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Lung Ventilation/Perfusion Single Photon Emission Computed Tomography (SPECT) in Infants and Children with Nonembolic Chronic Pulmonary Disorders

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Single photon emission computed tomography (SPECT) provides high contrast three dimensional images of the regional distribution of a radiotracer. SPECT is a widely used technique in pulmonary investigations of the ventilation (V) and perfusion (Q) in the adult patient, mainly in the diagnosis of pulmonary embolism. However, safety concerns among practitioners due to radiation exposure and the use of macroaggregate albumin for the perfusion scan have historically precluded the use of SPECT in pediatric patients with nonembolic pulmonary disorders. Additionally, patient cooperation at ventilation tracer administration and image artifacts from patient movements due the long acquisition times, have further limited the application of SPECT in pediatric patients. With the introduction of technegas aerosol for ventilation studies and the use of high sensitive multihead gamma cameras, both the total amount of administered activity and acquisition time have drastically been reduced allowing the application of SPECT in pediatric patients. Modern hybrid gamma camera/computed tomography systems (SPECT/CT) also brings the possibility of adding a fully diagnostic CT to the SPECT images, incrementing the clinical value of the investigation. Besides pulmonary embolism, there is now some clinical evidence that lung SPECT has diagnostic value in several pulmonary pathologies causing V/Q mismatching, which are specific to the pediatric age group. In this work, we will exemplify and briefly discuss some of these applications based on the literature and our routine clinical experience. Consideration to the risks and safety aspects associated to performing pediatric V/Q SPECT are also discussed.
Semin Nucl Med 49:37-46

Introduction

Pediatric nuclear medicine has its roots in the early 1940s with studies of the thyroid uptake of radioiodine in children using Geiger-Müller tubes.[1] Thereafter, with the development of the gamma camera[2] and the clinical introduction of Technetium-99m (^{99m}Tc),[3] the use of radioisotopes imaging (RI) in children become clinical routine in studies of the skeleton, kidney function and brain. RI studies of the pulmonary physiology of ventilation (V) and perfusion (Q) distribution and their V/Q matching in the adult patient, were also reported early in the development of nuclear medicine.[4-7] Even though the variety of possible indications for pediatric lung scintigraphy is much wider than in adults,[8-11] the use of radioactive gases such as Xenon-133 (^{133}Xe) and Kryptom-81m (^{81m}Kr) for ventilation studies[12] and Technetium-99m labeled human macro albumin particles ([^{99m}Tc]MAA) for perfusion studies, have historically raised many safety concerns among practitioners. These concerns were mainly related to the relatively high radiation doses involved in a V/Q examination, (mainly associated to the use of ^{133}Xe), the nonphysiological behavior of ^{133}Xe, and the safety in administering MAA particles. Further, the need of children cooperation for continuous administration of these radioactive gases, the lack of nuclear medicine equipment suited for pediatric patients, the high costs and low availability of ^{81m}Kr and the arguably

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https://doi.org/10.1053/j.semnuclmed.2018.10.006
0001-2998/

diagnostic quality of two-dimensional (planar) imaging (static or dynamic) at low activity levels, have further limited the application of lung scintigraphy imaging in infants and children. This did not change even with the advent of SPECT,[13,14] which allows for a better image contrast (higher sensitivity) and three-dimensional detection of the radioisotope distribution. Consequently, lung scintigraphy (planar or SPECT) is to date not a commonly performed pediatric nuclear medicine investigation.[15] The clinical value of pediatric V/Q-SPECT is therefore still unknown for many conditions and published data is scarce.

The development of technegas (Cyclomedica, Sydney, Australia), a suspension of ultrafine carbonaceous particles labeled with ^{99m}Tc in argon gas,[16] opened the possibility to perform lung ventilation SPECT studies. The small particle size at nanometer (nm) range is well suited for lung ventilation studies and results in high and persistent alveolar deposition with less impaction in central airways, as compared to ^{99m}Tc labeled diethylenetriamine-pentaacetic acid aerosol ([^{99m}Tc]DTPA). Further, the technegas high labeling efficiency with fixed alveolar deposition, are optimal characteristics to perform V-SPECT studies. However, the application of technegas in pediatric patients has been limited by both, the need of patient cooperation and the negative effect in oxygen saturation at administration, causing hypoxemia. Modifications of the first generation of a commercial technegas generator were carried by Sanchez-Crespo et al,[17] enabling technegas administration to infants and children. This pioneering work enables a passive technegas administration while keeping arterial oxygen saturation stable during administration. Further reduction in aerosol mean particle size (less than 100 nm) ensured adequate alveolar deposition of the ultrafine particles. This modified technegas generator in combination with a modern high sensitivity multihead gamma-cameras, capable of performing SPECT (and SPECT/CT) with short acquisition times, allows the application of V/Q SPECT in infants and children. The functional information of the regional distribution of V and Q and V/Q matching clearly outperforms the restricted anatomical information of a single chest x-ray (up to date the diagnostic golden standard for most pediatric pulmonary conditions). Besides pulmonary embolism, there is now some clinical evidence that lung V/Q SPECT has diagnostic value in several pulmonary pathologies causing V/Q mismatching, which are specific to the pediatric age group. In this work, we will exemplify and briefly discuss some of these applications based on the literature and our routine clinical experience. Consideration to the risks and safety aspects associated to performing V/Q-SPECT at infancy and childhood are also discussed.

SPECT in the Management of Infants with Bronco Pulmonary Dysplasia

Bronco Pulmonary Dysplasia (BPD) is a common chronic lung disease in infants and the major morbidity in extreme preterm and surviving infants with congenital diaphragmatic hernia.[18] Advances of neonatal care have resulted in a remarkable improvement in survival rates of preterm born infants over the past decade, to the cost of an increasing prevalence in BPD. Many issues regarding diagnosis and management of BPD are still unclear and most of these infants will grow up with an uncertain pulmonary future. Based on planar perfusion scintigraphy imaging, Soler et al[19] showed that the number of perfusion defects correlated with the severity of BPD. However, clinical severity grading based on oxygen demand at 36 weeks' postmenstrual age is known to have low predictive value for future pulmonary morbidity.[20] In a recent prospective SPECT study in 6-month postmenstrual age BPD neonates, Kjellberg et al[21] revealed that there are significant lung abnormalities in the V/Q distribution, even in patients who were originally clinically graded as mild or even listed as no-BPD in control studies. Further, this study also shows that patients clinically graded as severe BPD could also show a normal V/Q distribution. Hence, oxygen requirement for these patients may not be related to BPD. These findings reflect the high sensitivity of SPECT, compared to planar scintigraphy, in detecting regional pulmonary abnormalities. The specificity is however low because SPECT alone cannot identify the cause of these V/Q abnormalities as a variety of other cardio respiratory pathologies can lead to V/Q mismatch. The results presented by Kjellberg et al expose problems with the current clinical categorization and management of today's babies suffering from BPD and the need to incorporate lung SPECT in the neonatal care. Figure 1 shows the SPECT maximum intensity projections in two patients clinically graded as mild BPD (A and B) and two patients clinically graded as severe BPD (C and D), all at 6 months postmenstrual age. Figure 2 shows the corresponding lung V/Q ratio distributions. These distributions are centered approximately on V/Q = 1.0 but with different widths and degrees of skewness, representing deviation from a normal V/Q distribution as seen in healthy individuals.[22-25] For these patients, Table 1 shows the percentage of the total functional lung volume with matched V/Q, which to be consistent with previous publications[17,21,26] is computed in the interval [0.6-1.4]. As Figures 1 and 2 and Table 1 revealed clinical grading at 36 weeks' postmenstrual age is not necessarily correlated to the regional V/Q ratio distribution as measured with SPECT at 6 months postmenstrual age. Particularly patient C have more than 75% of the total lung volume with matched V/Q ratios. This value is comparable with the results obtained in young healthy individuals.[22,25] This result is in contradiction with the patients BPD grading at 36 weeks postmenstrual age. Likewise patients B and D have much lower percentage of total lung volume with matched V/Q ratios, which for patient B is also in contradiction with the initial clinical grading. Thus the clinical value of V/Q SPECT in this patient group is the possibility of excluding BPD (with normal V/Q scan).

SPECT in the Follow-up of Infants and Children with Congenital Malformations

Congenital Diaphragmatic Hernia

Survivors of Congenital Diaphragmatic Hernia (CDH) repair may develop long-term pulmonary sequelae in the form of vascular pulmonary hypoplasia and BPD. Lung scintigraphy is a particularly well-suited imaging technique for the follow-up of this group of patients. Planar lung scintigraphy in CDH children has been performed to determine the degree of

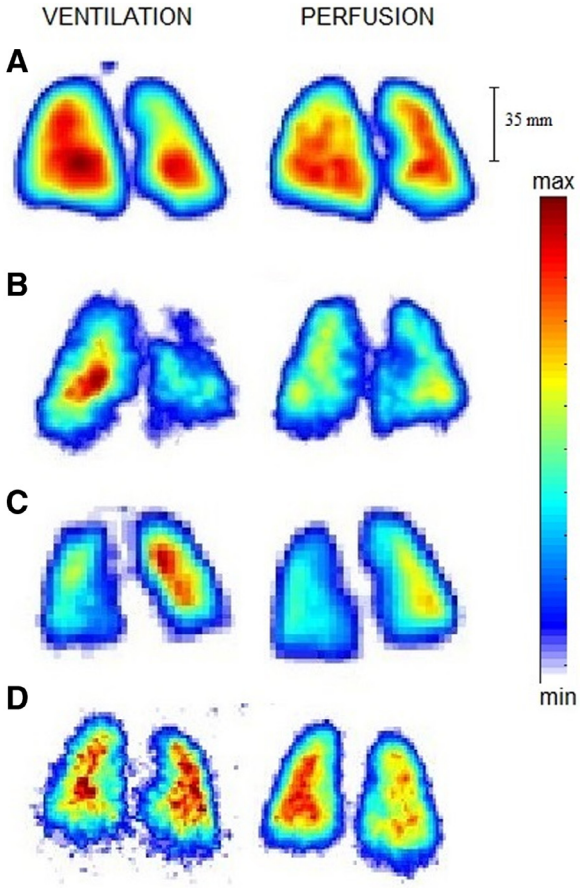

Figure 1 Lung ventilation and perfusion maximum intensity SPECT projections in four different, 6-months old preterm-born infants clinically graded with a mild (patients A and B) and severe (patients C and D) bronco pulmonary dysplasia.

bilateral pulmonary asymmetry of the V and Q distributions after surgical repair.[27-32] More recently V/Q SPECT was performed on a set of survivors to CDH repair at the mean age of 6 months.[26] This study revealed varying degrees of V/Q abnormalities which correlated with the presence of pulmonary artery hypertension. Furthermore, this study also found that patients treated on extracorporeal membrane oxygenation, representing a risk factor, showed more V/Q abnormalities and asymmetrical Q distribution. Okuyama et al[33] presented a long-term longitudinal study in CDH survivor using planar scintigraphy. In this study, the variation of V and Q of the ipsilateral lung expressed as a percentage of that of the contralateral lung measured postsurgically at hospital discharge and 1 year later were monitored. The results revealed that V and Q of the ipsilateral lung are significantly lower in patients presenting pulmonary morbidity compared to the patients without pulmonary morbidity one year after repair. Following these results, lung scintigraphy and particularly SPECT is recommended at our institution for the clinical follow up of high risk CDH survivors to predict long-term pulmonary morbidity. Figure 3 shows an example of SPECT investigation in the follow up of two left-sided CDH survivors, with normal right/left lung-side V and Q distribution (patient A) and absence of both V and Q in the left lung-side (patient B). Quantitatively, patient A shows a right/left ratio of 1.3 and 1.4 for Q and V, respectively. These ratios become basically one after lung volume difference normalization. Additionally, about 96% of the total lung volume has matched VQ ratios in the interval [0.6-1.4]. For patient B, all pulmonary blood flow and ventilation is located in the right lung-side. Further, approximately 94% of the total right lung has matched V/Q ratios in the interval [0.6-1.4]. Hence, the clinical value of V/Q SPECT is very high, as patient

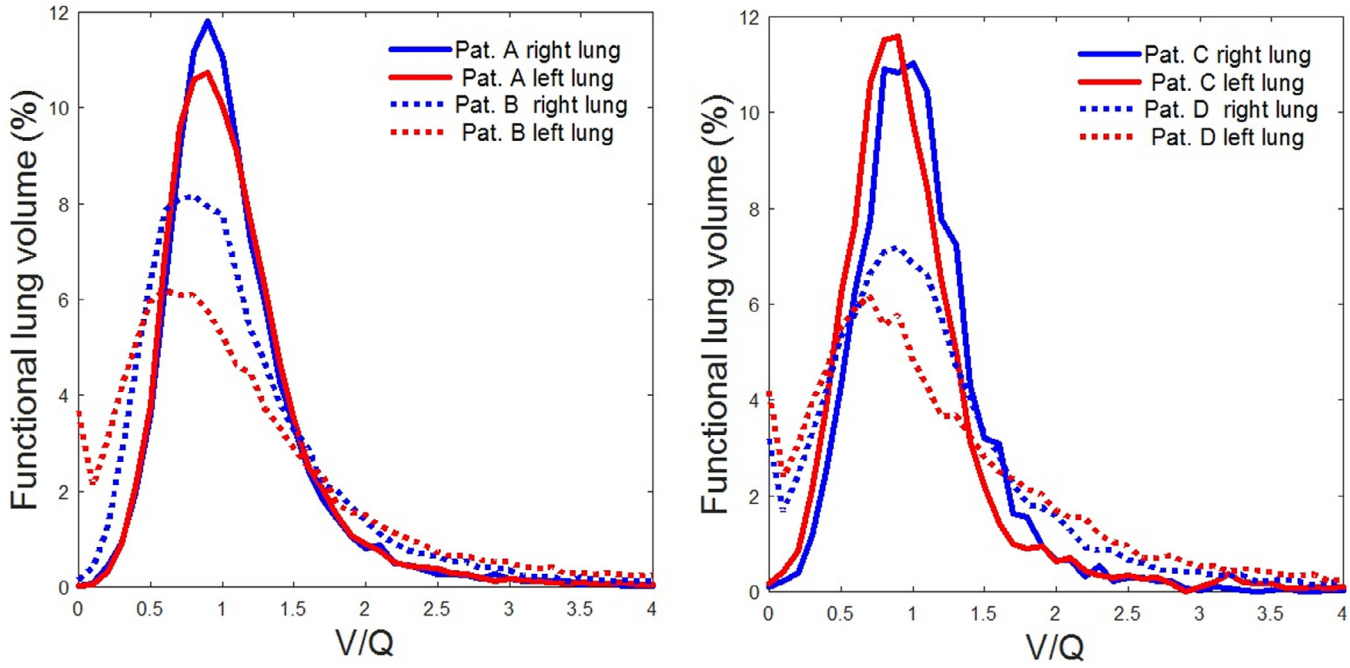

Figure 2 Distribution of the SPECT measured Ventilation/Perfusion ratio (V/Q) in the right and left lungs of the four patients shown in Figure 1.

Table 1 SPECT Derived Percentage of the Right and Left Lung Volumes with Matched V/Q Ratios in the Interval [0.6-1.4] for the Four BPD Patients of Figure 1

	BPD Clinical Grading at 36 Weeks Postmenstrual Age	Functional Lung Volume with Matched V/Q	
		Right (%)	Left (%)
Pat. A	Mild	76	75
Pat. B	Mild	60	45
Pat. C	Severe	77	75
Pat. D	Severe	55	43

management may change upon the V/Q results. Particularly, patient B has no pulmonary redundancy capacity and is in need of tighter controls to avoid lung infections.

Tetralogy of Fallot's Anomaly

Tetralogy of Fallot's Anomaly (TOFA) is a congenital heart disease associated with several abnormal pulmonary blood flow patterns in children. In patients with combined TOFA and CDH (or even lung hypoplasia), the anatomical size of the pulmonary artery and the corresponding perfusion distribution at the capillary bed may not be correlated. The goal with SPECT imaging in this group of patients is to measure asymmetry of pulmonary perfusion and V/Q imbalance after initial repair.[28,34] Following TOFA repair, lung V/Q- SPECT in combination with pulmonary arteriography should be the investigations of choice to help the practitioner in the decision making for disease management.[35] Figure 4 shows the results of a V/Q-SPECT/CT in a patient with TOFA. As this figure shows in the left panel, the V distribution and the lung parenchyma (as shown in the CT images) are normal, while there was no perfusion on the left lung-side. Furthermore the V/Q distribution was also normal in the right side. For this group of patients, the V/Q SPECT may be decisive for the correct management of the disease.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is a condition characterized by shunting of pulmonary blood past the lung capillary bed. This is caused by elevated vasoactive humoral substances (like NO) secondary to hepatic disease. In this situation Q-SPECT may not show the degree of shunting. The MAA particles will pass the lungs (or portions of the lungs) to the systemic circulation and accumulate in richly perfused organs, especially the brain and kidneys.[36] This provides a theoretical basis for quantification of the shunt, by making a whole-body planar image registration after administration of [^{99m}Tc]MAA and comparing the lung uptake with the extrapulmonary activity. A homogeneous general pulmonary blood shunt will not be detectable at Q-SPECT alone, since we cannot directly correlate the pixel-wise intensity of the Q_SPECT images with the actual total cardiac output. However, local pulmonary shunts are visible at V/Q examinations in regions with normal distribution but with absent Q. Figure 5 exemplifies this in a 7-year-old patient with hepatopulmonary syndrome. The SPECT results show a total absence of perfusion in the anterior-basal portions of the lungs while there is normal ventilation distribution in the entire lungs. These Q-defects are also observable in the skewed V/Q distribution toward high V/Q ratio values as shown in Figure 5. Hence V/Q SPECT/CT is then crucial in order to confirm pulmonary shunt and no other lung disorders, which may preclude from liver transplantation.

SPECT in Children with Postinfectious Bronchiolitis Obliterans

This is a rare condition in childhood characterized by the constriction or complete obliteration of small airways due to a severe inflammation. Very few clinical data on the value of V/Q scintigraphy on Bronchiolitis Obliterans (BO) is found in the literature and the indication for SPECT in postinfectious BO is not well documented. Xie et al,[37] published an interesting prospective study on 25 children postinfectious BO at a mean age 41 months, using planar V/Q scintigraphy. The authors provide evidence that the degree of V/Q abnormalities can be used to assess disease severity and may be predictive of patient's outcome. Based on this result, we use V/Q SPECT/CT at our institution to determine the need for pulmonary lobectomy.

V/Q Lung Scintigraphy in Other Pediatric Pathologies Affecting Normal Lung Function

There are some published data on the use of planar lung scintigraphy for different non-PE pediatric lung conditions such as intrapulmonary right to left shunt,[38,39] bronchiectasis,[40] pneumonia,[41,42] sequelae of foreign body inhalation,[43] and emphysema.[44] Planar lung scintigraphy has higher sensitivity than chest radiographs to determine the extent of parenchymal disease and air trapping in children with congenital cystic fibrosis.[8,45-48] Komori et al,[49] using ^{133}Xe and [^{99m}Tc]MAA planar imaging, revealed that children with cystic fibrosis younger than 1 year of age at the time of pulmonary lobectomy, showed significantly lower air trapping compared with patients who were older at surgery. Using SPECT, Donnelly et al[50] showed that morphologic changes depicted by high resolution computed tomography correlate with decreased lung perfusion.

Safety and Risk/Benefit of V/Q SPECT in Infants and Children

Patient Hypoxia at Technegas Administration

As previously mentioned, the administration of technegas aerosol suspended in Argon to an infant can cause

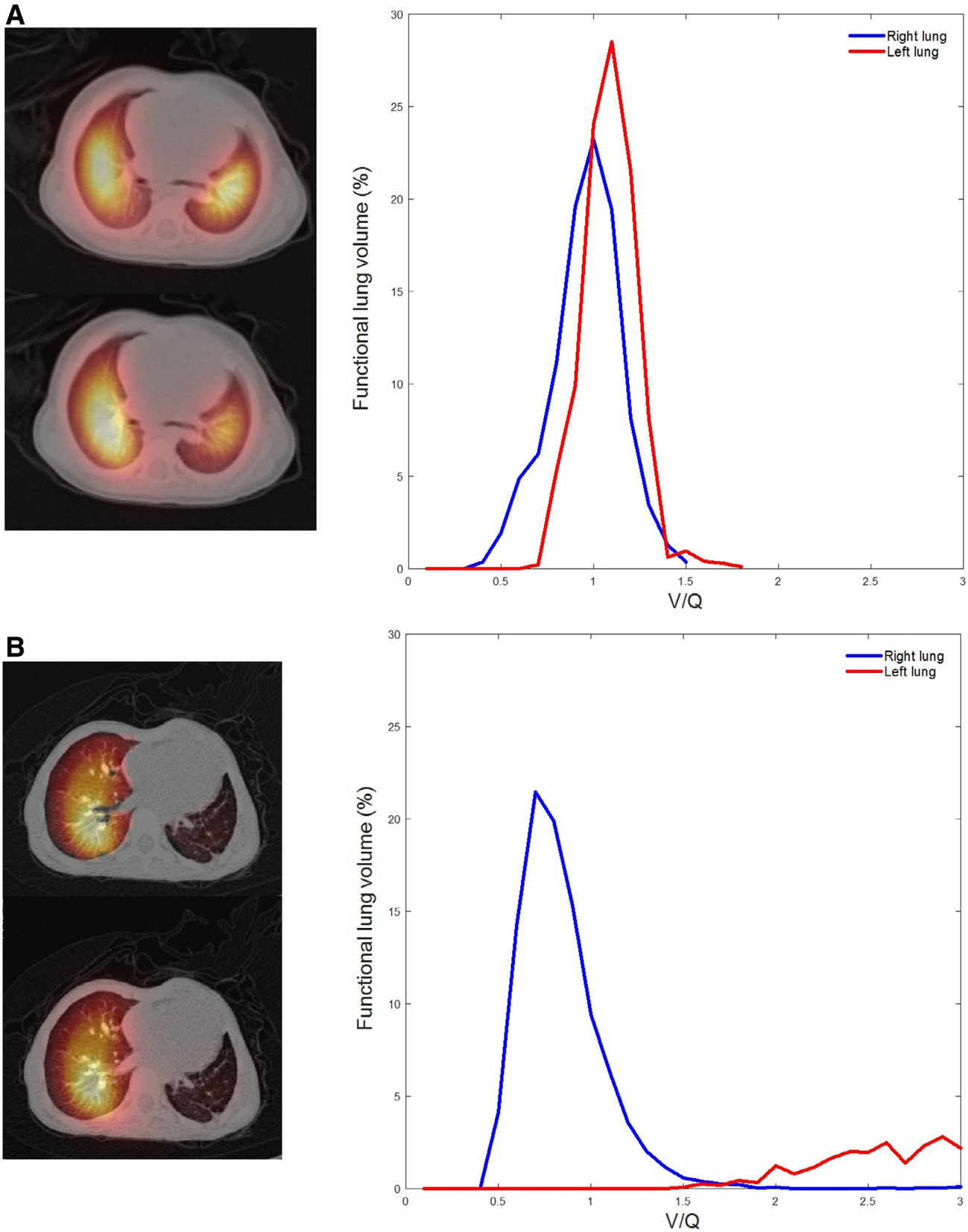

Figure 3 Left panel, transversal section at mid-lung of the fused SPECT/CT of the ventilation (on top) and perfusion (on the bottom) in two left-sided survivors of CDH, patients A and B (3- and 7-year old, respectively). The right panel reveals the corresponding total volume functional V/Q ratio distributions.

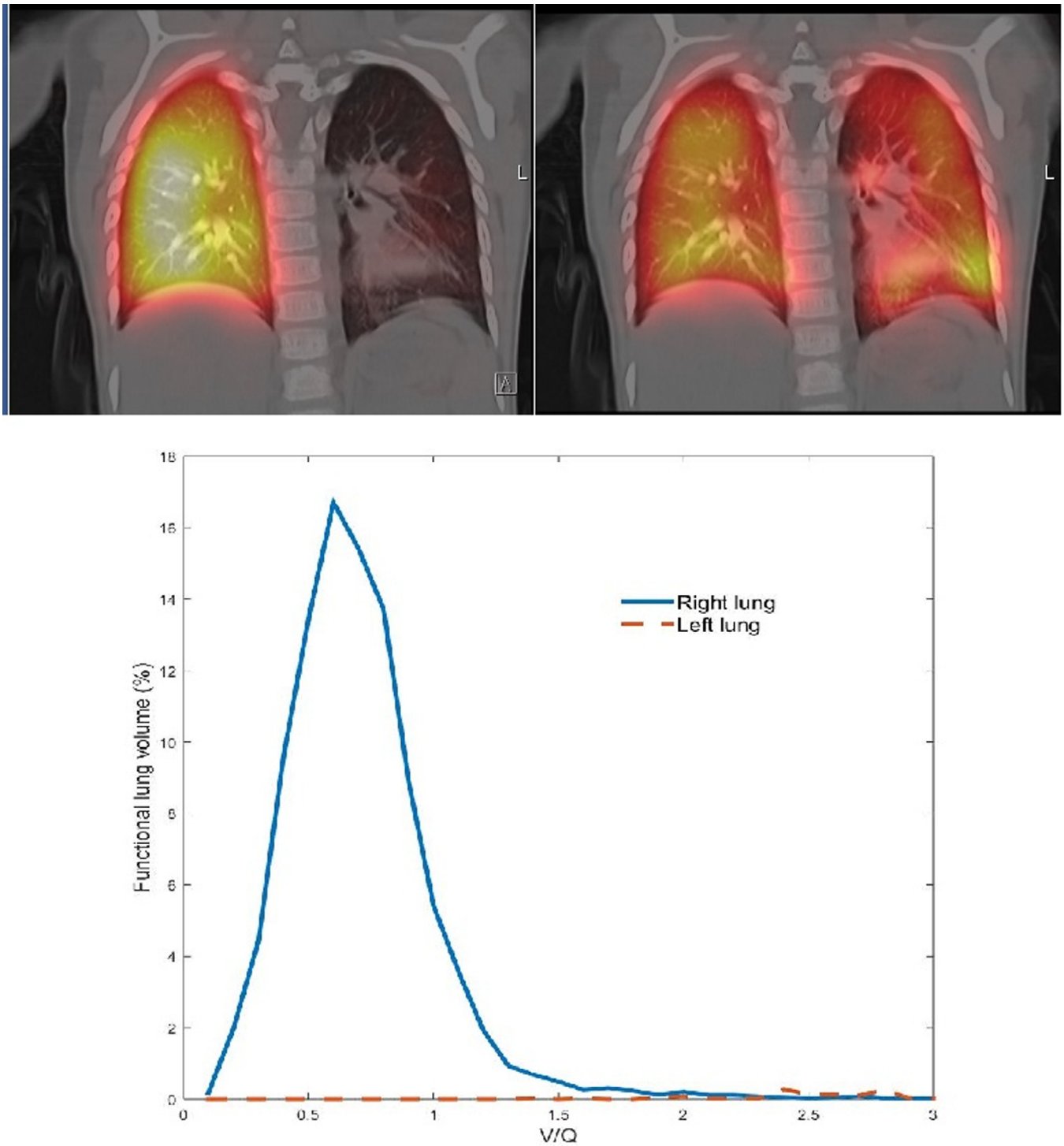

Figure 4 Upper panel, coronal section of the fused SPEC/CT of the pulmonary perfusion (left) and ventilation (right) distributions in a 5-year-old patient with Fallot anomaly. The bottom panel shows the corresponding total lung volume functional V/Q ratio distribution.

hypoxemia. To avoid this problem, air with oxygen and Technegas aerosol can be mixed as described by Sanchez-Crespo et al,[17] and flowed continuously toward the facemask of the patient at approximately 6-10 L/min. Alternatively, short intervals of Technegas administration followed by air with oxygen should be alternated to keep normal oxygen saturation levels.

Safety at Administration of MAA Particles

The number of MAA particles shall be adjusted to the patient size and the presence of cardiac right-to-left shunts and pulmonary hypertension. MAA particles temporarily occlude a few per thousand of the total number of capillaries of the pulmonary bed. These microembolisms are in direct proportion to the local blood flow and will fragment in the

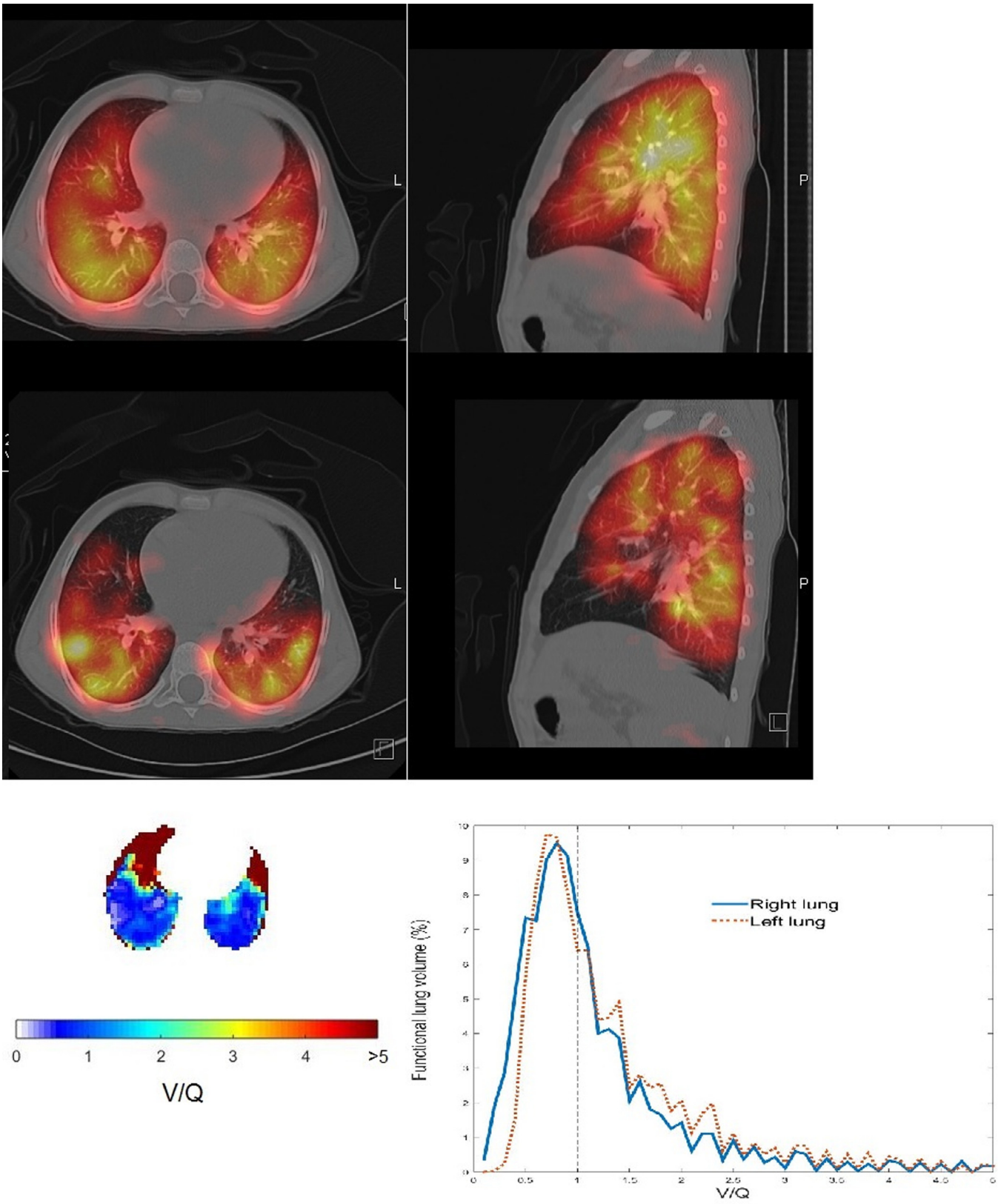

Figure 5 Pulmonary ventilation and perfusion fused SPECT/CT in a 7-year-old patient with pulmonary blood shunting. The first row represents the ventilation distribution in selected transversal and sagital sections. The second row shows the corresponding perfusion distribution. The third row shows to the left, the corresponding V/Q ratio of the selected transversal section and to the right, the total lung functional V/Q ratio distribution.

Table 2 Sample Calculation to Determine the Lifetime Attributable Risk of a Radiation-Induced Cancer (LAR) in Pediatric Patients, due to Radiation Exposure from a Ventilation Perfusion SPECT Scan at Different Ages

	1-year-old Infants	10-year-old Children
Reference weight (kg)	10	32
Administered Tc99m-MAA (MBq)*	$5.6 \times 2.71 = 15.2$	$5.6 \times 7.29 = 40.8$
Administered Technegas activity (MBq)†	5.1	13.6
Total effective dose equivalent (mSv)‡	$(0.063 \times 15.2) + (0.087 \times 5.1) = 1.4$	$(0.025 \times 40.8) + (0.03 \times 13.6) = 1.43$
LAR§	$\frac{1}{700} \times \frac{1.4}{10} = \frac{1}{5000}$	$\frac{1}{1000} \times \frac{1.43}{10} = \frac{1}{6993}$
Number of individuals that naturally will die from cancer‖	1100/5000	1538/6993

*According the EANM pediatric dosage card; Baseline activity (MBq) × Multiplier.
†One third of the Tc99m-MAA activity.
‡ICRP 53[60].
§Sex average, attributable risk levels of 1 in 700, 1 in 1000 for 1- and 10-year old, respectively, from a 10 mSv exposure (Fahey et al[54]).
‖22% in the United States (Fahey et al[54]).

following 24 hours, primarily by mechanical erosion, as a result of the systolic-diastolic pulse pressure in the capillaries, and enzymatic degradation. Eventually the small fragments will translocate to the circulatory system where they are removed by phagocytosis and pinocytosis. The adverse effect of MAA is related to particle size, particles larger than 100 micrometers can block bigger blood vessel, with the risk for increasing pulmonary blood pressure. At our institution, we use Technescan LyoMAA (Mallinckrodt Medical BV, The Netherlands). In this product 95% of the particles are in the range 10-90 micrometers. A vial of LyoMAA contains 2 mg of human serum albumin in the form of 4.5×10^6 particles. For pediatric applications, we label LyoMAA with about 3.5 GBq of ^{99m}Tc in 10 ml final product. This results in a total number of administered particles between 2×10^5 and 5×10^4 (depending on the administered activity, see Table 2), which is less than 0.02 mg albumin. The safety in administrating these amounts of MAA particles in children is well documented.[51,52]

Absorbed Radiation Doses with SPECT

Radiation dose reduction and standardization is a work in progress in pediatric nuclear medicine RI.[53-55] There exist differences between international guidelines that require harmonization.[56] The pediatric SPECT procedure should be planned with the goal of reducing patient dose but without compromising the diagnostic ability of the examination. There is a minimum activity needed to perform a SPECT examination below which no useful information can be expected due to lowest number of photons required to perform a tomographic reconstruction. Above this level, the diagnostic quality of the investigation will increase steeply with increasing administered activity, mainly due to reduction in image noise. Once the value of the diagnostic information is maximized, further increase in activity will not improve the clinical value of the examination.[57] The relationship between diagnostic quality (and image quality in terms of lesion contrast) and administered activity, heavily depends on the performance of the gamma camera used and the radiopharmaceutical chemical stability and should be optimized at each site.

Table 2 summarizes the calculations followed to determine the lifetime attributable risk of a radiation-induced cancer in pediatric patients of different ages from standard amounts of administered activities. The intention is to give the practitioner with a basis for understanding the long-term radiation risk in relation to clinical benefits of the V/Q SPECT scan and to provide the support information for a correct communication of this risk to the parents. Table 2 was calculated taking in consideration the current knowledge about the long-term risks associated to medical exposure,[54,58] the European pediatric dosage recommendations for different radiopharmaceuticals[56,59] and a V/Q SPECT protocol with a three to one administered activity of [^{99m}Tc]MAA and Technegas, respectively. Table 2 shows that adjusting correctly the administered doses to the patient age, results in the same effective dose and image quality (as the activity increases with age) for both age groups, but as expected, with a decreasing associated risk with age. The long-term probability of developing cancer following the radiation exposure from a pulmonary V/Q SPECT in children and infants is, as described in Table 2, as low as 0.02% and 0.01%, for 1 and 10 years old, respectively. This practically means that the increase in lifetime probability of dying from cancer after performing a pulmonary V/Q SPECT is negligible compared to inherent risk of naturally develop cancer (22% according to Fahey et al[54]). It is important to mention that Table 2 does not take into consideration individual patient variations. In despite of this, Table 2 demonstrate that if there is a clear clinical indication to perform a pediatric V/Q SPECT examination, the associated radiation doses should not be used as criteria for choosing another diagnostic technique.

Conclusions

Modern pulmonary V/Q SPECT, with the addition of diagnostic CT, allows for noninvasive morphofunctional studies of the regional distribution of blood in the pulmonary vascular bed and ventilation in the alveolar tree, practically without patient collaboration. Despite of this, the number of publications describing its use in pediatric

patients with nPE is scarce. V/Q SPECT and simultaneous SPECT/CT has proven superior sensitivity than planar imaging and conventional morphologic techniques in the staging and follow-up of pediatric patients presenting diverse chronic pulmonary disorders. According to our own clinical experience, pulmonary V/Q SPEC/CT has a wide range of pediatric applications beyond PE. It is simple to implement and the distribution and intensity of V and Q defects can be quantified and localized anatomically. The long-term risk in developing malignancies associated to radiation exposure from this procedure in infants and children is very low. V/Q SPECT is a safe procedure in pediatric patients (from basically new-born to teenagers) and provides with unique and valuable diagnostic information.

Acknowledgments

I would like to express my gratitude to Prof Hans Jacobson for his invaluable help in reviewing this manuscript.

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