Contrast-Enhanced Ultrasound of the Brain

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An ultrasound (US) is a type of medical imaging that is commonly used in pediatric radiology due to its multiple advantages for the imaging of young patients. Advancements in technology have allowed the use of contrast-enhanced ultrasounds (CEUS) with high-frequency transducers, which in turn, led to new possibilities in diagnosing a variety of diseases and conditions in the field of radiology, including neonatal brain imaging. CEUS overcomes some of the limitations of conventional US and Doppler US. It allows the visualization of dynamic perfusion even in the smallest vessels in the whole brain and allows the quantitative analysis of perfusion parameters.

brain contrast-enhanced ultrasound (CEUS) imaging

1. Introduction

The most widely utilized ultrasound contrast agent (UCA) is SonoVue® (Bracco, Milan, Italy), which is marketed as Lumason® in the USA. This UCA is made up of tiny bubbles (i.e., microspheres) made of sulfur hexafluoride gas enclosed by a layer of phospholipids on the outside. When they are exposed to a US pulse, these microbubbles vibrate and reflect strong signals. Imaging is carried out at low acoustic power, typically using a mechanical index (MI) below 0.1, and a high frame rate. If the MI is too high, it can cause the microbubbles to rupture, resulting in suboptimal enhancement. SonoVue® is a blood pool agent that remains within the intravascular space. Because of the small size of the microbubbles, which are less than 6 µm, they can reach even the smallest capillaries when injected intravenously (IV). The core of the microsphere is a harmless gas that is excreted through the lungs. The phospholipid microbubble shell is broken down and excreted through the liver. The majority of the applied dose of UCA is eliminated from the body in a few minutes [1].

2. Safety Considerations

UCAs are very safe, with the frequency of adverse events lower than that of other contrast agents (i.e., CT and MRI contrast agents) [2][3]. Additionally, the rate of contrast-related adverse events in children is lower than it is in adults [4]. A recent meta-analysis of nearly five thousand IV CEUS examinations of children reported that adverse events were rare, and most of them were not severe [5]. Mild adverse events, such as a headache, nausea, altered taste, tinnitus, light headedness, urticaria, and hyperventilation, were reported in only 1.1% of the IV examinations. Severe adverse events, such as anaphylactic reactions, were extremely rare, occurring in only 0.2% of the IV examinations. Nonetheless, a contrast reaction kit should be available nearby whenever one is performing any examination with IV contrast media, including CEUS [6].

CEUSs have unique safety concerns related to bioeffects. In theory, if the MI used is too high (MI > 1.9), the microspheres may rupture during oscillation, potentially causing damage to the adjacent cells. This process is called sonoporation or microcavitation [7][8]. The oscillation of microbubbles may also cause tissue heating due to acoustic energy dissipation. However, these bioeffects occur only with high dosages of UCA, long pulse lengths, and high MIs and should not occur during diagnostic examinations due to safety precautions incorporated into the US machines designed for diagnostic use [7][9].

In the USA, the IV use of UCAs by children was approved by the FDA in 2016 for the characterization of liver lesions. In Europe, the use of UCAs by children is only registered for intracavitary use in the diagnosis of vesicoureteral reflux; therefore, the IV use of UCAs is off label. However, in its 2011 recommendations, the European Federation of Societies for Ultrasound in Medicine and Biology (UFSUMB) recommended the off-label use of UCAs by children for many other indications as well, including IV use, due to their proven effectiveness and safety [10][11]. At the same time, it should be emphasized that a large proportion of medicines taken by children are used off label.

3. Contrast-Enhanced Ultrasound (CEUS) Technique

Before performing a CEUS, it is important to perform a detailed grayscale US examination to evaluate the region of concern. This initial assessment can be beneficial in customizing the subsequent CEUS protocol. Most newer US scanners have the ability to perform CEUS imaging. CEUS imaging is typically performed using a contrast-specific mode with a dual-display option. This allows the concurrent viewing of a grayscale and contrast-only image. To achieve the best detection of microbubbles, the gain setting should be barely above the noise floor, which ensures that only the microbubbles are visualized [12]. The choice of a transducer depends on the location and vascularity of the examined organ and the size of the patient. For larger and older children, convex transducers with lower frequencies are used, while neonates and infants with superficial lesions require convex transducers with higher frequencies or linear transducers. However, due to the microbubbles' size and their oscillating frequency, using higher-frequency transducers results in a suboptimal image, which, in turn, requires a higher dose of the UCA to compensate for it [13].

Note that a CEUS is not only a still image technique. A CEUS is a real-time imaging technique that allows the visualization of blood flow and contrast agent distribution over time. Therefore, typically, a CEUS examination is conducted recording a cineloop. For CEUSs with the IV application of UCA, two people are typically needed, with one person acquiring the US images or cineloop, while the other prepares and administers the UCA through a central or peripheral line. The dose for pediatric IV administration approved by the FDA is 0.03 mL/kg up to 2.4 mL. The application of a UCA can be repeated once during the examination [14]. After injecting the contrast bolus, the examiner flushes the IV cannula with normal saline to push any remaining UCA through the vein and activates the timer to capture a continuous cineloop of 60–120 s. It is important to maintain the same US scan settings during image acquisition to accurately quantify the vascular perfusion parameters. In cases of a repeated examination, it is necessary to allow enough time between the injections for the UCA to clear from the body, which is usually 10–15 min [15]. The quantitative assessment of contrast kinetics can be achieved using specialized software that

analyzes US images and cineloops to calculate various imaging parameters, such as the peak enhancement, time to peak enhancement, the area under the curve, regional blood volume, regional blood flow velocity, and slopes of the ascending and descending curves [16].

Brain CEUS examinations are conducted using high-frequency curved-array transducers with a frequency range of 2–11 MHz. Typically, a smaller probe that fits well within the space of the open fontanelle of an infant is used. Linear array transducers with a frequency range of 8–20 MHz are used for evaluating the extra-axial space and superficial brain structures. The image settings are optimized before contrast injection, with a low MI during CEUS to ensure microsphere stability. The gain is adjusted to ensure minimal background noise before contrast administration. A cineloop is obtained in the mid-coronal plane with the basal ganglia in view. A sweep of the entire brain is then conducted to screen the rest of the brain parenchyma. An additional microbubble injection can be used to perform a sweep through the entire brain or a specific region of interest during peak enhancement for re-evaluating or validating the findings [17][18]. For known regions of abnormality, dedicated static images and cineloops can be obtained.

4. Quantification Methods

Quantification methods can be used to measure tissue perfusion using time–intensity curve analysis. This method evaluates changes in the signal intensity over time in a region of interest, allowing for the quantification of various perfusion kinetics parameters. These parameters include the time to peak, wash-in slope, peak intensity, wash-in and washout area under the curve, and the washout slope. These parameters can be visually displayed as a color-coded map [19][20]. In a normal brain, the peak enhancement is typically achieved within 15–20 s of administering the microbubble injection, but this timing can vary depending on various factors [17]. Washout, which refers to the clearance of microbubbles from the region of interest, can occur within 10 min of administering the injection, but it may be delayed in the presence of a brain injury or other factors [21].

Another method for measuring tissue perfusion is the infusion-based destruction-replenishment method. This method involves destroying microbubbles in the field of imaging using a short acoustic pulse and studying the replenishment kinetics as circulating microbubbles flow back into the same region [22].

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