

Techniques for dose reduction in pediatric cardiac CT

Marek Kardoš

Department of Functional Diagnostics, Children's Cardiac Center, Bratislava, Slovakia

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Zvýšené používanie CT vyšetrení u detí v posledných desaťročiach vyvolalo obavy z dlhodobých rizík ožiarenia z diagnostického zobrazovania. Deti sú zraniteľnejšie voči škodlivým účinkom žiarenia, pretože majú dlhší život, čo umožňuje viac času na akumuláciu účinkov súvisiacich so žiarením. Technologické inovácie v oblasti počítačovej tomografie umožnili výrazné zníženie ožiarenia u dospelých aj pediatrických pacientov a zároveň zachovali kvalitu diagnostického zobrazovania.

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ABSTRACT

The increased use of CT scans in children over the past decades has raised concerns about the long-term risks of radiation exposure from diagnostic imaging. Children are more vulnerable to the harmful effects of radiation because they have a longer lifespan, allowing more time for radiation-related effects to accumulate. Technological innovations in computed tomography have facilitated significant reductions in radiation exposure for both adult and pediatric patients while preserving diagnostic imaging quality.

Introduction

The increased use of CT scans in children over the past decades has raised concerns about the long-term risks of radiation exposure from diagnostic imaging. Children are more vulnerable to the harmful effects of radiation because they have a longer lifespan, allowing more time for radiation-related effects to accumulate. Although the immediate benefit to individual patients can be substantial, there is a higher risk of future cancer in patients undergoing multiple CT scans during their follow-up.¹⁻⁵

While CT imaging can provide substantial immediate benefits to individual patients, there are concerns regarding the potential for increased future cancer risk associated with the growing prevalence of CT examinations, particularly in patients undergoing multiple CT scans during the course of their follow-up care. The retrospective study by Pearce et al. demonstrates a significant association between the estimated radiation doses from CT scans to the red bone marrow and brain, and the subsequent incidence of leukemia and brain tumors. Assuming typical radiation doses for scans performed after 2001 in children under 15 years old, the cumulative ionizing radiation exposure from 2–3 head CT scans could substantially increase the risk of brain tumors, while 5–10 head CT scans could significantly elevate the risk of leukemia. Based on

this knowledge, it is necessary to carefully indicate and perform CT scans in patients who are expected to require extensive imaging during follow-up.⁶

Technological innovations in computed tomography, including automated exposure regulation, adaptive tube voltage selection, optimized detector configurations, dynamic collimation, and iterative reconstruction algorithms, have facilitated significant reductions in radiation exposure for both adult and pediatric patients while preserving diagnostic imaging quality. While some pediatric CT scans can be replaced by MRI techniques that avoid radiation, the longer MRI scan times and enclosed environment often require general anesthesia for infants and young children.^{7,8}

This manuscript reviews computed tomography acquisition methods as part of a comprehensive approach to minimize radiation exposure and optimize image quality for infants and young children.

Imaging scenarios where cardiac CT may be useful

Cardiovascular imaging with computed tomography is the current optimal diagnostic modality for various clinical indications.

Address: MUDr. Marek Kardoš, Department of Functional Diagnostics, Children's Cardiac Center, Pod Krásnou hôrkou 1, 833 48 Bratislava, Slovakia,
e-mail: kardi.marek@gmail.com
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Owing to the diminutive size of coronary arteries in young pediatric patients, cardiac computed tomography demonstrates distinct advantages over cardiac magnetic resonance imaging and echocardiography for evaluating the coronary vasculature. With relatively modest radiation exposure, cardiac CT allows visualization of the origins of coronary arteries, as well as their proximal and distal courses, including the identification of anomalous origins, acute angulation at the origin, or intramural segments in both congenital and acquired coronary abnormalities, even in infants with complex cardiac defects, and this can be achieved with relatively modest radiation exposure.⁹⁻¹¹ Individuals with repaired or palliated congenital heart disease demonstrate an elevated prevalence of coronary artery anomalies. Current clinical guidelines advise imaging of the coronary arteries “at least once in adulthood” for any patient who has undergone surgical manipulation of the coronary vessels.¹² Cardiac CT imaging enables the detection of coronary artery abnormalities, including dilation and stenosis, in individuals with acquired coronary disorders such as Kawasaki disease or in patients with transplant coronary artery disease.

Cardiac computed tomography represents a rapid diagnostic approach for critically ill ICU patients in comparison to cardiac magnetic resonance imaging and invasive angiography. Furthermore, cardiac CT can be effectively performed without the need for sedation in infants and young children, making it an attractive alternative to cardiac MRI in this patient population when functional assessment is not required and only anatomical evaluation is the primary objective such as in cases of severe outflow tract obstruction or in patients with Williams syndrome.¹³

Cardiac CT may be the preferred imaging modality for patients with intrathoracic metallic implants, such as pacemakers and defibrillators, compared to cardiac MRI.^{14,15}

Optimization of radiation dose

When performing a CT scan on children, who are sensitive to radiation, dose reduction is crucial. The radiation level is directly proportional to factors such as kilovoltage, tube current, scan time, slice thickness, and field of view. In recent years, various techniques have been developed to reduce radiation dose. These include the availability of low tube potential settings, ECG-based tube current modulation, and anatomic-based tube modulation. Furthermore, iterative reconstruction algorithms enable a reduction in tube current and radiation dose while maintaining acceptable image quality. Advancements in detector technologies have also contributed to lowering radiation exposure.¹⁶⁻²⁵

Low-kilovolt imaging

Utilizing lower x-ray tube potentials represents one of the most effective methods for minimizing radiation exposure in pediatric CT imaging. Optimal application of this approach necessitates an understanding of the interdependent relationship between tube potential, tube current, image noise, image contrast, and radiation dose. Lowering the tube potential results in decreased photon

flux and increased tissue attenuation of lower-energy photons, which in turn leads to elevated image noise. This generally necessitates an increase in the tube current to maintain the desired image quality. The size of the patient has a direct impact on the magnitude of this phenomenon, with examinations on small pediatric patients resulting in a lower noise penalty. Consequently, at low tube potential, the necessary increase in the tube current for children is less than that required for adults. Furthermore, the use of a lower tube potential during contrast-enhanced CT examinations can enhance the iodine contrast-to-noise ratio. This improvement is attributed to the increased photoelectric absorption of the lower-energy photons by the iodinated contrast agent, leading to significantly greater contrast attenuation. Increased CNR ratio offers an additional benefit for cardiac CT, as it enables the use of a reduced volume and/or injection rate of iodinated contrast agent due to its enhanced attenuation at a lower tube potential. The higher CNR can be beneficial for very small newborns or infants (who can receive only an extremely small amount of contrast material [5 mL]), as well as children at risk of contrast-induced kidney injury and those requiring injections into smaller blood vessels. Multiple vendors have developed solutions for automated selection of tube voltage settings (kV Assist [GE Healthcare]; Care kV [Siemens Healthineers]; Sure kV [Canon Medical Systems]). These automated tube potential selection tools determine the optimal tube potential based on an estimation of the patient's size derived from the attenuation data in the localizer radiograph, along with the user's selected examination type.^{26,27} The use of automatic tube potential selection tools in pediatric patients has been shown to decrease the median radiation dose, as measured by CTDIvol, by 68% for thoracic CT angiography, while preserving acceptable image.²⁸ Using lower-kilovolt settings in cardiac CT can increase streak artifacts from metallic implants, but newer techniques for reducing these artifacts and iterative reconstruction can help address this issue.

Tube current modulation

Tube current modulation or automatic exposure control represents a beneficial dose-minimizing technique that tailors the CT radiation dose based on the patient's body size, shape, and tissue attenuation. Understanding the different methods of tube current modulation is crucial for properly using this technique. Modulation may be applied along the x-y plane, the z-axis, or a combination of these approaches. The reference for modulation can be based on standard deviation, noise index, reference mA, or reference image. Dose reduction can vary in pediatric cardiac computed tomography examinations (up to 26%).²⁹ Dose modulation is affected by various factors, including the distance from the gantry isocenter, kV level, and scan direction.

Imaging without ECG synchronisation or with prospective triggering

The presence of an experienced cardiovascular imaging specialist is essential to adapt the scan protocol to the specific patient characteristics and clinical requirements.

Assessment of extracardiac thoracic vascular structures, such as the aorta, pulmonary arteries, and pulmonary

and systemic veins, can typically be performed without the need for ECG-synchronization.^{30–33} When assessing the aortic or pulmonary roots, ECG-synchronized imaging is necessary to mitigate pulsation-related artifacts.³⁴ ECG-synchronized imaging is essential for comprehensive assessment of coronary artery morphology and detailed evaluation of intracardiac structures. When ECG-synchronization is employed, the CT scanning modality with the lowest radiation exposure should be utilized, such as prospective ECG-gated acquisition targeting a specific phase of the cardiac cycle. In prospectively triggered acquisitions, the scanner forecasts the timing of the R-wave and subsequently initiates the scan acquisition at the cardiac cycle phase specified by the operator. This method facilitates dose optimization by restricting radiation delivery to a predefined narrow temporal window within the cardiac cycle, leading up to a 69% reduction in dose compared to retrospective ECG-gating.^{35–38}

Rapid scanning using a wide-area detector

Computed tomography imaging with wide-area detector technology utilizes an extensive detector array that permits the acquisition of an entire anatomical region (up to 16 centimeters) within a single gantry revolution (0.28–0.35 seconds), without requiring patient table movement. At present, there are two distinct scanner configurations available, one featuring a 320-row or a 640-row detector assembly (Aquilion One, Canon Medical Systems) and the other incorporating a 256-row detector assembly (Revolution, GE Healthcare). This technique allows for a single rapid axial scan to cover a 16–32 cm field of view. Alternatively, the scanner can acquire multiple contiguous axial scans to cover larger anatomic regions, with a time delay between each acquisition step. Helical acquisition with partial detector row activation, involving half or fewer of the 256 or 320 or 640 detector rows, is also an option.^{39,40}

Reduction of Z-axis coverage and Z-overranging

Tailoring the scan range along the z-axis based on individual clinical needs is an effective and straightforward approach to reducing the CT radiation dose. This is because the CT radiation exposure is directly proportional to the scanning range, assuming all other CT parameters remain constant. Extended scan coverage may be required to assess the infracardiac variant of total anomalous pulmonary venous connection or major aortopulmonary collaterals in pulmonary atresia patients. If there is any doubt regarding the appropriate range for the scout image, it is preferable to repeat the scout imaging rather than conducting the entire examination again following an unsuccessful study, as the latter scenario represents the worst-case scenario for minimizing the CT radiation dose. The contribution of 'z-overranging' to the overall CT radiation dose is inversely proportional to the z-axis scan range. This relationship can be explained by the physical characteristics of 'z-overranging': the effect is directly proportional to the beam collimation, the reconstructed slice width, and the pitch, while it is independent of the planned scan length. To maximize the dose-saving benefits of limiting the z-axis coverage, the use of adaptive collimation technology is strongly advised to eliminate 'z-overranging' (Fig. 1).⁴¹

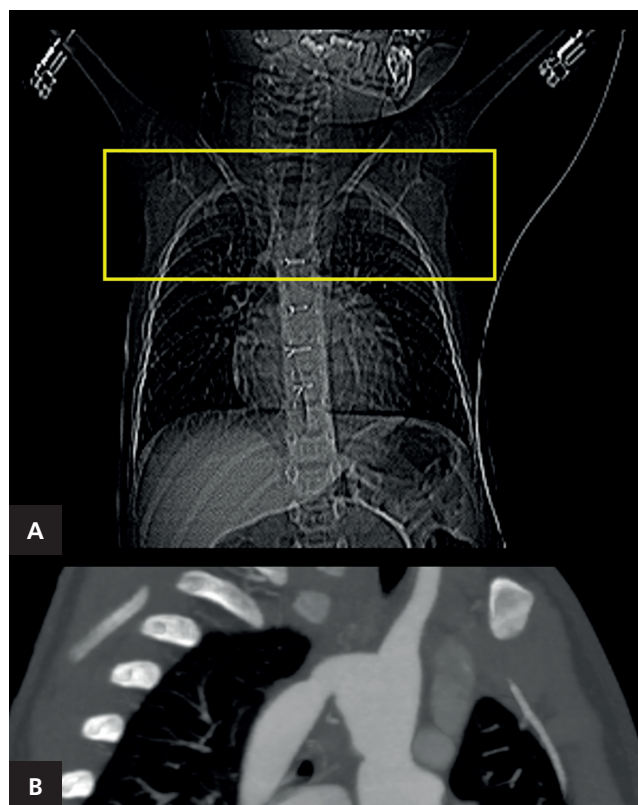


Fig. 1 – This figure depicts focused CT angiography. Part 1A shows the selection of the CT scanning range in a patient with recoarctation of the aorta. Part 1B presents a modified sagittal view, revealing the presence of recoarctation of the aorta within the predefined CT range.

Optimization of contrast agent administration

The goal of cardiac CT is to achieve homogenous opacification in the region of interest. The required volume of contrast agent depends on the patient's size, and may also be influenced by the specific clinical diagnosis. The rate of iodinated contrast administration is determined by the size of the intravenous access and the maximum permissible volume of contrast, typically ranging from 0.5 to 5 milliliters per second. The contrast dose is typically 1–3 mL/kg, with an upper limit of approximately 125–150 mL for an adult-sized patient.

There are three main methods for determining the optimal scan delay when administering contrast:

Bolus tracking: This uses a region of interest to automatically trigger the scan when a specific Hounsfield unit threshold is reached. Prolonging the scan time during bolus tracking to 1.5 to 2 seconds is optimal. The radiation dose from the bolus tracking alone accounts for approximately 25% of the total radiation exposure during the entire CT examination.

Test bolus: A small test dose of contrast is administered, and the scan is triggered based on the time to peak opacification of the structure of interest. An additional 2–3 second delay is added for neonates, or up to 8 seconds for older children.

Empirical timing: The scan is triggered at a set time after contrast administration, without using bolus tracking.

Contrast agent 1 mL/kg	<p>E.g. newborn patient, weight 3.5 kg:</p> <ol style="list-style-type: none"> 1. Contrast agent – 4 mL 2. Contrast agent + saline flush – 4 mL (2 mL + 2 mL) 3. Saline flush – 10 mL (to flush all of the contrast agent from the connection tube) <p>E.g. 30 kg boy:</p> <ol style="list-style-type: none"> 1. Contrast agent – 30 mL 2. Contrast agent – 30 mL (15 mL + 15 mL) 3. Saline flush – 25 mL
Contrast agent 0.5 mL/kg + Saline flush 0.5 mL/kg 1 : 1	
Saline flush volume depending on patient's size	

Fig. 2 – The figure represents triphasic contrast agent protocol with examples.

This method may be less reliable than the other two approaches.

All three techniques can be effective for optimizing the scan delay and contrast enhancement.

Contrast administration may involve a biphasic or triphasic approach. Biphasic administration typically starts with full-strength contrast or a contrast-saline mixture, followed by a normal saline flush. The triphasic approach begins with full-strength contrast, followed by a contrast-saline mixture, and then a normal saline flush. The saline flush helps to clear the intravenous tubing and central veins of dense contrast material, which can cause streak artifacts in young children, as smaller total amounts of contrast are administered in these patients (Fig. 2).

Careful attention should be paid when performing imaging studies on patients with Fontan circulation. A thorough understanding of the unique Fontan anatomy is essential, with the aim of adequately opacifying the superior and inferior vena cava as well as the pulmonary arteries. This is crucial to prevent the pitfall of unenhanced blood appearing similar to thrombus within the Fontan pathway. Various contrast administration techniques have been described. One approach involves simultaneous injection of contrast into the upper and lower extremities, with imaging performed during the early arterial phase. Alternatively, a delayed scan can be acquired after allowing for at least 70 seconds of contrast recirculation.

The same approach should be considered for patients with Glenn anastomosis. It is essential to avoid performing scans in both the arterial and early venous phases, as this can lead to suboptimal imaging. To prevent this, the bolus tracking method can be used to monitor the jugular veins. Once these veins are adequately opacified, the scanning can commence. This approach ensures a homogenous opacification of the Glenn anastomosis and pulmonary arterial branches (Fig. 3).⁴²⁻⁴⁵

Iterative reconstruction algorithms

Various techniques have been developed to lower radiation exposure in CT scans, including both technical improvements and specialized clinical practices like reduced-dose CT. However, technical approaches alone have not



Fig. 3 – The figure depicts a volume rendering technique, which clearly visualizes the Glenn anastomosis and pulmonary branches. The CT scanning was initiated after tracking the incoming contrast agent in the jugular veins.

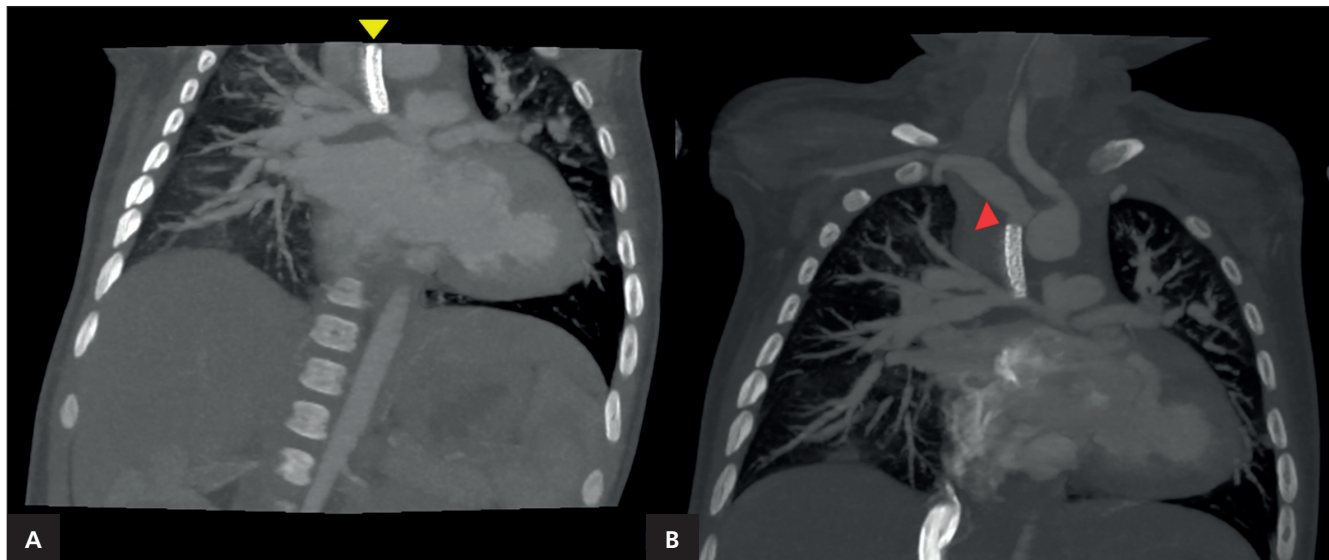
been enough to address the image quality issues caused by increased noise and artifacts in low-dose CT scans. Advances in computing power have now enabled the use of software-based iterative reconstruction methods that can simultaneously reduce image noise and improve overall image quality in CT.⁴⁶

Patient immobilization

Effective pediatric CT imaging necessitates the immobilization of infants and children during the acquisition process, in order to minimize motion artifacts and avoid



Figs 4A, 4B – Proper fixation of a newborn patient using a pediatric restraint tray and bands is crucial to minimize patient motion and avoid the need for repeated CT scans. (Blue arrowheads: fixation bands, red arrowhead: restraint tray.)



Figs 5A, 5B – Computed tomography angiography in a patient following a right-sided modified Blalock–Taussig shunt procedure. (A) Due to patient movement during the initial CT scan, a repeat acquisition was required, as the proximal portion of the shunt was not adequately visualized. (B) After repositioning the patient, the repeat scan allowed for complete depiction of the entire shunt structure. (Yellow and red arrowhead – modified Blalock–Taussig shunt.)

the need for repeat scans. As an alternative, immobilization devices can be employed to restrict movement throughout the image acquisition procedure (Figs 4, 5) (Table 1).⁴⁷

How do I do that?

Based on the author's experience, performing cardiac CT in children, manual scanning is the preferable method over automatic approaches. Contrast density in the vascular system can be challenging to evaluate automatically in the paediatric population due to variations in weight

and height. The radiologist should define the acquisition timing based on the specific pathology. They should closely supervise each scan acquisition, ensuring appropriate contrast visualization within the target vessels through careful preparation. The author prefers to place the region of interest(s) in the chamber(s), setting a target of up to 200 Hounsfield units, and initiate scanning once this value is reached by tracking the density curves. It is also important to consider a brief delay, approximately 2 seconds, between the command to start the scan and the actual scanning process.

Table 1 – Dose reduction techniques in pediatric cardiac CT angiography

Low-kilovolt imaging
Tube current modulation
Imaging without ECG-synchronisation/with prospective triggering
Rapid scanning using a wide-area detector
Reduction of Z-axis coverage and Z-overranging
Optimization of contrast agent administration
Iterative reconstruction algorithms
Patient immobilization
Photon-counting detector computed tomography
The integration of artificial intelligence

Using the bolus tracking method is desirable to set the monitoring time between 1.5–2 seconds, depending on patient’s size and heart rate. Extending this monitoring duration can decrease the radiation dose, as the density monitoring accounts for approximately 20% of the total radiation dose during each CT examination. Reducing the tube current from the vendor-recommended 50 mA to 20 mA in small patients can also help decrease the radiation dose during CT examinations (Fig. 6). When appropriate

CT parameters are used, the delivered dose of this scan technique is usually in the range of 0.5–2 mSv in children (unpublished data). The author has over 5 years of experience with a 320-row CT scanner (Canon Medical Systems), performing 100–150 CT examinations per year on patients with congenital heart disease.

A range of scanning modalities is available, with the most common being prospective and retrospective ECG-gating. Author’s preferred approach is prospective target mode with volume scanning encompassing 16 cm of the thorax, although this may not always be necessary and depends on the patient’s size. Helical scanning utilizing retrospective ECG mode is required for adolescent patients, though we aim to avoid this technique if possible. Additionally, scanning without ECG synchronization can also be an option if warranted.

The triphasic contrast injection protocol is the preferred technique, involving an initial bolus of full-strength contrast agent, followed by a contrast-saline mixture, and finally a normal saline flush. This approach helps to clear the intravenous tubing and central veins of dense contrast material, which can otherwise lead to streak artifacts in young children who receive lower total contrast volumes. For venous access, the right upper limb or lower limb is preferred, as the left upper limb should be avoided due to the potential for streak artifacts in the left brachiocephalic vein. The contrast agent administra-

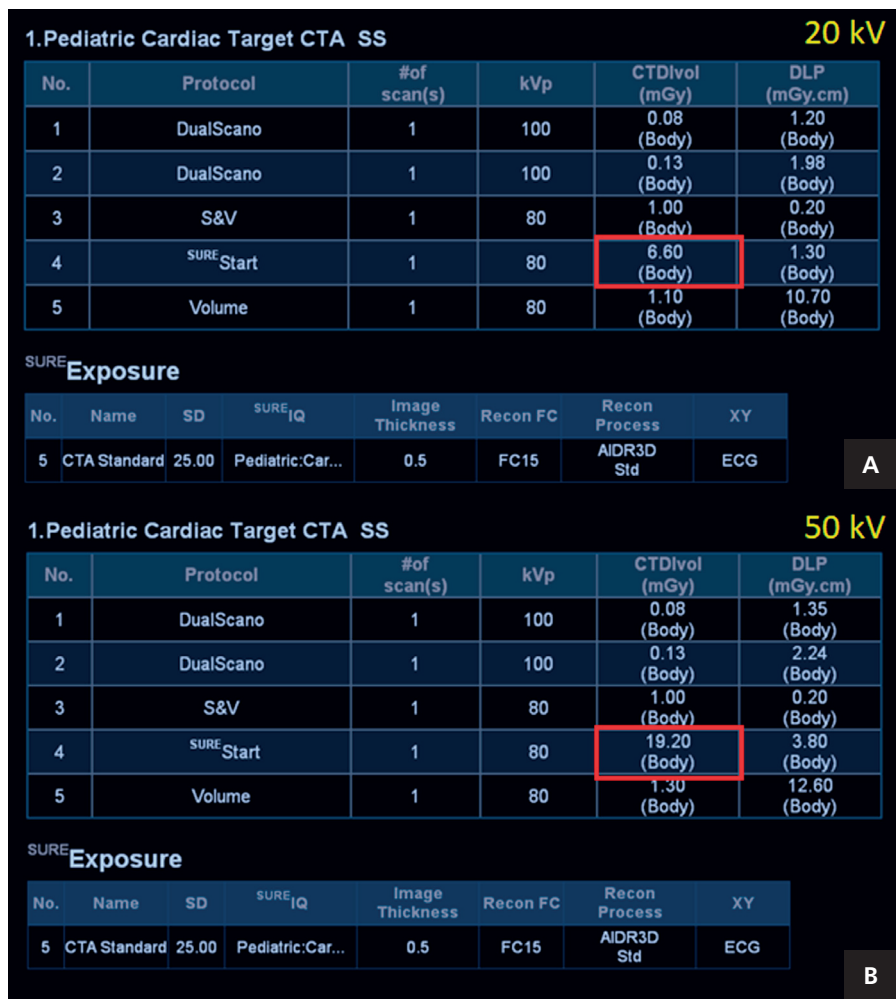


Fig. 6 – The figure presents a comparison of two bolus tracking approaches. Approach A utilized a tube current of 20 kV, while approach B employed a tube current of 50 kV. The difference in radiation dose between these two bolus tracking methods exceeds 60%.

Weight-based contrast dose (mL/kg)	1.5 × kg = total amount of contrast agent
	Injection rates (mL/s)
< 5 kg	Up to 1mL/s
5–10 kg	1,5–2,0 mL/s
10–20 kg	2,0–2,5 mL/s
20–30 kg	2,5–3,0 mL/s
>30 kg	~3,5 mL/s
>50 kg	~4,0 mL/s

tion rate should be tailored to the patient's size, with a rate of 0.7–0.8 ml/s typically used in newborns and up to 4.0–4.5 ml/s in adolescents (Table 2).

Future perspectives

Photon-counting detector computed tomography (PCD CT) represents an evolving modality that offers a viable alternative to traditional CT systems. Traditional computed tomography systems employ energy-integrating detectors, where each detector element absorbs incident X-rays and subsequently converts them into visible light. An electrical signal is consequently produced, its magnitude directly correlating with the visible light detected by a photodiode, as opposed to representing the energy of a discrete X-ray photon.^{48,49}

PCD CT has been described as offering improved spatial and contrast resolution, reduced electronic noise, less blooming, fewer metal and beam-hardening artifacts, and an increased iodine signal following contrast medium application.^{50–52}

Study of Hellms et al. reveals that pediatric cardiac computed tomography can achieve over a 40% reduction in radiation exposure while fully preserving both quantitative and qualitative image integrity. Furthermore, PCD CT technology did not exacerbate common artifacts, such as beam hardening, typically observed in lower-dose protocols, when compared to conventional CT scanners utilized for the assessment of congenital heart diseases.⁵³

The integration of artificial intelligence (AI) is currently revolutionizing medical imaging, yielding profound implications across virtually all facets of diagnostic imaging, encompassing modalities such as computed tomography. AI offers significant promise for lowering radiation exposure during CT scans. AI-driven technologies that automate patient centering and scan range definition enhance the precision of positioning and scan range, which in turn leads to reduced radiation doses and minimizes excessive scanning. AI methods have successfully tackled the balance between image quality and radiation dosage in CT imaging.^{54,55}

Discussion

The increased use of CT scans in children has raised concerns about long-term radiation risks. Children are more

vulnerable to radiation's harmful effects due to their longer lifespans, allowing more time for radiation-related issues to develop.^{1–3} A study by Pearce et al. found a significant link between CT radiation doses to the bone marrow and brain, and the subsequent incidence of leukemia and brain tumors.⁶ Technological advancements in CT, such as automated exposure regulation, adaptive tube voltage, optimized detectors, dynamic collimation, and iterative reconstruction, have significantly reduced radiation exposure for both adults and children while maintaining diagnostic quality. While some pediatric CT scans can be replaced by MRI to avoid radiation, the longer MRI times and enclosed environment often require general anesthesia for infants and young children.

Cardiovascular imaging with computed tomography is the optimal diagnostic modality for various clinical indications. However, it should only be used for patients who need to visualize the coronary arteries or are critically ill, as the long duration of MRI can worsen their condition. MRI should be reserved for stable patients.^{7,8} When performing CT scans on children, who are sensitive to radiation, dose reduction is crucial. This can be achieved through low tube potential settings, ECG-based tube current modulation, and anatomic-based tube modulation. Additionally, iterative reconstruction algorithms enable a reduction in tube current and radiation dose while maintaining acceptable image quality. Advancements in detector technologies have contributed to reducing radiation exposure in pediatric CT imaging. Utilizing lower x-ray tube potentials is one of the most effective methods for minimizing radiation dose. Lowering the tube potential decreases photon flux and increases tissue attenuation of lower-energy photons, which elevates image noise. This typically requires increasing the tube current to maintain the desired image quality. Using a lower tube potential during contrast-enhanced CT examinations can enhance the iodine contrast-to-noise ratio, leading to greater contrast attenuation. The increased contrast-to-noise ratio offers an additional benefit for cardiac CT, as it enables the use of a reduced volume and/or injection rate of iodinated contrast agent due to its enhanced attenuation at a lower tube potential. This can be advantageous for very small newborns or infants who can only receive a minimal amount of contrast material.^{26,27} Tube current modulation or automatic exposure control is a beneficial technique that adjusts the CT radiation dose based on the patient's physical characteristics, such as body size, shape, and tissue density. Reducing the tube current to 10–20 mAs during the bolus tracking phase can significantly decrease the overall radiation exposure, as this phase accounts for approximately 25% of the total radiation dose in pediatric CT examinations.²⁹ When feasible, CT scanning without ECG synchronization is recommended. This technique encompasses the assessment of all extracardiac thoracic vascular structures, excluding the aortic root and pulmonary trunk root, which are susceptible to motion artifacts. Conversely, ECG-synchronized imaging is essential for comprehensive evaluation of coronary artery morphology and detailed assessment of intracardiac structures. When ECG synchronization is employed, the CT scanning modality with the lowest radiation exposure should be utilized, such as prospective ECG-

gated acquisition targeting a specific phase of the cardiac cycle. Another option is to employ rapid volumetric scanning using a wide-area detector, which can capture up to 16–32 cm of the thorax within a single gantry rotation. This technique can be highly beneficial for imaging newborns with elevated heart rates. In certain cases, such as patients with coarctation of the aorta or subvalvar aortic obstruction, it is possible to reduce the radiation dose by tailoring the CT scan range to individual clinical requirements. It is not always necessary to cover the entire thorax; instead, the CT examination can be focused on the specific region of interest. This approach is effective because the CT radiation exposure is directly proportional to the scanning range, assuming all other CT parameters remain constant. However, this technique may not be applicable for patients with total anomalous pulmonary venous drainage or those with multiple aorto-pulmonary collaterals, which require a more comprehensive assessment. Optimizing the contrast agent administration helps achieve homogenous opacification in the area of interest, avoiding the need for repeat scans. Radiologists must understand the complex hemodynamics in patients with congenital heart defects and after their surgery. Furthermore, effective pediatric CT imaging necessitates the immobilization of infants and children during the acquisition process. This is essential to minimize motion artifacts and avoid the need for repeat scans.^{34–38}

Conclusions

Numerous techniques exist to minimize radiation exposure during pediatric cardiac CT imaging. Therefore, radiologists performing these examinations should be well-versed in these methods. Reducing the radiation dose is paramount when imaging children. When feasible, alternative modalities such as MRI or transthoracic echocardiography should be utilized in lieu of CT scanning.

Conflict of interest

None.

Funding

No funding was provided.

Ethical statement

The presented study followed international and national regulations and was in agreement with the Declaration of Helsinki, and ethical principles.

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