction of the images and correlation of the blood radioactivity and brain decay using input functions.[23]

BED SIDE MEASUREMENT OF CEREBRAL BLOOD FLOW

The major draw backs of the above mentioned techniques is difficulty in obtaining the CBF quantification at bedside as they have to be done in specialised areas or suites. To avoid transfer of critically ill patients, certain bed side methods of measuring the CBF have been developed. However there are major limitations for their use. Some of them are surrogate markers of CBF; some methods are still experimental or commercially not widely approved.

Diffuse correlation spectroscopy

It is a new optical method to non-invasively measure the cortical blood flow using the technique of fluctuations in near infrared spectroscopy (NIRS) light reflected from the tissue surface.[24] Light fields are generated by illuminating the brain surface with NIR laser light; some of the NIR light propagates through the scalp and skull and into the brain where it is scattered by moving red blood cells (RBCs) in tissue vasculature before emerging from the tissue surface. This 'dynamic' scattering from moving cells causes the detected intensity to temporally fluctuate [Figure 7], and the time scale of these fluctuations is quantified by the intensity temporal autocorrelation function of the collected light. The equipment consists of three parts; (a) a long-coherence-length (>5 m) laser operating in the NIR to deliver light to the tissue; (b) single photon counting avalanche photodiode (APD) detectors that output an electronic pulse for every photon received; and (c) a photon correlator that keeps track of the arrival times of all photons detected by the APDs and derives an intensity correlation function from the temporal separations of all pairs of photons.

For tissue blood flow measurement, the laser placed on the tissue surface (e.g., skin) launches long-coherence NIR light into the tissue via a multiple-mode source fibre, and the light transported/scattered through the tissue was collected by a single-mode (or a few-mode)

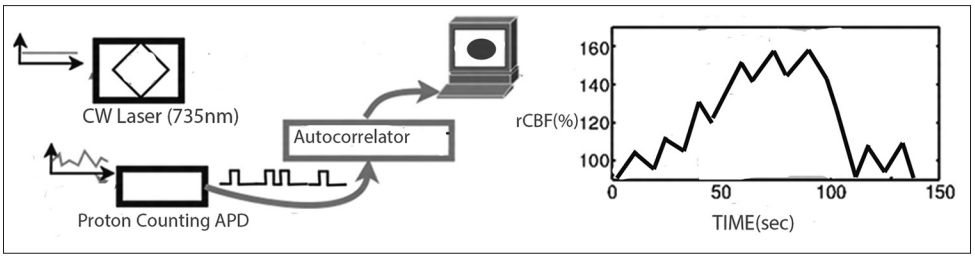

Figure 7: The principle of diffusion correlation spectroscopy for measurement of regional cerebral blood flow

detector fibre placed millimetres to centimetres away from the source fibre. The detected light is then delivered via the detector fibre to APD detector, where the count of photons per unit time (i.e., light intensity) is recorded. The temporal fluctuation of light intensity in a single speckle area of tissue collected by the detector fibre is associated with the motion of moving scatters (primarily RBCs in microvasculature) and can be quantified by calculating the decay of light intensity autocorrelation function using the auto correlator. The electric field temporal autocorrelation function of light is determined from the normalised light intensity autocorrelation function, and it obeys the correlation diffusion equation in highly scattering media. By fitting the electric field autocorrelation curve to an analytical solution of correlation diffusion equation and assuming a particular flow model, the blood flow index is yielded.

OPTICAL TECHNIQUES

Optical approaches have gained increasing attention for detection of CBF as they are simple to use, bed side and reduced risk of radiation and shifting of patients to complex radiological suite. Three different methods have described in the measurement of CBF.

Laser Doppler flowmetry

Laser-Doppler flowmetry (LDF) is a non-invasive technique for continuous measuring of CBF with instantaneous recording of dynamic changes of erythrocyte flow. LDF can measure changes in the rCBF.[25] However, LDF is of limited utility in the evaluation of absolute CBF. The LDF uses a laser probe which emits photons at a wavelength of 780 nm. The photons will be reflected or scattered by the tissues and the moving RBCs and they are captured by a detector which converts to electrical signal. The non-moving tissues (brain) will not cause change in the photons, whereas the RBCs will cause change in the frequency. The equipment uses the principle of Doppler shift. Analysis of the backscattered light gives the mean Doppler shift, which is proportional to the velocity of the RBCs, and the amplitude of the Doppler-shifted signal, which is proportional to the volume of moving elements in the tissue. The CBF equivalent (CBFLDF) is derived from the multiplication of the mean Doppler shift by the fraction of light that is Doppler shifted. The values of blood flow are not expressed as absolute flow values (ml/g/min) but in LD units relative to the initial values. Blood flow measured by the laser Doppler technique is called 'flux': A quantity proportional to the product of the average speed of the blood cells and their number concentration (often referred to as blood volume). Flux = k2 × Average Speed of blood cells × Number Concentration of Blood Cells (k2 is the constant).

Optical micro-angiography

Optical micro angiography (OMAG) is a newly developed non-invasive technique for measuring the tissue blood flow.[26] OMAG produces 3D images of dynamic blood perfusion within micro-circulatory tissue beds at an imaging depth up to 2.0 mm. Imaging contrast of blood perfusion in OMAG is based on endogenous light scattering from moving blood cells within biological tissue; thus, no exogenous contrast agents are necessary for imaging. Imaging is achieved by the efficient separation of the moving scattering elements from the static scattering ones within an illuminated tissue. In essence, OMAG mathematically maps the backscattered optical signals from the moving particles into one image – that is, the blood flow image – while it simultaneously maps the backscattered optical signals from the static particles into a second image, which is the microstructural image. The system employed a broadband infrared super luminescent diode (Denselight, Singapore) with a central wavelength of 1300 nm to illuminate the tissue. The light emerging at the output of interferometer was sent to a home built high-speed spectrometer that employed a line scan infrared. In GaAs detector to capture the backscattering light emerged from the illuminated tissue surface.

Optical imaging of indocyanine green molecular dynamics analysis

Indigocyanin green emits fluorescent light when stimulated by photo diodes in the range of 760 nm. Intravenously injected indocyanine green (ICG) will bind to albumin and will be distributed intravascularly. NIRS has been used primarily to detect ICG absorption signals in the brain. Four CBF parameters are computed based on the ICG dynamics such as arrival time, rising time and MTT of a bolus and blood flow index. CBF maps were generated using the parameters to estimate the status

of CBF, and they dominantly represented intracerebral blood flows in mice even in the presence of an intact skull and scalp.[27] The advantage of this technique is it is non-invasive and can be performed bedside. Good clinical correlation has been found to occur with respect to changes in CBF in the cited literature available.

Jugular thermodilution technique

The methods described above as well as techniques based on radiological methods have a major disadvantage in that they cannot be used at bedside where critically ill patients needs to be monitored for cerebral ischaemia. Jugular venous thermodilution is an attractive technique which is similar to the principle used for coronary sinus blood flow. A thermodilution catheter is inserted retrograde into the jugular vein and the tip is placed in the jugular bulb. A fluid (indicator at room temperature, usually 20 ml at a rate of 38 ml/min) capable of readily mixing with blood is injected at a lower temperature compared to the blood and the change in temperature is monitored 25 mm distally using thermistors. A graph is constructed by changes in the temperature between the injected indicator and blood mixed with indicator distal thermistors. The heat lost by the blood is equivalent to the heat gained by the cold saline. The CBF can be calculated using the formula:

$$\text{CBF}\,(\text{ml}/\text{min}/100\text{g}) = \frac{\text{JBF} \times 2 \times 100}{\text{Brain weight}\,(\text{g})}$$

(2 is for multiplication from both hemispheres)

JBF = Jugular blood flow = Fi × 1.1 × [Tm − Ti]/[Tb − Tm]

Fi = flow rate of indicator, 1.1 = constant for saline, Tm = temperature of mixture, Tb = temperature of blood, Ti = temperature of indicator in Celsius

Jugular thermodilution has been validated against Kety-Schmidt method and found to be accurate and can be used at bedside.[28] Another advantage is it can be measured repeatedly as well as continuously using a computer algorithm. However, the method remains unpopular and commercial kits are not available readily.

Electroencephalogram and processed electroencephalogram

Electroencephalogram (EEG) has been evaluated as a bedside indicator of changes in CBF in the critical care units and operation theatres. Since the brain activity is very sensitive to changes in CBF, EEG can reflect the onset of impending schema caused by disturbance in regional or global CBF. Attempts have been made to correlate the critical EEG change with the CBF measurement. Sharbrough *et al*., have found in patients undergoing carotid endarterectomy, There was a high correlation between the CBF (millilitre/100 g/min) during carotid occlusion and alterations in the EEG: No EEG change was seen with the flow above 30 ml/100 g brain per minute, major changes were not seen with a flow between 18 and 30 ml, and changes invariably occurred with a flow below 17 ml. The degree of EEG change reflected the severity of flow reduction but was always reversible with the placement of a shunt.[29]

The EEG criteria for ischemic changes were defined in patients undergoing carotid endarterectomy by Blume *et al*.[30] They have defined a major EEG change as an attenuation of 8–15 Hertz activity to minimal or nil and/or a 2-fold or more increase of delta activity at one Hertz or less. A moderate change consisted of clearly persisting 8–15 Hertz activity whose amplitude was attenuated by at least 50% and/or an obvious and persistent in - crease of delta activity at > 1 Hertz. Though EEG is a simple real time bedside surrogate monitor of CBF, the major difficulty is expert evaluation is required to detect ischaemia and may be affected by artefacts, anaesthesia or sedation, temperature changes, seizures etc.

Use of processed EEG such as bispectral index and entropy as an indicator for cerebral ischaemia is practiced in the OR and Intensive Care Unit. However, there are limited validational studies compared to other methods of CBF measurement. That also cannot be representative of global CBF changes due of limited application of electrode position. They also share the other drawbacks of EEG method described.[31,32]

Transcranial Doppler

Transcranial Doppler (TCD) is a simple, non-invasive technique which uses ultrasound waves to detect and quantify the blood flow in the vessels. TCD uses a 2 MHz probe which is placed over the different windows focusing on the cerebral vessels. Most commonly employed technique is insinuation of middle cerebral artery using a transtemporal window. TCD utilises the Doppler shift to assess the changes in flow velocity of the moving RBC. It should be remembered that TCD measures only the flow velocity and not the absolute CBF value. The correlation between CBF and flow velocity is variable.[33] When the CBF increases, there may be increase or normal in flow velocity depending on the degree of calibre of vessels. However an increase in the flow velocity does not corresponds to increased blood flow as in case of vasospasm following subarachnoid haemorrhage where the blood flow is reduced. TCD has been clinically used to monitor the CBF in cardiopulmonary bypass, carotid endarterectomy, head injury, vasospasm, brain death, etc. Its use also has been described to monitor the CBF in resuscitation during cardiac arrest.[34,35]

RECOMMENDATIONS FOR PERFUSION IMAGING IN CEREBRAL ISCHAEMIA

Acute stroke

It is important to differentiate the reversible or irreversible cause of neurological deficit either a transient ischemic attack (TIA) or an acute stroke. Measurement of CBF will help in differentiating the TIA (normal perfusion) form ischemic stroke (reduced perfusion).[36] The demonstration of a normal level of CBF suggests that reperfusion has occurred spontaneously and that no acute vascular thrombolysis or flow augmentation is necessary.

Traumatic brain injury

Traumatic brain injury (TBI) is one of the leading causes of death in young adults worldwide. Cerebral ischaemia is one of the major factors associated with the development of secondary brain damage. Experimental evidence show the CBF is altered following head injury and the responses is variable. Changes in CBF following TBI have been described as a triphasic pattern. During the first and acute phase, there is a 50% decrease in CBF. During the initial 12 h post-injury, the second phase begins, marked by a rise in CBF that approaches or exceeds normal values in some patients and typically persists for the next 4–5 days. This phase is followed in turn by a third period of low CBF that lasts for up to 2 weeks post-injury. Monitoring of the CBF thus becomes important in head injured.[37] Many methods have been used to estimate CBF in these patients. Xe CT has been considered as the most useful of them. PET can be used to measure CBF as well as cerebral metabolism. However, all these techniques require shifting of the patients to radiology suite. NIRS can be used as an indirect marker for CBF. Even though cerebral ischaemia has been shown to be associated with poor outcome, there is no level 1 evidence showing that monitoring and management of patients by using CBF has improved the outcome.

Chronic cerebrovascular disease

Patients with chronic cerebrovascular disease will have abnormal blood flow in the distal vessels. They may be dependent on the leptomeningeal and other collaterals and if the collateral flow is reduced they may develop cerebral infarcts. Various perfusion techniques can help in identifying these high risk patients and their status of the collateral flow. Moreover perfusion techniques will also help in quantifying the cerebral flow following carotid endarterectomy or bypass procedures for cerebral ischaemia.[38]

Other uses

CBF studies have been used to identify the areas of MRI negative epilepsy, various tumours diagnosis as well as tumour type, giant intracranial aneurysms for collateral circulation, identifying various dementias, etc.

LIMITATIONS OF CEREBRAL BLOOD FLOW MONITORING TECHNIQUES

Though measurement of absolute as well as rCBF can help in understanding the pathophysiology of cerebral circulation there are many limitations in the monitoring techniques as well as its applicability.

- Though a low CBF is considered to be detrimental to brain and maintenance of CBF is essential for perfusion of the brain, evidence is lacking that measures to increase in CBF improves the overall outcome of the patients with critically ill neurological diseases such as head injury, stroke, subarachnoid haemorrhage, etc
- CBF is affected by various factors like blood gas like PaO_2, $PaCO_2$, state of the function of the brain, haematocrit, and temperature etc., the measured CBF in a patient could be affected by all these factors and difficult to differentiate from the pathological changes in CBF
- Unlike the surrogate marker of cardiac output like arterial blood pressure which can be obtained bedside in critically ill, there are no similar bedside continuous markers for CBF available. All the current techniques like radioactive tracers, MRI to CT based measurement require transfer to specialised areas and continuous/repeated measurement is difficult to obtain. Indirect measurements like TCD, NIRS are not accurate.

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Conflicts of interest

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