Chapter

Measurement of Cerebral Circulation in Human

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Abstract

In this chapter, we review state-of-the-art non-invasive techniques to monitor and study cerebral circulation in humans. The measurement methods can be divided into two categories: direct and indirect methods. Direct methods are mostly based on using contrast agents delivered to blood circulation. Clinically used direct methods include single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI) with contrast agents, xenon computed tomography (CT), and arterial spin labeling (ASL) MRI. Indirect techniques are based on measuring physiological parameters reflecting cerebral perfusion. The most commonly used indirect methods are near-infrared spectroscopy (NIRS), transcranial Doppler ultrasound (TCD), and phase-contrast MRI. In recent years, few more techniques have been intensively developed, such as diffuse correlation spectroscopy (DCS) and microwave-based techniques, which are still emerging as methods for cerebral circulation monitoring. In addition, methods combining different modalities are discussed and, as a summary, the presented techniques and their benefits for cerebral circulation will be compared.

Keywords: SPECT, PET, CT, ASL, MRI, NIRS, TCD, microwave, cerebral blood flow

1. Introduction

Human cerebral circulation involves a complex mechanisms [1] that attract researchers around the globe. The main purpose of cerebral circulation is to maintain energy and oxygen supply to the brain which is essential for normal brain function. The most important parameters reflecting cerebral circulation are cerebral blood flow (CBF), cerebral perfusion pressure (CPP), cerebrovascular resistance (CVR), and intracranial pressure (ICP). These have also an important role in diagnostics of many brain disorders, such as stroke, hemorrhage, head trauma, and carotid artery disease.

Human cerebral circulation monitoring can be performed using direct techniques, where CBF is directly measured, and indirect techniques that reflect relative changes in the cerebral circulation. At present, there are several imaging techniques that are commonly used in hospitals as stationary systems and require own imaging facilities due to

complex imaging procedures. At first, these will be shortly introduced. Next, commonly known indirect methods are presented. These are typically portable devices and still are more commonly exploited in medical research. The chapter ends by presenting a few emerging methods that already show high potential for CBF monitoring but are still in the proof of concept phase.

2. Clinical stationary imaging devices

In this section, we present the most common cross-sectional imaging devices which can be utilized to measure CBF-related parameters. There are two nuclear medicine-based procedures, which are usually time-consuming, since radiotracers typically require several hours to accumulate in the tissue. These include positron emission tomography (PET) and computed tomography (CT). The first uses positron emitter radiotracers and the latter X-rays. During imaging, a narrow beam of positrons or X-ray irradiates the patient and quickly rotates around the head/body. Because of the harmful radiations, PET and CT techniques are usually used only for clinical diagnosis, although the radiation exposure is minimal. In general, these techniques do not provide continuous information on CBF [2]; however, they provide images with high spatial resolution and thus are used to detect possible cerebral circulation anatomy-related abnormalities.

Magnetic resonance imaging (MRI) is becoming the main technique for cross-sectional imaging of the brain since it is considered as a safe technique. In MRI, high-intensity alternative magnetic fields to align the protons in the imaged tissue. When the field is turned off, the protons are back to their initial direction by releasing stored energy. The amount of energy and the relaxation time is dependent on the chemical nature of the molecule and based on this information, the identity of the molecules can be determined [3]. The released energy is received by surrounding RF coils and prepared for data processing. Furthermore, functional MRI (fMRI) can detect magnetic changes associated with blood flow and thus can be exploited for imaging CBF, however, at lower spatial resolution than nuclear medicine-based techniques. In the following, the clinically available techniques are presented: PET, Single-Photon Emission CT (SPECT), Xenon CT (Xe-CT), and fMRI techniques based on contrast imaging that can be used for cerebral circulation imaging.

2.1 Positron emission tomography

PET can provide high-resolution images of cerebral circulation [4, 5]. It utilizes positron emitter radiotracers to generate high-quality images. The emitted positrons immediately collide with their antiparticles, electrons, then two gamma photons will be created. This process is called “annihilation”. The gamma photos are irradiated in the same energies but in opposite directions with 180° different from each other, see **Figure 1**. The pair of photons are simultaneously captured by the surrounding detectors, and powerful signal processing can generate the reconstructed image based on the detected photons [7].

In order to provide a quantitative measure of CBF [8], the PET scanner needs special radio-markers for each measurement and uses ^{15}O-labeled water. The radiotracer is produced by a cyclotron and injected into the patient before scanning, which increases the complexity of PET measurement.

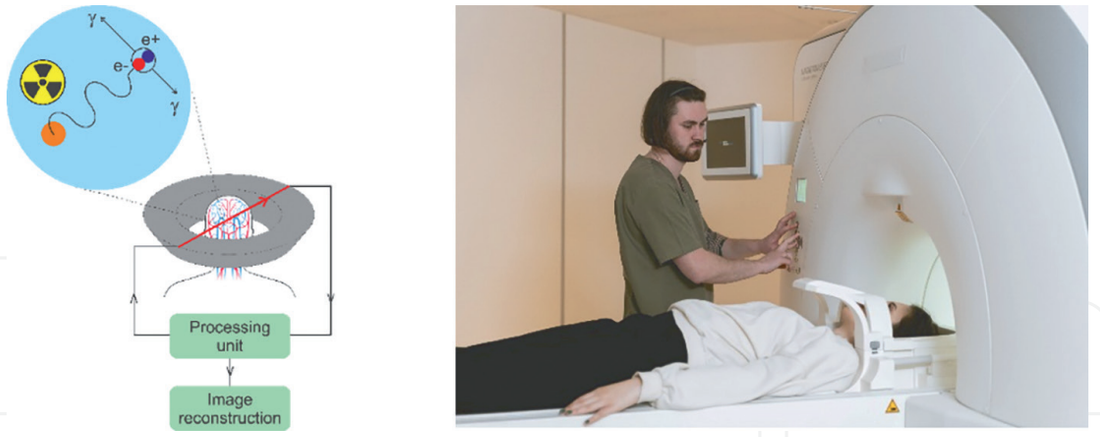

Figure 1.
The principle of PET scanning simplified from Ref. [6]. The emitted positron collides with an electron, then annihilation will happen. The basis of this phenomenon is the emission of two same-energy gamma photons in opposite directions. Finally, gamma detectors capture the photons and process them to reconstruct a 3D image. On the right, preparations to start brain imaging (Photo by MART PRODUCTION from pexels.com).

Clinical neurology usage of PET gradually started in the 1980s [9]. With ^{15}O tracers, it can provide essential information on patients with cerebral vascular disorders and information also on oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen $CRMO_2$. However, most techniques require an additional $C_{15}O$ scan for compensating cerebral blood volume (CBV) [10].

2.2 Single-photon emission computed tomography (SPECT)

Similar to PET, Single-Photon Emission Computed Tomography (SPECT), see **Figure 2**, is also a nuclear imaging technique utilizing a gamma-emitter radiotracer while PET employs positron emitters. In 1963, the first prototype of SPECT was presented by Edwards and Kuhl [12], but dedicated brain SPECT systems were introduced in 1980–1986, and then clinical brain imaging started immediately [13]. SPECT uses ^{99m}Tc radiotracer for CBF measurement [14]. The radiotracer penetrates through the blood-brain barrier (BBB) and diffuses in the brain tissue, proportionally to blood flow [15]. As a result, the gamma emission and SPECT scanner generate a comparative image. SPECT is a semi-quantitative CBF measurement technique and provides less spatial resolution compared to PET [16, 17].

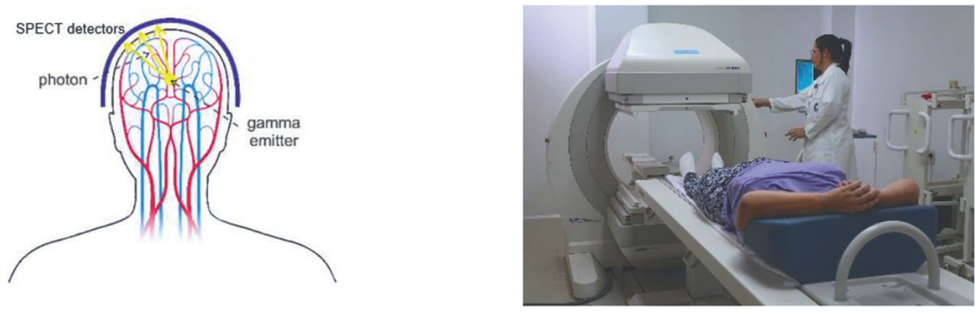

Figure 2.
SPECT device uses gamma-emitter radiotracers, which can be given by injection, inhalation, or orally. The SPECT detectors receive the gamma radiation and deliver the signal to the image processing and reconstruction unit [11]. The image on the right is courtesy of IAEA Imagebank.

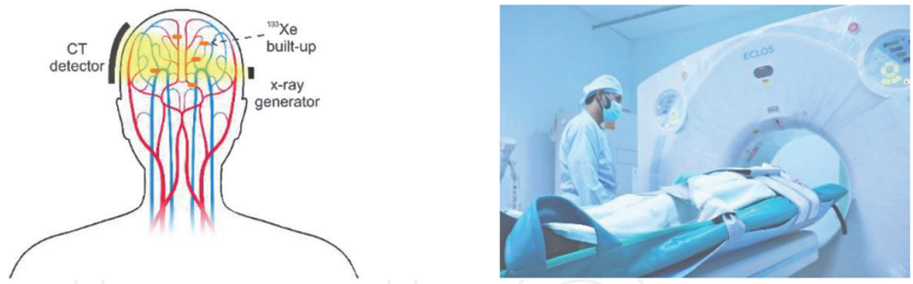

Figure 3.
Xe-CT system contains a rotating X-ray source and an array of detectors that generate a tomographic image. The inhaled xenon gas can partly block X-ray and provide quantitative indicators for CBF measurement. High-resolution Xe-CT CBF imaging (see on the right) takes about 10 min [14].

2.3 Xenon computed tomography (Xe-CT)

Xe-CT is one of the most accurate methods for obtaining quantitative CBF imaging. The system contains a rotating X-ray source and an array of detectors that generate a tomographic image of the brain or other organ [18], see **Figure 3**. The technology has been available since 1977, but its usage was not widespread until the 1990s. The scanning procedure is simple and quick and therefore is nowadays a commonly used clinical imaging device.

Xenon is an inert as well as radiopaque gas which can across the BBB and thus can reach deep brain tissue. Moreover, due to the short half-life of ^{131}Xe, it delivers a low amount of dose to the patient and allows multiple scans during CBF measurement [19]. However, a limitation of this technique is difficulty with the assessment of CBF in the posterior fossa and infratentorial region. The bones of the upper cervical spine, cranium, and facial structures produce artifacts on baseline CT images and make interpretation of blood flow difficult [20, 21]. Another limitation is the high sensitivity to motion artifacts. If a patient is not able to stay still during the scanning sequence, when xenon gas is being administered, it reduces the reliability of the blood flow information.

2.4 Arterial spin labeling MRI

Arterial spin labeling (ASL) is a non-invasive imaging technique using standard MRI. The measurement of blood flow is based on magnetically labeled arterial blood water protons that are used as tracers [22]. The techniques are suitable also for imaging children as the use of radioactive and contrast agents can be restricted. The ASL method was originally proposed by Williams and his colleagues when they attempted to measure CBF from rats using water as a diffusible tracer [23]. In 1994, the method was extended to human brain imaging [24].

The main idea was to provide the same image with and without magnetization of the blood flow [25], by giving radiofrequency pulses to invert or saturate the water protons in blood [23]. With the fact that the relaxation time of water in the blood is about 1–2 s, the brain will not be overflowed with spin-labeled water [24, 26]. By subtracting the image with magnetization from the other one, it results in CBF information.

Different techniques of ASL including continuous arterial spin labeling (CASL) [23], pseudo-continuous ASL (PCASL), and velocity-selective ASL (VS-ASL) are possible. The two latest methods were developed to solve problems and challenges encountered in CASL. Modified ASL techniques, such as territorial ASL (TASL) can be used for imaging

Figure 4.
In MRI, the magnet firstly applies a powerful field to align the protons. When it is turned off, the protons release their energies and turn back to their initial state. At this stage, head coils receive the released energy. On the right, performing fMRI brain imaging in Oulu University Hospital.

collateral and visualization of perfusion of individual arteries [27–29], whereas ASL at multiple delay times (Tis) is capable of depicting areas with low CBF (**Figure 4**) [30].

ASL-MRI holds high potential. For instance, patients with ischemic stroke suffer from decreased cerebral perfusion [31]. ASL has been used to assess various perfusions, e.g., hemispheric perfusion deficits, post-ischemic hyperperfusion, or perfusion-diffusion mismatches [32]. Furthermore, several studies in dementia employed ASL to assess regional hyperperfusion from patients with Alzheimer's disease (AD), front temporal dementia, and mild cognitive impairment [26, 33]. The results were in line with the previous studies using PET and SPECT. Sandson et al. used ASL to study parieto-occipital and temporo-occipital among controls and AD subjects [34]. They could separate these groups based on the decreased perfusion in those regions. ASL technique was also found useful in epilepsy studies as the abnormal tissue had a lower metabolic rate and blood flow than the other [35]. It was suspected that the hypoperfusion interictal pattern was associated with neuronal loss, although the mechanism behind the hypoperfusion interictal is still unknown. Based on a study during the interictal state, hypoperfusion occurred in the involved cortex [36].

2.5 Contrast-enhanced MRI (CE-MRI)

As ASL MRI uses magnetically labeled arterial blood water protons as tracers [22], contrast-enhanced MRI (CE-MRI) employs pharmaceutical tracers to enhance image quality. This improves the visibility of the internal structures and emphasizes the difference between normality and abnormalities in brain tissue e.g., tumors or disrupted blood-brain barrier, and can enhance diagnosis and staging of malignancies, treatment planning, and monitoring the response to therapy [37]. Other current applications of CE-MRI include the assessment of vascular disease (stroke and vascular malformations) and monitoring of inflammatory, neurodegenerative and infectious diseases. Perfusion imaging using CE-MRI is used in brain tumor imaging, based on the principle of increased tumor vascularity. CE-MRI technique has been developed with variations such as dynamic contrast-enhanced (DCE) MRI and dynamic susceptibility contrast (DSC) MRI, which also have a role in tumor imaging to assess vascular permeability and angiogenesis, respectively [37].

Young et al. pioneered the use of ferric chloride as the contrast agent in the MRI for gastrointestinal track in 1981 [38]. Since 1988, the most commonly used in clinical practice are contrast agents with the lanthanide ion gadolinium (III) (Gd^{3+}), which were introduced to evaluate BBB disruption and vascular features with MR imaging.

Gd^{3+} possesses a high magnetic moment and is the most stable ion with unpaired electrons [39]. Several different variations of Gd^{3+} chelates are used for MRI contrast, often described under the group name of Gd-based contrast agents (GBCAs).

When using GBCAs the T1 or T2 relaxation times of nearby water protons are shortened; as a result, T1-weighted images have an increased signal intensity, while T2-weighted images signal intensity is reduced [39]. Contrast agents from the second group may contain e.g., transition metal manganese (Mn^{2+}), which has been suggested as being particularly effective for functional brain imaging, as it enters cells through calcium channels [40]. In general, these agents are injected systemically and enhance the overall image quality, without focusing on a specific area.

Despite the excellent quality obtained by using GBCAs in MRI imaging, the method still requires development, and its main challenge is the toxicity of the used substances. Gadolinium-based contrast agents were initially considered entirely safe, but eventually in 2006 were associated with nephrogenic systemic fibrosis and significant negative consequences in certain vulnerable patients, particularly for patients with impaired renal functionality [41]. Persons with normal kidney function have not been thought to be at risk, although some amounts of gadolinium can remain in the organs. Accumulation of gadolinium in the body is still being investigated. The long-term effects of retained gadolinium are unknown. For this reason, there are ongoing investigations into alternative compounds which could be used as contrast agents. Several types of gadolinium-free contrast agents have been investigated, for instance, organic radical contrast agents (ORCAs), which have low cytotoxicity and high biodegradability, reducing the potential for side effects [42]. However, further investigation and performance development need to be performed before newer contrast agents can be used in clinical practice.

3. Portable devices (indirect methods)

3.1 Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) refers to an optics-based measurement method using two or more wavelengths in the near-infrared (NIR) range (650–950 nm), see **Figure 5**. When NIR light illuminates sculp, it experiences scattering and absorption. A part of the incident light reaches the brain cortex and reflects and scatters back to sculp which can be detected by a sensitive photodetector. When

Figure 5.
fNIRS and diffuse correlation spectroscopy (DCS) are two optical technologies for human brain monitoring that are sensitive to changes in hemoglobin concentrations and blood flow, respectively. Typically, light source and detector are placed at a distance of 3–4 cm from each other in order to form an optical measurement volume that reaches 1–2 cm depth. As illustrated on the left, the measurement volume can be shown as a banana-shaped area. On the right, performing fNIRS measurement in Oulu University Hospital.

using at least one wavelength on both sides of the isosbestic point at ~810 nm, cerebral hemodynamics can be quantified based on the modified Beer-Lambert law [43]. The most common signals to read are oxy- and deoxy-hemoglobin, abbreviated here as HbO and HbR, respectively, while MRI can only provide blood-oxygenation-level-dependent (BOLD), which is basically HbR [44]. Furthermore, fNIRS can be used to measure cerebral blood volume (CBV) based on quantifying HbT [45], various additional hemodynamic parameters [46–49], and cytochrome c oxide [50].

fNIRS provides a more affordable solution when compared to devices presented in the clinical stationary imaging devices sub-section. Several measurement principles in fNIRS include continuous wave (cwNIRS), time-domain (TD-NIRS), frequency-domain (FD-NIRS), and frequency-coded NIRS systems [51]. The technique is fully safe and can also be realized as a wearable continuous monitoring setup. For example, SPECT and PET cannot measure dynamic changes in cerebral circulation whereas fNIRS is capable of that [52], however, it suffers from low spatial resolution. Kusaka et al. [46] emphasized that monitoring of cerebral circulation in infants is needed in general clinical practice, however, for this purpose e.g., MRI or PET are not suitable. They evaluated fNIRS to measure oxygen saturation (ScO_2), CBV, CBF, and cerebral metabolic rate of oxygen to study cerebral circulation in infants and concluded that fNIRS is a potential technique for bedside brain monitoring in a neo-natal intensive care unit (NICU).

3.2 Diffuse correlation spectroscopy

DCS is a non-invasive method based on speckle fluctuations caused by the interference of the multiple and random paths of photons traveling in tissue. The speckle fluctuations are mostly caused by the motion of red blood cells and recorded signal fluctuations thus reflecting blood flow in the microvasculature. For this, a blood flow index (BFI) value is provided. The measurement setup is similar to fNIRS, see **Figure 5**, but DCS requires the use of laser light with a long coherence length for detection of temporal speckle effects. It measures the decorrelation time scale of the intensity fluctuations of the scattered light, which relates to the motion of moving scattering centers, mostly consisting of red blood cells in CBF [53]. The principle of the DCS technique is well described in several papers [54–56]. This still a relatively new method shows increasingly high potential for human cerebral circulation monitoring, especially for clinical monitoring newborns [57–59]. At present, portable, low-cost DCS setups are being developed and apparently will be in near future utilized in clinics and patient bedsides [55, 60]. These will be most likely used combined with fNIRS to provide comprehensive information on cerebral hemodynamics and circulation [61].

3.3 Transcranial Doppler ultrasound

Transcranial Doppler (TCD) is a non-invasive method used for the measurement of blood flow velocity within the large arteries of the circle of Willis. It was introduced in 1982 by R. Aaslid, who tested the applicability of existing range-gated ultrasound Doppler instruments in cerebral circulation monitoring [62]. It was initially suggested as a method for the detection of vasospasm following subarachnoid hemorrhage and for evaluating cerebral circulation in occlusive disease of the carotid and vertebral arteries. However, thanks to constant experiments and advances of the technique, current applications are extensive and TCD is widely used in neurological disorders diagnosis and monitoring. Moreover, the development of transcranial color-coded duplex (TCCD) examination provided a possibility of direct visualization of the

cerebral anatomy vessels and enabled accuracy improvement as well as broadening the scope of applications.

Ultrasound-based techniques measure the frequency change in pulse reflecting from the particular structure. When used in medical applications, it allows defining the speed of the red blood cells in vessels and arteries, as well as the flow direction. The ultrasound probe is emitting the pulse of known frequency toward the flowing blood, then the same probe is detecting the pulse-echo. The frequency of the ultrasound pulses used in TCD is relatively low (2.0–2.5 MHz), as it needs to penetrate through the skull. To reduce signal attenuation, the probe is placed above thinner parts of the skull (insonation windows), such as the transtemporal, transforaminal, transorbital, and transcervical windows. Each of the windows allows better access to different branches of the circle of Willis: *transtemporal window*: terminal internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), and communicating arteries, *transorbital window*: ophthalmic artery (OA) and ICA siphon (carotid siphon), *suboccipital window*: vertebral artery (VA) and basilar artery (BA); *submandibular window*: extracranial ICA and common carotid artery.

Figure 6 shows how the TCD probe is placed over a transtemporal window, with an ultrasound penetrating toward the brain vasculature.

TCD does not measure the diameter (or cross-sectional area) of the artery, due to low penetration of the ultrasound. Thus, the actual value provided in this technique is the relative velocity in the artery of interest, calculated using the formula for the Doppler shift [14]. With the assumption that vessel diameter (and insonation angle) remains constant, detected changes in blood flow equal to changes in CBF. Consequently, vessel diameter stability affects estimates of CBF using TCD, which should be especially considered during interventions. In order to approximate flow velocity as an estimate of flow and minimize the method inaccuracy, different indices are calculated, such as the pulsatility index (PI) and the resistance index (RI).

Conventional TCD enables the measurement of blood flow velocity and its changes with high temporal resolution (above 10 Hz). However, correct probe placement and the identification of the vessel require a skilled person, as only blood flow velocity changes in time are visible. This TCD type is non-duplex: there is no imaging available, and the artery identification is done based on audible Doppler shift and the spectral display. Applications of TCD include diagnosis of acute ischemic stroke, vasospasm, traumatic brain injury, measurement of cerebrovascular reserve capacity, examination of autoregulation and neurovascular coupling, microembolus

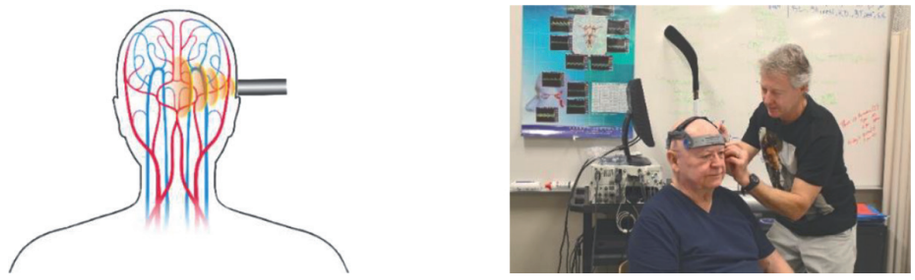

Figure 6.
TCD probe placement (on the left) over the transtemporal window is the easiest to access and the most widely used in clinical practice. The image on the right, showing TCD measurement, is courtesy of Journalism School Newswire.

detection, ultrasound enhanced thrombolysis, assessment of increased intracranial pressure (ICP), detection of the stop of brain circulation in brain death, and monitoring of cerebral circulation during carotid or heart surgery [63]. The accuracy of the conventional TCD can be improved by using an ultrasound contrast agent in contrast-enhanced TCD (c-TCD) [64]. This technique may also improve the detection of flows in non-conclusive TCD, however, its limitations are availability and cost [64].

Adding imaging features to the TCD technique improved the measurement's quality and broadened the scope of applications. Transcranial color-coded duplex (TCCD) uses a combination of pulsed-wave Doppler ultrasound and a cross-sectional view of the area of insonation. It provides real-time visualization of measured intracranial arteries in relation to various anatomic locations, thus simplifying corrections of insonation angles and improving measurement accuracy. The color-coded Doppler also presents the direction of the flow in relation to the probe. TCCD is mostly used in hemodynamic assessment, but is applicable in many other neurocritical care scenarios, such as detection of intra- and extra-axial intracranial hematomas, midline shift, hydrocephaly, cerebral tumors, cerebral aneurysms, as well as investigation of arteriovenous malformations and cerebral parenchyma [63, 64].

There are several unquestionable advantages to the TCD technique, namely its non-invasive nature, the fact that it is radiation-free, and high temporal resolution. The technique is portable, relatively low-cost, and widely available. However, it is important to note several major limitations. TCD measurement has poor spatial resolution and thus is limited to large basal arteries. It can only provide an index of global rather than local CBF velocity [65]. Also, recorded values are relative. The measurement can only be performed through the insonation windows, and it is essential to choose the appropriate one. In some cases, the chosen insonation window might be inaccessible (up to 15% of the population), e.g., due to thick bone structure causing the signal amplitude reduction. It has been observed especially among older or female patients. Another limitation is the influence of the insonation angle, as the wrong angle can affect in recording inaccurate velocities. Therefore, careful probe placement is crucial and might be challenging, especially in conventional TCD, where operator dependency is a significant drawback itself.

4. Emerging methods

There are several new methods in development that potentially can be exploited in CBF studies. In addition, combining different techniques can provide better, more comprehensive information on cerebral circulation.

4.1 Ultrasound-tagged NIRS

Ultrasound-Tagged (UT) NIRS is a relatively new technique based on the acousto-optic effect where photons are modulated or tagged at the acoustic frequency [66]. Basically, a low-power ultrasound transducer is used to modulate the high coherent near infra-red photons, then due to blood flow, the Doppler effect will rise [67]. In other words, when the tagged photons collide with blood content, a frequency shift will be observed, as an indicator of blood flow. The UT-NIRS system employs both optical contrasts as well as ultrasound resolution to provide a deep CBF measurement, while other optical CBF techniques can measure blood flow in the outer part of the cerebrum [2]. Moreover, UT-NIRS is a real-time technique. Measurement depth can

be adjusted by changing the focus point of the US transducer introduced by Tsalach et al. [2]. UT-NIRS can provide a cerebral flow index (CFI), a unitless and non-calibrated number from 0 to 100, reflecting CBF. Compared to fNIRS, the UT-NIRS technique has the capability of detection of intracerebral blood flow variation [68]. However, further studies and validation of its measurement accuracy still need to be conducted [66].

4.2 Microwave-based methods

The usability of microwave-based techniques has been studied for different medical diagnosis and monitoring applications for years since they could enable safe, reliable, low-power and low-cost, portable solutions which could be used also outside the hospitals. Besides, microwaves enable screening of the whole head, especially at lower microwave frequencies. Microwave-based techniques have been actively studied e.g., for detection of brain hemorrhages and strokes [69–73], brain water dynamics [74], tumors [75, 76]. Recently, microwave techniques have also been recognized to have the potential for monitoring cerebral circulation [77–81].

There are two approaches for microwaves-based cerebral circulation monitoring: In the first approach, the microwave-based technique is used to measure temperature and conductivity changes in the tissues which are caused by the changes in blood flow, see **Figure 7a**. Another approach is based on detecting changes in the blood volume which directly corresponds to the blood flow, see **Figure 7b**. The basic idea of these techniques is briefly described in the following subsections.

4.2.1 Detection of changes in temperature and conductivity

Microwave radiometry can be used to sense thermal radiation (electromagnetic noise) emitted in the microwave frequency spectrum by any material above absolute zero temperature. The thermal radiation is received by one or several sensitive antennas and converted, with proper calibration, into a measure of absolute temperature taken from a weighted average of the antenna's radiation pattern [82–85]. The basic idea of passive temperature sensing with microwaves is illustrated in **Figure 7a**. There are several studies on the non-invasive temperature measurement of the human brain which were originally targeted for observing the brain recovering from hypothermia [86, 87].

Figure 7.
(a) Passive microwave radiometry multi-antenna setup for monitoring cerebral circulation through temperature changes. The sensitive antennas are placed around the head for sensing the radiation. The received signals from the antenna ports are fed to a radiometer, which expresses changes in voltage. (b) Transmitter-receiver multiantenna setup for detecting changes in blood volume using reflected wave analysis: Tx antenna transmits microwaves and several Rx antennas are placed around head detecting signals reflected from tissue boundaries. ToF analysis indicates distances from different tissue borders detecting hence also blood volume changes.

Furthermore, fluid movements within an organ produce an elevation in the thermal conductivity, which is approximately a linear function of flow within the organ [88].

Recently, it has been recognized that measuring local changes in temperature and conductivity can be applied to estimate changes in blood flow or volume [77]. Various experiments, conducted both with tissue-mimicking phantoms as well as with human volunteers, have verified the contribution of microwave radiometry to temperature distribution imaging as well as tracking the changes in conductivity.

The most recent study in this field presents a new prototype of a passive microwave radiometry monitoring device for detecting changes in the temperature and the conductivity using four unipolar elliptical on-body antennas [77]. The sensitive antennas are placed around the head for sensing the radiation. The received signals from the four antenna ports are fed to a custom-made radiometer operating at 1.5 GHz, which is a suitable frequency to provide sufficient penetration of microwave radiation into the head tissue. Besides, the use of multiple antennas around the biological body enhances the in-depth detection ability as well as the sensitivity of the system. The experimental results presented in [77] prove that the system can sense local temperature or conductivity changes at a distance up to 5 cm in a brain phantom. The increased blood flow was indicated as 0.2–0.4 mV changes in the radiometer. More comprehensive studies on the accuracy of this method on exact blood flow measurements have not yet been published.

4.2.2 Detection of changes in blood volume

An increase in cerebral circulation can be observed as increased blood volume in the active brain areas, which can also be monitored in microwaves by detecting changes in blood volume with the analysis of electromagnetic (EM) propagation between the antennas located around the head. The technique is based on the physical phenomenon of EM propagation on the boundary between two media with different impedances: as the EM wave, transmitted from the transmitter antenna (Tx) encounters the border between two tissues, the fraction of the energy will be reflected and the remaining fraction will be propagated further deeper inside the tissue, as presented in **Figure 7b**. The time of flight (ToF) of the reflected wave can be measured with several sensitive receiver antennas (Rx), indicating the distance from the object that caused the reflection. Hence, if the local changes in blood volume inside the brain can be detected precisely enough with the analysis of the signals reflected from different head tissues, it can be indicated which parts of the brain are active at a time.

Originally, detection of the changes in blood volume in the brain area was applied for the detection of brain hemorrhage [72, 73]. The idea was further extended in [81] for initial blood circulation detection studies using a single chip implementation of an ultra-wideband impulse radar. Although the presented experimental setup did not reach in the required level of accuracy, it showed that UWB impulse radar is a promising technique for brain imaging and monitoring applications and inspired several new studies on higher-resolution brain activity monitoring [78–80, 89].

The recently presented idea to increase resolution in cerebral circulation monitoring is to provide diversity either using (a) antenna pattern reconfiguration or (b) Tx-signal waveform variation. Ojaroudi et al. [78] presented a study on applying these two diversity techniques for functional microwave imaging using an antenna array radar setup. Both diversity techniques have advantages in increasing either resolution, contrast, or target localization. In general, frequency selection and the

properties of the antennas play a significant role in terms of achieved resolution and propagation depth [78, 81, 89]. Furthermore, the use of novel localization algorithms presented e.g., in [79] can further improve the resolution in brain imaging and hence also in detection of blood circulation. The above-mentioned techniques are recently published in initial studies on applying microwaves for cerebral circulation monitoring. More comprehensive studies on the accuracy of these methods on exact blood flow measurements have not yet been published.

5. Combining different methods

Simultaneous measurement using different techniques is increasingly being utilized in both research and clinical practice [90], since it allows a broader view on human physiology and underlying mechanisms. Brain studies can particularly benefit from a multimodal approach, because of the connection between neuronal activity and cerebral blood flow. Combining hemodynamic measurements with neuroimaging enables analysis of their dynamics in relation to each other and brain function, as well as it can provide complementary information on the relationship between systemic blood flow and influence on cerebral hemodynamics. On the other hand, combining modalities with different working principles enables to benefit from strong features present in each of them; an example can be combining the modality with high temporal resolution and modality with high spatial resolution. It might also be used as an alternative to methods of high cost, or to validate the accuracy of other measurement methods [47]. Not all of the modalities can be combined though, due to problems with compatibility. For instance, systems with ferromagnetic materials cannot be used within MRI environments [47] because of a large static magnetic field [91] whereas magnetoencephalography (MEG) is easily disturbed by electromagnetic interferences [92]. Thus, it is crucial to analyze the safety of the combined use of the devices before the measurements are conducted. In the following several combination techniques are listed, illustrating how multimodal measurements can be employed, depending on the signal/feature of interest.

Combining fNIRS with fMRI allows to study cerebral blood oxygenation during brain activation. fNIRS provides the benefit of accurate temporal resolution, whereas MRI performs with great spatial accuracy. Accurate anatomical information obtained using MRI enables to estimate NIR light propagation in the human head through different tissue layers [90]. On the other hand, fNIRS can measure complementary parameters (such as HbR and HbO), enabling estimation of the cerebral metabolic rate of oxygen.

Rostrup et al. [93] compared ΔHbO and ΔHbR from fNIRS with DCBV and DCBF changes from PET during various respiratory conditions. The values of DCBV from NIRS were similar to those from PET, but with much smaller magnitudes. Thus, fNIRS has the potential for cerebral circulation studies. Eke et al. [45] assess CBV based on the HbT concentration using a commercial multiwavelength fNIRS measured from the forehead. The periodogram of HbT was obtained from 0.000122 to 1 Hz using fast Fourier transform. Based on the fractal analysis on this periodogram to assess the self-similarity, its pattern started to change at a certain frequency, called as cut-off frequency. Interestingly, the range from minimum to the cut-off frequencies is narrower and narrower as age increases. Within female subjects, the pre- and post-menopausal age groups show different behavior. However, there is no significant difference between male and female subjects. They found a strong correlation between CBV changes measured by PET and HbT changes from NIRS.

TCD can be targeted to detect the increase in blood flow velocity in a specific vessel. However, due to poor spatial resolution, it is impossible to distinguish, if these changes are caused by the local or global increase in CBF. Using TCD simultaneously with fNIRS could improve overall spatial accuracy, due to the information on regional cerebral oxygenation provided by fNIRS [94, 95].

Furthermore, combining standard blood pulse measurement methods with brain activity monitoring can be used to investigate the interconnections between CBF and systemic circulation. It is a setup used e.g., in studies on cerebral autoregulation/cerebral reactivity. Systemic blood flow can be tracked using invasive or non-invasive monitors. If the study is performed in the MRI chamber, it is necessary to use MRI-compatible blood pulsation tracking, e.g., utilizing fiber optics-based equipment [96].

Respiration measurement using e.g., pulse oximetry is often combined with brain monitoring methods such as fNIRS during sleep studies [97, 98]. Studies on cerebral hemodynamics during sleep are performed e.g., in order to assess the influence of various sleep-disordered breathing events (such as apnea) on the brain, as well as to understand the physiological and pathological mechanisms responsible for respiratory events during sleep.

The above-mentioned combined methods present just examples of using different measurement techniques simultaneously to emphasize its potential. However, more does not necessarily always mean better. Multiple metrics resulting from measuring with several techniques can be difficult to interpret, especially in clinical settings [99]. A method of data interpretation and analysis should also be planned when performing multimodal measurements. Understanding the benefits and drawbacks of available techniques will help to design the combination best suited for the pursued goals.

6. Summary

Table 1 compares the presented techniques used for monitoring cerebral circulation, particularly their output, resolution, and cost.

Clinical stationary imaging devices have the high spatial resolution, but the temporal resolution is usually relatively low. fMRI, for example, has low temporal resolution due to hemodynamic response time, which is much slower than the underlying neural process [100]. This problem has been solved by manipulating event-related stimuli and applying appropriate analysis methods [101].

Portable devices generally offer relatively low cost and rely on the indirect methods, which must be validated carefully. They are commonly suitable for bedside and continuous measurements, even for daily use. Particularly, optic-based methods have already shown their high potential for cerebral circulation studies. The penetration depth and spatial accuracy, however, are limited. TCD technique is non-invasive, radiation-free, and provides high temporal resolution. The device is widely available and of relatively low cost. However, the measurement has poor spatial resolution and provides only relative values on blood flow velocity. Monitoring with non-duplex TCD is also highly dependent on the skills of the operator. Insonation windows might be inaccessible for some patients, in which case the measurement cannot be performed.

There are several emerging techniques that can offer promising techniques for developing portable, low-cost, and safe devices for cerebral circulation monitoring. In particular, published initial feasibility studies show that functional microwave-based approaches show high potential. The benefit of cerebral circulation monitoring by detecting changes in the brain temperature/conductivity is the simplicity: the passive

Technology	Principle	Output	Temporal resolution	Spatial resolution	Cost
SPECT	Nuclear imaging technique utilizing a gamma-emitter radiotracer	3D image	Low	High	High
PET	Positron emitter radioactive tracers	3D image	Very low	High	High
ASL-MRI	Magnetically labeled water proton as tracers	3D image	Low	High	High
CT	Rotating x-ray beam	3D image	Low	High	High
fNIRS	Optic-based method	HbO, HbR, water, lipid	High	Low	Low
DCS	Optic-based method	Blood flow index	High	Low	Low
TCD	Ultrasound	Blood flow	High	Low	Low
Microwave	1. Sensing temperature and conductivity changes with mw antennas 2. Measuring signals reflected from the tissue boundaries	1. Temperature and conductivity changes, also converted to a voltage 2. Blood volume and images	High	Still unspecified	Medium or low

Table 1.
Comparison of selected techniques.

system just monitors the natural radiation and converts it to temperature values or voltage. The deficiency of this technique is the lack of accuracy in terms of the monitored area. However, the use of several antennas can improve accuracy clearly. The advantage of cerebral circulation monitoring by detecting changes in the blood volume is the possibility for higher resolution and localization accuracy, especially if advanced antennas, diversity techniques, and developed algorithms are utilized. The deficiency is the increased computational complexity in signal processing, which may require more expensive computers or distributed computing.

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