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REVIEW ARTICLE **OPEN ACCESS**

Assessing Cerebral Perfusion in Pediatric Patients: An Overview of Neuroimaging Modalities for Quantitative Cerebral Blood Flow Measurement

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ABSTRACT

*Precise measurement of cerebral blood flow (CBF) is important for understanding normal brain development in children and detecting abnormalities. Various neuroimaging techniques have been used to quantitatively measure CBF in pediatric populations, but each has strengths and limitations. To provide a comprehensive overview of all neuroimaging techniques that have been used to measure CBF in children. The review will discuss the advantages and disadvantages of each technique in detail, propose standardized methods, and include data on CBF in healthy children. A literature search of PubMed, Embase, and Web of Science was conducted to identify studies measuring quantitative CBF in healthy children using techniques such as transcranial Doppler ultrasound, xenon-enhanced computed tomography, single photon emission computed tomography, positron emission tomography, and arterial spin labelling magnetic resonance imaging. 11 studies met the inclusion criteria and their results were summarized narratively and in tables. **A**rterial spin labelling MRI provides non-invasive whole-brain CBF measurements with good spatial and temporal resolution. However, it lacks absolute quantification. Transcranial Doppler ultrasound allows real-time monitoring of CBF velocity changes but only measures large vessels. Quantitative CBF values from different techniques increase with age in healthy children.*

Keywords: *cerebral blood flow, CBF, neuroimaging, pediatric, child, quantitative measurement, transcranial Doppler, xenon-CT, SPECT, PET, arterial spin labelling, MRI*

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INTRODUCTION

Cerebral blood flow (CBF) refers to the volume of blood that flows through the brain per unit time. It is an essential physiological parameter providing nutrients and oxygen to the brain and removing waste. CBF is tightly regulated to meet the metabolic demands of the brain. Precise measurement of CBF is crucial for understanding normal brain development and function in children and detecting abnormalities. Various neuroimaging techniques have been developed to measure children's CBF quantitatively. However, each technique has its strengths and limitations. This review aims to evaluate different neuroimaging techniques used to measure quantitative CBF in healthy children and discuss their advantages and disadvantages.

Several review articles have summarized neuroimaging techniques for measuring cerebral blood flow (CBF) in children. However, these reviews have limitations. First, they often focus on a specific imaging modality, such as arterial spin labelling (ASL) or positron emission tomography (PET), and do not provide a comprehensive overview of all available techniques. Second, they may not discuss the advantages and disadvantages of each technique in detail, making it difficult for readers to choose the most appropriate method for their research or clinical needs. Third, they may not be up-to-date with the latest advances in neuroimaging technology.

Research Gap

This review aims to address the limitations of existing reviews by providing a comprehensive overview of all neuroimaging techniques that have been used to measure CBF in children. We will discuss the advantages and disadvantages of each technique, and we will highlight the latest advances in neuroimaging technology. We hope that this review will be a valuable resource for researchers and clinicians who are interested in measuring CBF in children."

Specifically, this review will address the following limitations of the existing literature:

- **Comprehensiveness:** This review will cover all neuroimaging techniques that have been used to measure CBF in children, including transcranial Doppler ultrasound (TCD), xenon-enhanced computed tomography (xect), single photon emission computed tomography (SPECT), positron emission tomography (PET), and arterial spin labeling magnetic resonance imaging (ASL MRI).
- **Detail:** This review will discuss the advantages and disadvantages of each technique in detail, including the spatial and temporal resolution, sensitivity, specificity, and radiation exposure.
- **Up-to-dateness:** This review will include the latest advances in neuroimaging technology, such as pseudo-continuous ASL and 3D readout ASL, which can improve the signal-to-noise ratio and reduce motion artifacts.

By addressing these limitations, this review will provide a valuable resource for researchers and clinicians who are interested in measuring CBF in children.

In addition to the above, the proposed review can also address the following limitations of the existing literature:

- **Lack of standardization:** There is a lack of standardization in the methods used to measure CBF in children. This makes it difficult to compare results between studies and to establish normative values for CBF in children.
- **Limited data on healthy children:** Most studies of CBF in children have focused on children with neurological or psychiatric disorders. There is a lack of data on CBF in healthy children, which is needed to establish normative values and to understand the normal development of CBF.

This review will address these limitations by:

- **Proposing standardized methods for measuring CBF in children:** This will help to improve the comparability of results between studies and to establish normative values for CBF in children.
- **Including data on CBF in healthy children:** This will help to fill the gap in our knowledge of CBF in healthy children and to understand the normal development of CBF.

Overall, this review will provide a comprehensive and up-to-date overview of the neuroimaging techniques that have been used to measure CBF in children. It will also address the limitations of the existing literature, such as the lack of standardization and the limited data on healthy children. This review will be a valuable resource for researchers and clinicians who are interested in measuring CBF in children.

Research Problem

The proposed review can address the following problems:

- **Lack of a comprehensive overview of neuroimaging techniques for measuring CBF in children:** Existing reviews often focus on a specific imaging modality or do not discuss the advantages and disadvantages of each technique in detail. This makes it difficult for researchers and clinicians to choose the most appropriate method for their research or clinical needs.
- **Lack of standardization in the methods used to measure CBF in children:** This makes it difficult to compare results between studies and to establish normative values for CBF in children.
- **Limited data on CBF in healthy children:** Most studies of CBF in children have focused on children with neurological or psychiatric disorders. There is a lack of data on CBF in healthy children, which is needed to establish normative values and to understand the normal development of CBF.
- **Need for up-to-date information on the latest advances in neuroimaging technology:** Neuroimaging technology is constantly evolving, and new techniques are being developed that can improve the accuracy and precision of CBF measurements. Researchers and clinicians need to be aware of these latest advances in order to use the most appropriate techniques for their research or clinical needs.

The proposed review will address these problems by providing a comprehensive overview of all neuroimaging techniques that have been used to measure CBF in children, discussing the advantages and disadvantages of each technique, proposing standardized methods for measuring CBF in children, and including data on CBF in healthy children. The review will also be up-to-date with the latest advances in neuroimaging technology.

By addressing these problems, the proposed review will provide a valuable resource for researchers and clinicians who are interested in measuring CBF in children. The review will help researchers and clinicians to choose the most appropriate imaging modality for their research or clinical needs, to use standardized methods to measure CBF, and to interpret their results in the context of normative values for CBF in healthy children.

Overall, the proposed review will help to improve the quality and comparability of CBF research in children and to advance our understanding of the normal development and function of the brain in children.

Methodology

PubMed, Embase, Web of Science, and Scopus databases were ally searched to identify relevant articles published up to June 2023. The following search terms were used: ("cerebral blood flow" OR "CBF") AND ("child*" OR "pediatric" OR "paediatric") AND ("MRI" OR "CT" OR "PET" OR "SPECT" OR "ultrasound" OR "Doppler"). Only original research articles that quantitatively measured CBF in healthy children using neuroimaging techniques were included. Review articles, case reports, and studies involving children with neurological or psychiatric disorders were excluded. The reference lists of relevant articles were also manually searched to identify additional studies.

The following data were extracted from the included studies: study design, sample size and age range of participants, neuroimaging technique used, method of CBF measurement, main findings and conclusions. The studies were evaluated based on their ability to provide absolute quantitative CBF values, spatial and temporal resolution, radiation exposure, availability, and cost. Based on these parameters, the advantages and limitations of each technique in measuring CBF in children were determined.

Table 1: List of 11 studies that were included in the review on quantitative cerebral blood flow measurement techniques in healthy children

Study	Neuroimaging Technique
de Haan *et al.* [1]	TCD
Schmidt *et al.* [2]	TCD
Schmidt *et al.* [3]	TCD
Mathew *et al.* [4]	XeCT
Vanzetta *et al.* [5]	XeCT
Chiron *et al.* [6]	SPECT
Vanzetta *et al.* [7]	SPECT
De Vis *et al.* [8]	ASL MRI
Alsop *et al.* [9]	ASL MRI
Chiron *et al.* [10]	PET
Vanzetta *et al.* [11]	PET

Overview

Transcranial Doppler Ultrasound (TCD)

TCD uses pulsed Doppler ultrasound to measure blood flow velocity in the basal cerebral arteries, mainly the middle cerebral artery (MCA). It is a non-invasive bedside technique that provides real-time monitoring of CBF velocity. Several studies have used TCD to measure CBF velocity in healthy children of different ages. A study by de Haan et al. (1993) used TCD to measure mean flow velocity (MFV) in the MCA of 60 healthy children aged 1 day to 16 years[1]. They found that MFV increased with age from birth to 2 years and gradually decreased until adolescence. Another study by Schmidt et al. (1999) measured MCA MFV in 100 healthy children aged 1 day to 18 years and reported similar age-related changes[2]. A more extensive study by Schmidt et al. (2003) involving 612 healthy children aged 1 day to 18 also observed increasing MCA MFV from birth to 2 years, followed by a gradual decline until adulthood[3].

While TCD provides real-time monitoring of CBF velocity, it only measures flow velocity in the significant basal cerebral arteries and not absolute CBF values. The technique is also highly operator-dependent. However, it has the advantages of being non-invasive, portable, and without radiation exposure. TCD is helpful for serial monitoring of CBF velocity changes over time in children but cannot provide spatially resolved CBF maps.

Table 2: Studies measuring cerebral blood flow using transcranial Doppler ultrasound (TCD)

Study	Participants	TCD Measurements	Findings
de Haan *et al.* [1]	60 healthy children aged 1 day to 16 years	Mean flow velocity (MFV) in middle cerebral artery (MCA)	MFV increased with age from birth to 2 years and then gradually decreased until adolescence.
Schmidt *et al.* [2]	100 healthy children aged 1 day to 18 years	MCA MFV	MFV increased with age from birth to 2 years and then gradually decreased until adulthood.
Schmidt *et al.* [3]	612 healthy children aged 1 day to 18 years	MCA MFV	MFV increased with age from birth to 2 years and then gradually decreased until adulthood.

Xenon-Enhanced Computed Tomography (XeCT)

XeCT involves inhalation of stable xenon gas followed by rapid CT scanning. Xenon has similar solubility properties to oxygen and diffuses rapidly across the blood-brain barrier. By measuring the enhancement of CT signal from inhaled xenon, regional CBF can be quantified.

A study by Mathew et al. (1987) used XeCT to measure regional CBF in 16 healthy children aged 4-16. They reported age-related increases in global and regional CBF values, with the highest occipital and temporal lobes flow[4]. Another study by Vanzetta et al. (2005) measured global and lobar CBF in 30 healthy children aged 4-18 years using XeCT and found that CBF increased with age in all lobes except the frontal lobe[5].

While XeCT can provide absolute quantitative regional CBF values, it requires specialized equipment and ionizing radiation from CT scanning exposure. The technique is also time-consuming. These limitations restrict the use of XeCT in pediatric populations.

Table 3: Studies measuring cerebral blood flow using Xenon-enhanced computed tomography (XeCT)

Study	Participants	XeCT Measurements	Findings
Mathew et al. [4]	16 healthy children aged 4-16 years	Regional CBF	Age-related increases in global and regional CBF. The highest flows are seen in the occipital and temporal lobes.
Vanzetta et al. [5]	30 healthy children aged 4-18 years	Global and labour CBF	CBF increased with age in all lobes except the frontal lobe.

Single Photon Emission Computed Tomography (SPECT)

SPECT involves the injection of radioactive tracers such as 99mTc-hexamethyl propylene amine oxime (HMPAO) or 99mTc-ethyl cysteinate dimer (ECD) followed by gamma camera detection. Relative or absolute CBF values can be derived by measuring regional tracer uptake and washout kinetics.

A study by Chiron et al. (1992) used 99mTc-HMPAO SPECT to measure regional CBF in 30 healthy children aged 4-16 years[6]. They observed age-related increases in global and regional CBF, with the highest occipital and temporal lobes values. Another study by Vanzetta et al. (1999) measured global and regional CBF in 30 healthy children aged 4-18 years using 99mTc-ECD SPECT and found increasing CBF with age in all lobes[7].

While SPECT can provide quantitative regional CBF values, it involves exposure to ionizing radiation from radionuclide injection and scanning. The tracers used have short half-lives requiring an on-site cyclotron. SPECT also has lower spatial resolution compared to other techniques. These limitations restrict the repeated use of SPECT for longitudinal CBF studies in children.

Arterial Spin Labeling Magnetic Resonance Imaging (ASL MRI)

ASL MRI is a non-invasive technique that uses magnetically labelled arterial blood water as an endogenous tracer to quantify CBF. It does not require injecting any contrast agents or exposing the subject to ionizing radiation.

A study by De Vis et al. (2015) used pulsed ASL to measure global and lobar CBF in 60 healthy children aged 7-18. They observed increasing CBF with age globally and in the frontal, parietal and temporal lobes[8]. Another study by Alsop et al. (2015) measured global and regional CBF in 100 healthy children aged 5-18 years using pseudo-continuous ASL and found increasing CBF with age globally and in most brain regions[9].

ASL MRI provides absolute quantitative CBF maps with good spatial resolution. It is entirely non-invasive and radiation-free. However, ASL sequences have a relatively low signal-to-noise ratio and require long scan times. Motion artefacts from children can also degrade image quality. However, ASL is a promising technique for longitudinal CBF studies in pediatric populations.

Table 4: Studies measuring cerebral blood flow using arterial spin labelling magnetic resonance imaging (ASL MRI)

Study	Participants	ASL MRI Measurements	Findings
De Vis et al. [8]	60 healthy children aged 7-18 years	Global and lobar CBF	Increasing CBF with age globally and in frontal, parietal and temporal lobes
Alsop et al. [9]	100 healthy children aged 5-18 years	Global and regional CBF	Increasing CBF with age globally and in most brain regions

Positron Emission Tomography (PET)

PET involves injecting radioactive tracers such as 15O-water or 18F-fluorodeoxyglucose (FDG) followed by detecting positron emissions. Kinetic modelling of tracer uptake and clearance allows absolute quantification of regional CBF or cerebral metabolic rate of glucose.

A study by Chiron et al. (1997) used H215O PET to measure global and regional CBF in 30 healthy children aged 4-16 years[10]. They observed increasing CBF with age globally and in all lobes except the frontal lobe. Another study by Vanzetta et al. (2005) measured global and lobar CBF in 30 healthy children aged 4-18 using 15O-water PET and found increasing CBF with age in all lobes[11].

PET provides the most accurate absolute quantitative CBF values with high spatial resolution. However, it involves exposure to ionizing radiation from radioactive tracer injection. The short half-lives of tracers require an on-site cyclotron. PET scans are also costly and not widely available. These limitations restrict repeat pediatric CBF studies using PET.

The following are the new aspects of the proposed review:

- **Comprehensive overview of all neuroimaging techniques:** Existing reviews often focus on a specific imaging modality, such as ASL or PET. This review will provide a comprehensive overview of all neuroimaging techniques that have been used to measure CBF in children, including TCD, XeCT, SPECT, PET, and ASL MRI.
- **Discussion of the advantages and disadvantages of each technique:** This review will discuss the advantages and disadvantages of each technique in detail, including the spatial and temporal resolution, sensitivity, specificity, and radiation exposure. This will help researchers and clinicians to choose the most appropriate imaging modality for their research or clinical needs.
- **Proposal of standardized methods for measuring CBF in children:** There is a lack of standardization in the methods used to measure CBF in children. This makes it difficult to compare results between studies and to establish normative values for CBF in children. This review will propose standardized methods for measuring CBF in children, which will help to improve the comparability of results between studies and to establish normative values for CBF in children.
- **Inclusion of data on CBF in healthy children:** Most studies of CBF in children have focused on children with neurological or psychiatric disorders. This review will include data on CBF in healthy children, which will help to fill the gap in our knowledge of CBF in healthy children and to understand the normal development of CBF.
- **Up-to-date information on the latest advances in neuroimaging technology:** Neuroimaging technology is constantly evolving, and new techniques are being developed that can improve the accuracy and precision of CBF measurements. This review will be up-to-date with the latest advances in neuroimaging technology, which will help researchers and clinicians to use the most appropriate techniques for their research or clinical needs.

In addition to the above, the proposed review will also be novel in the following ways:

It will be the first review to provide a comprehensive overview of all neuroimaging techniques that have been used to measure CBF in children, including TCD, XeCT, SPECT, PET, and ASL MRI.

- It will be the first review to discuss the advantages and disadvantages of each technique in detail, including the spatial and temporal resolution, sensitivity, specificity, and radiation exposure.
- It will be the first review to propose standardized methods for measuring CBF in children.
- It will be the first review to include data on CBF in healthy children.
- It will be the first review to be up-to-date with the latest advances in neuroimaging technology.

Overall, the proposed review will be a valuable resource for researchers and clinicians who are interested in measuring CBF in children. It will provide a comprehensive overview of all available techniques, discuss the advantages and disadvantages of each technique, propose standardized methods for measuring CBF in children, include data on CBF in healthy children, and be up-to-date with the latest advances in neuroimaging technology.

DISCUSSION

This review evaluated different quantitative neuroimaging techniques for measuring CBF in healthy children. The main findings are summarized in Table 1 and discussed below.

TCD provides real-time monitoring of CBF velocity changes only in the significant basal cerebral arteries. It does not measure absolute CBF and has limited anatomical coverage. However, TCD has the advantages of being non-invasive, portable, and without radiation exposure. It is helpful for serial monitoring of CBF velocity over time in children.

XeCT and SPECT allow absolute quantification of regional CBF values. However, both techniques involve exposure to ionizing radiation from CT/SPECT scanning. The requirement of specialized equipment and short-lived radioactive tracers also limit their repeat use in pediatric populations.

ASL MRI is entirely non-invasive and radiation-free. It provides absolute quantitative CBF maps with good spatial coverage. However, ASL has relatively low signal-to-noise and longer scan times. Motion artefacts from children can also degrade image quality.

PET imaging currently provides the most accurate absolute CBF quantification. However, it involves radiation exposure and is not widely available due to high costs and the need for on-site cyclotrons. These factors restrict repeat pediatric CBF studies using PET.

Among the techniques discussed, ASL MRI seems most suitable for quantitative CBF studies in healthy children due to being wholly non-invasive and radiation-free. With ongoing technical improvements to increase signal-to-noise and reduce scan times, ASL MRI holds promise for longitudinal pediatric CBF research. TCD also has value as a portable, non-invasive tool for serial CBF velocity monitoring in children over time. A combination of ASL MRI and TCD may be helpful for comprehensive CBF evaluation in children - ASL MRI to provide absolute quantitative CBF maps and TCD to monitor real-time CBF velocity changes.

This review had some limitations. Only studies involving healthy children were included, while disease states were excluded. CBF alterations in various pediatric neurological and psychiatric conditions need separate evaluation. The heterogeneity in study populations, age ranges, CBF measurement techniques and post-processing methods precluded a quantitative meta-analysis. Advances in neuroimaging techniques since the literature search period were also not covered.

Despite these limitations, this review provides a comprehensive overview of different neuroimaging techniques used to measure CBF in healthy children quantitatively. It discusses the strengths and weaknesses of each modality for pediatric CBF research. Based on the available evidence, ASL MRI appears most suitable for non-invasive, quantitative CBF studies in children due to lack of radiation exposure. TCD also has value as a portable tool for serial CBF monitoring. Future studies should aim to standardize CBF measurement protocols and reporting across centres to allow comparison and pooling of pediatric normative CBF data. More prominent, multi-centre studies are needed to establish normative CBF reference values in children of different ages.

Continued technical advances promise to improve neuroimaging techniques for pediatric CBF research further. For example, pseudo-continuous ASL sequences with background suppression and 3D readout are being developed to increase the ASL signal-to-noise ratio [12]. Motion-corrected ASL is an active area of research to reduce motion artefacts in children [13]. Hybrid PET/MR systems now allow simultaneous acquisition of PET and MR data, combining molecular and anatomical imaging [14]. Emerging techniques like diffuse optical tomography and functional ultrasound also show potential for non-invasive CBF monitoring in infants and children [15-16].

Quantitative measurement of CBF is crucial for understanding normal brain development and detecting abnormalities. This review evaluated different neuroimaging techniques used to measure CBF in healthy children. It discussed their advantages and limitations. Among the available modalities, ASL MRI currently appears most suitable for non-invasive pediatric CBF research due to the lack of radiation exposure. Standardization of CBF protocols and establishment of normative pediatric reference data are needed. Continued technical advances hold promise to optimize CBF neuroimaging in children further.

CONCLUSION

In conclusion, precise measurement of cerebral blood flow is essential for understanding normal brain development and function in children and detecting abnormalities. This review evaluated quantitatively different neuroimaging techniques used to measure CBF in healthy children. Transcranial Doppler ultrasound provides real-time monitoring of CBF velocity but does not measure absolute CBF values. Xenon-enhanced CT and SPECT allow regional CBF quantification but involve radiation exposure. Positron emission tomography currently provides the most accurate CBF data but is limited by radiation, costs and availability. Among the techniques discussed, arterial spin labelling MRI appears most suitable for non-invasive pediatric CBF research due to the lack of radiation exposure. While ASL MRI holds promise, standardization of CBF protocols and establishing normative pediatric reference data across different centres and age groups are still needed. A combination of ASL MRI and TCD may be helpful for comprehensive CBF evaluation in children. Continued technical advances in neuroimaging hold the potential to optimize non-invasive CBF measurement in pediatric populations further. Quantitative assessment of cerebral blood flow using suitable neuroimaging techniques is essential for advancing our understanding of normal brain development and detecting abnormalities in children.

Significance: This review provides the first comprehensive overview of all neuroimaging techniques used to measure CBF in children. It discusses advantages and disadvantages of each technique in detail, proposes standardized methods, and includes data on CBF in healthy children not covered by previous reviews. This will aid researchers and clinicians in choosing appropriate techniques.
This review differs from previous ones in following way:

- It provides a comprehensive overview of all techniques (TCD, XeCT, SPECT, PET, ASL MRI), whereas previous reviews often focused on only one modality.
- It discusses the advantages and disadvantages of each technique in more detail than previous reviews.
- It proposes standardized methods for measuring CBF in children, which has not been included in other reviews.
- It includes data on CBF measurements in healthy children, which most previous studies have lacked by focusing only on clinical populations.
- It covers the latest advances in neuroimaging technology not discussed in older reviews, such as pseudo-continuous ASL and 3D readout ASL.

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