https://doi.org/10.35845/kmuj.2025.23713

VIEWPOINT

Reviewing neuroimaging techniques to measure quantitative cerebral blood flow in healthy children

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ABSTRACT

Cerebral blood flow (CBF) is a critical physiological parameter for brain development and function in children. This viewpoint reviews the main neuroimaging techniques for quantifying pediatric CBF, including Positron emission tomography (PET), single photon emission computed tomography (SPECT), perfusion Magnetic Resonance Imaging (MRI), Computed Tomography Perfusion, arterial spin labelling (ASL) MRI, and Doppler ultrasound. Each modality has strengths and limitations related to radiation exposure, accessibility, resolution, and quantification. Reported average CBF values vary by technique and increase with age, reflecting neurodevelopment. ASL MRI offers a promising non-invasive method without radiation. Standardizing protocols across modalities and ages with validation against PET is needed. Quantitative CBF imaging provides a valuable window into understanding cerebrovascular changes in normal and abnormal neurodevelopment.

Keywords: Cerebrovascular Circulation (MeSH); Cerebral Blood Flow (MeSH); Neuroimaging techniques (Non-MeSH); Pediatric brain development (Non-MeSH); Perfusion Magnetic Resonance Imaging (MeSH); Arterial spin labeling MRI (MeSH); PET validation (Non-MeSH); Perfusion MRI (MeSH).

THIS ARTICLE MAY BE CITED AS: Malik MMUD. Reviewing neuroimaging techniques to measure quantitative cerebral blood flow in healthy children. Khyber Med Univ J 2025;17(1):119-22. https://doi.org/10.35845/kmuj.2025.23713

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Date Submitted: July 01, 2024
Date Revised: December 20, 2024
Date Accepted: January 11, 2025

Cerebral blood flow (CBF) is defined as the blood supply to the brain in a given period of time, measured in millilitres of blood per 100 grams of brain tissue per minute (ml/100g/min). CBF is vital for the continuous delivery of oxygen and nutrients to support normal brain function. Especially during childhood brain development, adequate perfusion is crucial for neurogenesis, synaptogenesis, myelination and maturation of the brain.[1] Disruption to CBF can impact these processes and influence neurodevelopmental disorders.[2] Therefore, having techniques to quantify CBF in children provides insight into cerebral physiology in health and disease.

Several neuroimaging methods allow non-invasive in vivo measurement of quantitative CBF in millilitres of blood per 100 grams of tissue per minute. The modalities include positron emission tomography (PET), single photon emission computed tomography (SPECT), perfusion magnetic resonance imaging (MRI), computed tomography perfusion (CTP), arterial spin labelling (ASL) MRI, and Doppler ultrasound. This review systematically evaluates these different techniques for measuring pediatric CBF, with a focus on application in healthy children.

Positron emission tomography: PET imaging uses radioactive tracers like 15O-water or 15O-carbon dioxide combined with tomographic reconstruction to generate quantitative maps of CBF.[3] The short half-lives of the tracers allows serial CBF measurements. PET has been used to measure global and regional CBF in infants and children. However, it has limitations including radiation exposure, need for on-site cyclotron, and sedation requirements for young pediatric subjects.[4] Studies report average gray matter CBF in healthy children from ages 5-16 years ranging from 90-100 ml/100g/min using 15O-water PET.

Recent technological advances have significantly addressed traditional PET limitations in pediatric imaging. New-generation PET scanners featuring enhanced detector sensitivity now enable high-quality imaging at lower radiation doses, particularly beneficial for pediatric populations. Alternative tracers such as 13N-ammonia, with longer half-lives than 15O-water, reduce dependence on on-site cyclotrons while maintaining quantification accuracy. Advanced motion correction algorithms and rapid acquisition protocols have minimized sedation requirements in young patients. The emergence of integrated PET/MR systems offers simultaneous acquisition of functional and anatomical data while reducing overall radiation exposure. However, these advanced systems remain primarily confined to major research centers, limiting their widespread clinical implementation.

Single photon emission computed tomography: SPECT also utilizes gamma-emitting radiotracers like 99mTc-HMPAO and 133Xe to measure rCBF. It is more accessible due to lack of onsite cyclotron. However, spatial resolution is lower than PET. The clinical impact of SPECT's lower spatial resolution (typically 8-10mm compared to PET's 4-6mm) requires careful consideration in pediatric applications. This resolution limitation particularly affects the detection of focal perfusion deficits in conditions like pediatric epilepsy and the assessment of small vessel disease. Despite these constraints, SPECT's wider availability and lower operational costs make it a practical choice for initial screening and follow-up studies, especially in settings where PET is unavailable. Centers have developed specialized pediatric protocols that optimize acquisition parameters and post-processing techniques to partially compensate for resolution limitations. The trade-off between accessibility and resolution must be evaluated based on specific

clinical requirements and the precision needed for particular diagnostic questions. Few pediatric studies have calculated whole brain or regional quantitative CBF values using SPECT. Reported average CBF is around 50 mL/100g/min in healthy children. Hyperperfusion related to age has been documented with SPECT.[5] Reported average CBF values across different modalities in healthy children are given in Table 1.

Perfusion MRI and CT: Perfusion MRI and CT generate hemodynamic maps of CBF by tracking intravenous contrast passage through cerebral vasculature. MRI offers better resolution and avoids ionizing radiation. Reported perfusion MRI CBF averages around 80 mL/100g/min in healthy children.[6] Age-related increases in grey matter CBF have been shown using both modalities.[7] Limitations include contrast usage, radiation with CTP, and reliance on contrast kinetics models. Recent developments in perfusion imaging have substantially improved quantification accuracy and clinical utility. Advanced computational methods, including artificial intelligence-based approaches, now enable more robust perfusion measurements while reducing processing time. New contrast agents with optimized kinetic properties provide better tissue characterization and reduced susceptibility to artefacts. Dual-energy CT techniques have enhanced tissue differentiation and reduced beam hardening artefacts, particularly beneficial in pediatric imaging where tissue contrasts can be subtle. The implementation of faster MRI sequences with improved motion correction has made these techniques more suitable for pediatric applications. However, challenges remain in standardizing quantification methods across different platforms and institutions, necessitating careful protocol optimization and validation for pediatric applications.

Table I: Reported average quantitative cerebral blood flow values in healthy children using different neuroimaging techniques

Neuroimaging technique	Reported average cerebral blood flow (CBF) (mL/100g/min)
Positron Emission Tomography (PET), with 15O-water	90-100
Single Photon Emission Computed Tomography (SPECT)	50
Perfusion Magnetic Resonance Imaging (MRI)	80
Arterial Spin Labeling (ASL) MRI	22-145
Doppler Ultrasound	28

Table II: Strengths and limitations of neuroimaging techniques for measuring cerebral blood flow in children

Neuroimaging technique	Strengths	Limitations
Positron Emission Tomography (PET)	Gold standard for absolute quantification	Requires on-site cyclotron, radiation exposure
Single Photon Emission Computed Tomography (SPECT)	More accessible than PET	Poorer resolution than PET
Perfusion Magnetic Resonance Imaging (MRI/CT)	Better resolution than SPECT (for MRI)	Semi-quantitative values, requires contrast, radiation for CT
Arterial Spin Labeling (ASL) MRI	Completely non-invasive, no tracers or radiation needed	Lower signal, sensitivity to artifacts, variability in quantification
Doppler Ultrasound	Portable, economical for neonates	Operator dependent, artifacts from bone, limited to large vessels

Positron emission tomography (PET), Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Arterial Spin Labeling (ASL)

Arterial spin labelling MRI: ASL MRI uses magnetically labelled arterial blood water in the neck as an endogenous tracer to quantify CBF. It does not require exogenous contrast or radiation. Literature documents average global gray matter CBF between 22-145 mL/100g/min in healthy children using ASL.[8] Challenges with ASL include lower signal, sensitivity to artifacts, and variability among methods. The reliability of ASL has improved significantly through recent technological innovations. Background suppression techniques now enhance signal-to-noise ratios, while multi-delay ASL sequences better account for arterial transit time variations common in pediatric populations. The implementation of standardized protocols, as recommended by the ISMRM Perfusion Study Group, has reduced inter-center variability. Machine learning approaches show promise in improving image quality and quantification accuracy, particularly in challenging pediatric cases where movement and varying cerebral blood arrival times pose significant challenges. Centers implementing these advances report more consistent results across different age groups, though standardization efforts continue to evolve.

Doppler ultrasound: Doppler ultrasonography measuring flow velocity in major cerebral arteries like internal carotid and vertebral arteries can estimate CBF in newborns and infants.[9] Average values around 28 mL/100g/min have been reported. The

Table III: Technical specifications of different cerebral blood flow measurement modalities

Modality	Spatial resolution (mm)	Temporal resolution	Scan time	Quantification accuracy
Positron Emission Tomography (PET)	4-6	1-2 min	15-20 min	Gold standard (±5 %)
Single Photon Emission Computed Tomography (SPECT)	8-10	30-60 sec	10-15 min	±10-15 %
Computed Tomography (CT) Perfusion	2-4	3-5 sec	5-8 min	±10-20 %
Arterial Spin Labeling (ASL) MRI	1-2	1-2 sec	5-7 min	±15-25 %
Doppler Ultrasound	0.5-1	Real-time	5-10 min	±15-30 %

Positron emission tomography (PET), Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Arterial Spin Labelling (ASL)

clinical impact of Doppler limitations varies with specific applications. Studies have documented measurement variability of up to 15% between different operators, particularly affecting longitudinal monitoring protocols. Movement artifacts pose significant challenges in awake infants, often necessitating multiple measurements to obtain reliable results. While bone artifacts limit assessment of deeper brain structures beyond the neonatal period, the technique's bedside availability and real-time capabilities make it invaluable in critical care settings. Centers have developed standardized scanning protocols and training programs to minimize operator-dependent variations, though challenges persist in achieving consistent measurements across different clinical settings. Table II summarizes the strengths and limitations of each neuroimaging technique for pediatric CBF assessment.)

DISCUSSION

PET with 15O-water is considered the gold standard for non-invasive absolute CBF quantification. But availability is limited due to infrastructure requirements and radiation exposure concerns in children.[10] The variability in CBF measurements across modalities presents significant implications for both clinical practice and research applications. Clinical interpretation requires careful consideration of modality-specific reference ranges, as absolute values may differ substantially between techniques. Research applications must balance factors such as required spatial resolution, temporal sampling needs, and the feasibility of repeated measurements. Ongoing multi-center initiatives are addressing these challenges through the development of standardized protocols and cross-validation methods. These efforts include the creation of age-appropriate phantoms for calibration, implementation of standardized post-processing pipelines, and harmonization of acquisition parameters across different platforms and manufacturers. Relative to PET, SPECT has poorer resolution. Perfusion CT and MRI estimate only semi-quantitative relative CBF values that depend on kinetic models and mathematical assumptions. Compared to other modalities, ASL MRI offers a completely non-invasive quantitative technique without requiring exogenous tracers or radiation exposure. It likely represents the most promising option for longitudinal pediatric studies. (See Table III for a comparison of technical specifications across imaging modalities). However Doppler ultrasound is portable and economical in neonates.

All modalities demonstrate age-related changes in CBF likely reflecting neural development. But average reported quantitative values vary, limited by factors like patient cooperation, sedation effects, radiation doses constraints, and differences in modelling methods among studies. Standardizing pediatric protocols tailored to developmental hemodynamics and validation against gold standards like PET warrants investigation to improve reliability across neuroimaging methods.

Future directions: The field of pediatric CBF quantification continues to evolve rapidly, with several promising developments on the horizon. Hybrid imaging systems, particularly PET-MRI, represent a significant advance in simultaneous acquisition of gold-standard CBF measurements alongside high-resolution anatomical and functional information. These systems offer potential reductions in total scan time and radiation exposure, particularly beneficial for pediatric populations.

Artificial intelligence and deep learning algorithms are transforming image processing and analysis across all modalities. These advanced computing solutions show promise in improving image quality, reducing artefacts, and automating quantification processes, potentially leading to more robust and standardized measurements in pediatric populations.

International collaborations are working to establish standardized protocols and quality control measures specific to pediatric CBF imaging. These initiatives include the development of age-specific phantoms, reference standards, and harmonized acquisition protocols across different platforms and institutions. The integration of CBF measurements with other physiological parameters, such as oxygen metabolism and vessel reactivity, may provide more comprehensive assessment of neurovascular health in developing brains.

CONCLUSION

Multiple neuroimaging techniques allow in vivo visualization and quantification of

pediatric cerebral blood flow as an important biomarker of brain development and function. Each modality has its strengths and weaknesses. More research is needed to standardize quantitative CBF measurement in children of different ages and validate findings against PET standards. Advances in MRI methods like ASL likely offer the best prospects for radiation-free quantification of cerebral perfusion changes from infancy through adolescence. Quantitative assessment of CBF with neuroimaging has great potential to elucidate cerebrovascular changes underlying normal neurodevelopment and pediatric neurological disorders.

ACKNOWLEDGEMENT

The author would like to extend our appreciation to those who offered helpful commentary during the drafting process of this manuscript.

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CONFLICT OF INTEREST

The author declares no conflict of interest - financial or otherwise - that could compromise the integrity, objectivity, or validity of the opinion or viewpoint expressed.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Author declared no specific grant for this research from any funding agency in the public, commercial or non-profit sectors

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