Case Report

Review of diagnostic uses of shunt fraction quantification with technetium-99m macroaggregated albumin perfusion scan as illustrated by a case of Osler–Weber–Rendu syndrome

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Submission: 14-08-2015
Accepted: 24-09-2015

Abstract:

Bilateral pulmonary arteriovenous malformations (AVMs) are rare and are often associated with the hereditary hemorrhagic telangiectasia (HHT/Osler–Weber–Rendu) syndrome. We present a woman who presented with neurological symptoms due to a cerebral abscess. On further evaluation, bilateral pulmonary AVMs were identified. The patient was diagnosed with HHT, based on positive family history and multiple cerebral AVMs recognized on subsequent catheter angiogram, in addition to the presence of bilateral pulmonary AVMs. Craniotomy with drainage of the brain abscess and endovascular embolization of the pulmonary AVMs was offered to the patient. As a preembolization work-up, the patient underwent nuclear lung perfusion scan with technetium-99m macroaggregated albumin (Tc-99m MAA) to assess the right-to-left shunt secondary to the pulmonary AVMs. Postembolization follow-up perfusion scan was also obtained to estimate the hemodynamic response. The case is presented to describe the role of Tc-99m MAA perfusion lung scan in preoperatively evaluating patients with pulmonary AVMs and to emphasize on the scan's utility in posttreatment follow-up. Various present day usages of the Tc-99m MAA lung perfusion scan, other than diagnosing pulmonary thromboembolism, are discussed. Providing background knowledge on the physiological and hemodynamic aspects of the Tc-99m MAA lung perfusion scan is also attempted. Various imaging pitfalls and necessary precautions while performing Tc-99m MAA lung perfusion scan are highlighted.

Key words:

Hepatopulmonary syndrome, perfusion imaging, technetium Tc 99m aggregated albumin, telangiectasia-hereditary hemorrhagic

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.180020

Nuclear imaging for lung perfusion assessment is relatively one of the older modalities of diagnostic imaging that was introduced quite a few decades earlier. Originally introduced for a physiological understanding of the lung perfusion, the nuclear lung perfusion scan has stood the time and its present day uses are versatile in the field of radiology. One of the most common indications is to rule out pulmonary embolism. Here, in this article, the authors intent to discuss various current practices of this imaging technique besides diagnosing pulmonary embolism, with a case example to begin with.

Case Report

A 53-year-old woman came with complaints of headache and fever associated with progressive expressive aphasia of 3 days duration. Her past medical history was unremarkable except for hypertension, hyperlipidemia, and pervious perforated left ear tympanic membrane. On examination, her vitals were stable (blood pressure of 132/72 mmHg, heart rate of 85 beats/min, and SpO_2 of 96% in the room air) with slightly raised

How to cite this article: Chokkappan K, Kannivelu A, Srinivasan S, Babu SB. Review of diagnostic uses of shunt fraction quantification with technetium-99m macroaggregated albumin perfusion scan as illustrated by a case of Osler–Weber–Rendu syndrome. Ann Thorac Med 2016;11:155-60.

temperature (37.7°C). Cardiac auscultation was unremarkable. Neurological examination revealed mild neck stiffness with no focal neurological deficits. Basic blood investigation was notable for mild leukocytosis (total white blood count of 12.6×10^9/L). Initial computed tomography (CT) of the brain showed an ill-defined lesion with heterogeneous internal densities in the left frontal lobe [Figure 1], with moderate surrounding white matter edema. Subsequent contrast enhanced magnetic resonance imaging (MRI) [Figure 1] helped characterizing the lesion by demonstrating diffusion restriction and rim of peripheral enhancement, and thereby pointing out to the diagnosis of the cerebral abscess. The patient then underwent frontal craniotomy with drainage of the abscess. Pus culture of the abscess grew *Fusobacterium nucleatum* and *Parvimonas micra*. With antibiotic therapy, the patient responded well and improved neurologically.

Meanwhile, contrast CT study of the chest was performed to evaluate incidentally identified lung opacity on chest radiograph. CT [Figure 2] revealed masses in bilateral lower lobes, made of serpiginous vessels with their feeding arteries and draining veins, in keeping with bilateral pulmonary arteriovenous malformations (AVMs). Considering the bilaterality of the pulmonary AVMs, catheter angiogram of the brain was performed, which demonstrate multiple intracranial AVMs [Figure 3]. These findings, along with patient's positive family history (of her sister having been diagnosed of pulmonary AVM and underwent embolization 20 years ago) substantiated the proposed diagnosis of hereditary hemorrhagic telangiectasia (HHT/Osler–Rendu–Weber syndrome). Retrospective examination of the patient did not, however, identified any muco-cutaneous telangiectasias.

Further evaluation with two-dimensional echo using microbubble contrast agent demonstrated a large amount of bubble contrast entering the left heart chamber soon after being visualized in the right heart, a finding which confirmed right-to-left (R-L) shunt secondary to the known pulmonary AVMs. Endovascular embolization treatment of the pulmonary AVMs was contemplated and was preceded by quantification of R-L shunt fraction by means of nuclear lung perfusion scan using technetium-99m macroaggregated albumin (Tc-99m MAA). Baseline R-L shunt fraction was calculated as 35.6% [Figure 4]. Two weeks after successful coil embolization of the AVMs [Figure 5], a follow-up perfusion scans showed a shunt fraction value of 19.48% [Figure 4], indicating a favorable hemodynamic response. Patient was discharged in a stable condition and advised for neurosurgical follow-up for the cerebral AVMs and for a repeat follow-up lung perfusion scan a year later, for interval assessment.

Discussion

Nuclear lung perfusion scan is one of the well-established techniques for quantitative assessment of lung perfusion. When introduced in 1961, the technique helped to illustrate the gravity-dependent gradient pattern of the lung perfusion.[1] Among few available agents used for lung perfusion imaging, denatured human albumin particles (macroaggregated albumin [MAA]) tagged to technetium 99m is the most common one.[2,3] Of late, the state of the art imaging modalities such as CT (with dual energy perfusion mapping) and dynamic

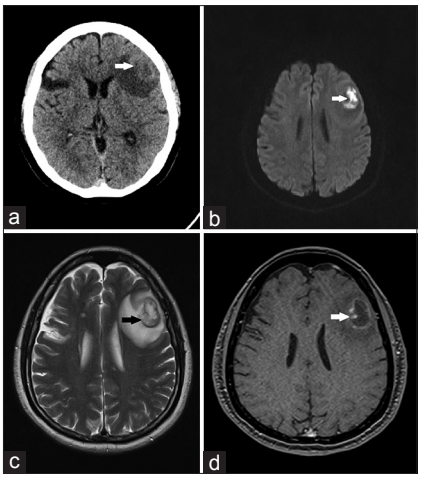

Figure 1: (a) Noncontrast axial CT section of the brain showing left frontal lobe space occupying lesion (arrow) with moderate surrounding white matter edema. (b) Magnetic resonance imaging – diffusion weighted axial section of the brain showed diffusion restricting nature (arrow) of the lesion. (c) In the axial T2 image the lesion appeared heterogeneous with pronounced white matter edema. (d) Lesion demonstrated peripheral rim enhancement (arrow) characteristic for brain abscess, along with other features

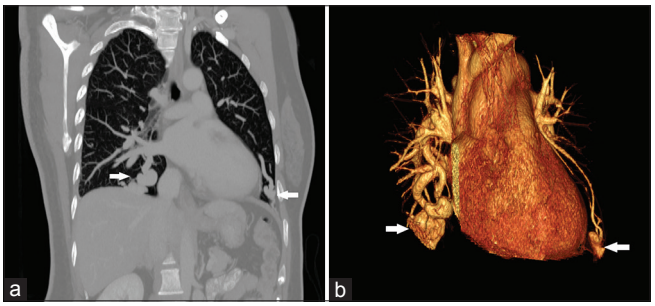

Figure 2: Contrast computed tomography of the chest. Coronal maximum intensity projection section of the lung in the lung window (a) and volume rendered three-dimensional reconstructed image (b) illustrating bilateral pulmonary arterio-venous malformations

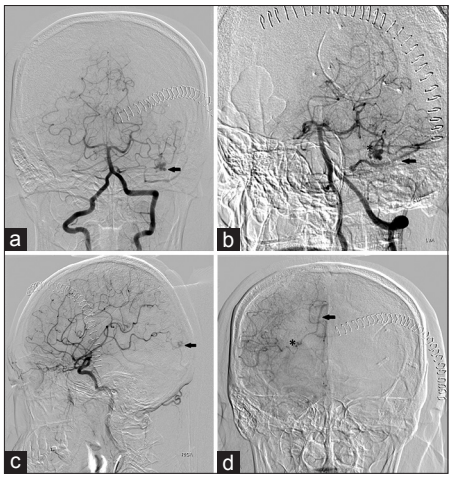

Figure 3: Digital subtraction angiogram of the brain. (a) Arterio-venous malformation in the posterior aspect of left temporal lobe (arrow) being supplied by branch of the left posterior cerebral artery. (b) Oblique view showing the same arterio-venous malformation in the posterior left temporal lobe (asterisk) and its draining vein (arrow). (c) Another smaller arterio-venous malformation (arrow) in the right occipital lobe being supplied by branches of the right middle cerebral artery. (d) Frontal view showing the same arterio-venous malformation (asterisk) and its draining vein (arrow)

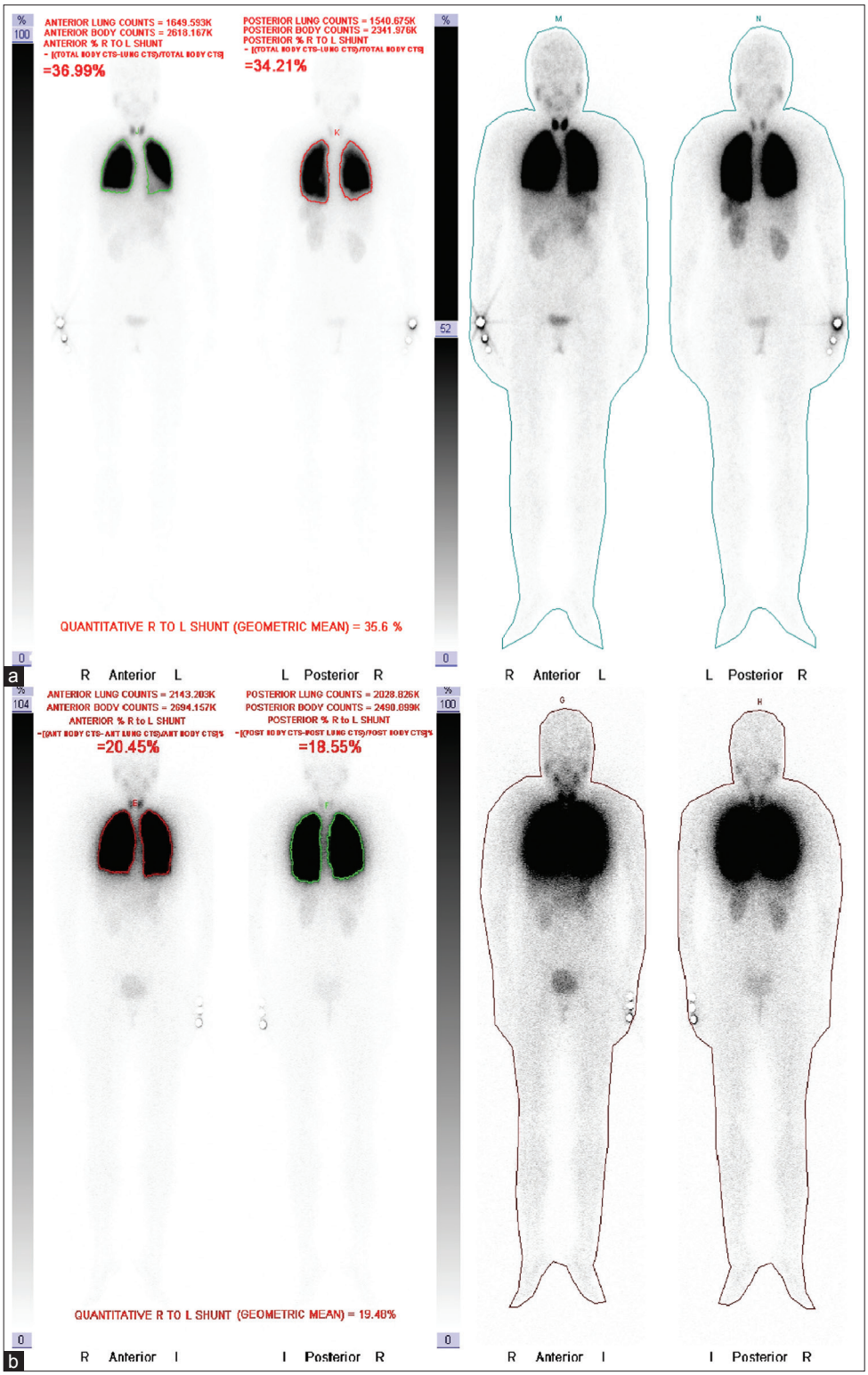

Figure 4: Tc-99m MAA nuclear lung scan. (a) Lung shunt fraction calculated before the embolization procedure was 35.6%. (b) Postembolization follow-up scan showed favorable reduction in the lung shunt fraction to 19.48%. Note that the activity seen in the thyroid, salivary glands and stomach in both the images a and b are secondary to presence of free pertechnetate, which could potentially result in over-estimation of the shunt calculation. But institutional quality control measure allows not more than 10% of free pertechnetate in the administered dosage, in order not to cause significant distortion of the results

contrast MRI have emerged as potential alternatives for measuring lung perfusion, with additional advantage of providing exquisite morphological details as well.

The size of the MAA particles (10–60 μm) is such that, when injected intravenously, most of them (>95% of injected dose) are filtered or micro-embolized at the pulmonary capillaries

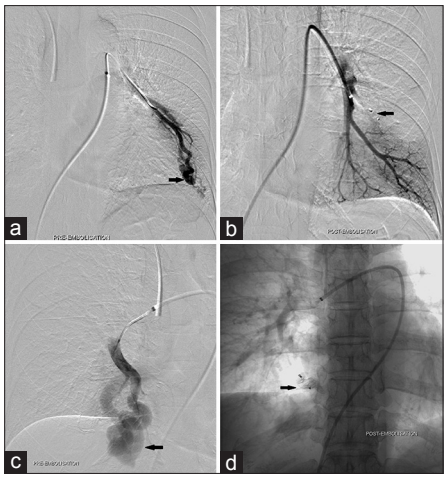

Figure 5: Endovascular embolization of bilateral pulmonary arterio-venous malformations using Amplatzer plugs. (a) Tortuous branch of left pulmonary artery supplying the arterio-venous malformation (arrow) in the left lower lobe. (b) Postembolization picture showing no filling of the feeding artery (arrow) as well as the arterio-venous malformation. (c) Catheter tip placed in the tortuous branch of right pulmonary artery feeding arterio-venous malformation (arrow). (d) Complete nonopacification of the arterio-venous malformation and its feeder artery postembolization. Arrow pointing the Amplatzer plug

and precapillary arterioles. Nevertheless, intravenous administration of MAA is safe, as the micro-embolization is temporary, and the particles occlude only one in several hundred thousand pulmonary capillaries.[4] In due time, the MAA particles disintegrate to smaller ones, negotiate through capillaries, enter into systemic circulation, and are removed by phagocytosis by the reticuloendothelial system of liver and spleen.[5] Half of the injected particles are removed from the lungs in about 4–8 h.[6] By assessing the radio-activity of the Tc-99m isotope bound to the MAA, qualitative assessment of essential information such as lung perfusion, segmental or lobar perfusion defects, differential perfusion of bilateral lungs, R-L shunt ratio and liver-lung shunt ratio can be performed, according to the clinical context.

Pulmonary AVMs are rare, and 70% of the cases are associated with HHT.[7] All symptomatic pulmonary AVMs, AVMs of size more than 2 cm and AVMs with arterial feeder of 3 mm or more should be considered for definitive treatment, in the view of chronic hypoxemia and paradoxical embolism risks.[7,8] Tc-99m MAA perfusion scan is not only useful in recognition and quantification of R-L shunts in pulmonary AVMs, but also useful in evaluating the response after therapeutic procedures such as lobectomy and embolization.[3] In the presence of AVM, a significant proportion of the injected MAA particles escapesin to the systemic circulation, through anomalous arteriovenous connections bypassing the pulmonary capillary bed. Most of the escaped MAA particles are diverted to highly vascular systemic end organ capillaries such as brain, kidney, and spleen. The amount of this extra-pulmonary uptake of the tracer is directly proportional to the volume and magnitude of the R-L shunt [Table 1]. Nuclear lung perfusion scan is superior to the 100%oxygen method in calculating the shunt fraction in that, no arterial blood sampling is necessary and over-estimation of the shunt fraction is a known problem in the 100% oxygen method. For estimation of R-L shunts in pulmonary AVMs, intravenous injection of Tc-99m MAA is done and whole body planar acquisition is done soon after the injection. Shunt fraction, which represents the percentage of total body tracer activity that bypasses from being filtered at the pulmonary capillaries, is calculated using the semi-quantitative formula proposed by Gates[9] namely:

Percentage of R-L shunt = [(total body geometric mean count – total lung geometric mean count)/total body geometric mean count] ×100

Another common indication of the Tc-99m MAA perfusion scan is in the workup of patient with hepatocellular carcinoma, before radioembolization treatment with yttrium-90 (Y-90) microspheres. Although hepatocellular carcinoma derives its blood supply predominantly from hepatic artery, and hence the radioactivity (beta emitting Y-90 with mean range of activity of about 2.5 mm) injected directly into the hepatic artery is supposed to be well localized to the tumor tissue, presence of varying degrees of intra-tumoral arteriovenous shunting can result in significant nontargeted radiation to the lungs.[10] Therefore, a thorough workup is needed in selecting the patient for Y-90 treatment. In this context, the MAA, particle size of which is approximately equal to that of Y-90 microsphere, is injected into the hepatic artery after selective catheterization, simulating Y-90 radioembolization procedure. Whole body scans should commence in <1 h of injection and lung shunt fraction (LSF) is calculated as:

$$LSF = (\text{geometric mean count}_{lungs}/[\text{geometric mean count}_{liver} + \text{geometric mean count}_{lungs}]) \times 100$$

In this above formula, the liver shunt fraction denotes the ratio of tracer activity injected into the hepatic artery that escapes into lungs via arteriovenous shunts within the tumor. In the presence of significant LSF (more than 20%), dreaded complication of progressive pulmonary insufficiency secondary to radiation pneumonitis is avoided by deferring the Y-90 radioembolization procedure. Usually, a LSF of less than 10% does not need any dose modification of Y-90 and LSF of 10–14.9% and 15–20% requires dose reduction of 20% and 40% of the original dose, respectively (according to the information page insert that comes along with the brand SIR-spheres). Excessive breathing movements during the perfusion scan may result in misregistration of liver activity as lung activity and potentially lead to the false calculation of high LSF precluding Y-90 treatment. However, with the advent of single-photon emission CT-CT (SPECT-CT), accurate assessment of LSF can be done via attenuation correction.[11] SPECT-CT correlation also helps in identifying extrahepatic shunting of MAA into abdominal organs such as stomach in certain patients, indicating potential complication of nonhealing ulcer that might happen with Y-90 treatment. Selective pretreatment embolization of left gastric and gastroduodenal arteries can be considered in such cases.

The role of Tc-99m MAA perfusion scan in diagnosing hepatopulmonary syndrome (HPS) in patients with the chronic liver disease is well-documented. Although etiology of HPS is not well-known, the characteristic hypoxemia has largely been attributed to intrapulmonary vasodilatation and abnormal arteriovenous communication secondary to nonclearance of circulating vasodilator substances by the diseased liver. The

Table 1: Causes of extra-pulmonary uptake of the Tc-99m MAA

Mechanism	Examples	Imaging findings
R-L shunt		
Intracardiac shunts	Patent foramen of ovale Atrial septa defect Anomalous pulmonary venous drainage	Activity in the kidney and brain (highly vascular) are more prominent than that in the liver (radioactivity reaches the liver through hepatic artery in these settings, and liver, as such, is predominantly supplied by portal vein)
Intrapulmonary shunts		
Congenital	HHT (Osler-Rendu-Weber)	
Acquired	Pulmonary hypertension	
	Acute massive pulmonary thromboembolism	
	Chronic obstructive pulmonary disease	
	Cavo-pulmonary shunts	
	Pulmonary metastasis	
	Liver cirrhosis	
	Schistosomiasis	
	Sarcoidosis	
	Actinomyosis	
	Primary biliary cirrhosis	
Radiopharmaceutical reaching the portal vein before reaching the right heart chambers	Patent ductus venosus	Uptake and activity in the liver is disproportionately greater than that in the brain and kidneys
	Superior and inferior vena caval obstruction with collateral development	
	Injection in to inappropriately positioned umbilical venous catheter in neonates	
Pharmaceutical problems	Contaminants	Pertechnatate preferentially accumulates in thyroid, salivary glands and stomach
	Degraded MAA in to submicron size	Nonparticulate contaminants, do not cross the blood brain barrier and seen only in the dural venous sinuses

Tc-99m MAA = Technetium-99m macroaggregated albumin, MAA = Macroaggregated albumin, HHT = Hereditary hemorrhagic telangiectasia, R-L = Right-to-left

intrapulmonary vasodilatation that occurs in HPS results in R-L shunt, which can be quantified by nuclear lung perfusion scan. A lung shunt fraction (LSF) of more than 6% is considered diagnostic of HPS in cirrhotic patients.[12] Here, for calculating LSF (the percentage of total administered radioactivity that entered systemic circulation) the following formula is used:

$$LSF = [\text{geometric mean count}_{brain}/(\text{geometric mean count}_{brain} + \text{geometric mean count}_{lung})] \times 100$$

Brain activity is considered to represent overall systemic activity in this formula.

Tc-99m MAA lung shunt scan is a problem-solving tool in cirrhotic patients with co-existing intrinsic lung diseases, as high LSF clearly points out HPS as the cause of hypoxia. Reversal of previously abnormal LSF has also been documented in cirrhotic patients, after clinically favorable response to medical treatment and after liver transplantation.[13] Hence, nuclear perfusion lung scans can be used in the posttreatment follow-up of known HPS in patients with the chronic liver disease.

Nuclear lung perfusion scan is widely used in the field of cardiology. In a patient with cardiac dysfunction and dyspnea, demonstration of R-L shunts in lung perfusion scan would help to exclude cardiac failure as a solecause of the symptoms.[14] Presence of R-L shunts in those patients signifies the dyspnea and hypoxia are, indeed, related to development of pulmonary hypertension and R-L shunt and explains why specific treatment directed towards the cardiac dysfunction might not help alleviating the symptoms. Various congenital heart diseases are associated with abnormal pulmonary blood flow. Lung perfusion scan is a simple and reliable method of assessing total and differential pulmonary blood flow in such cases and evaluating response after treatments such as reconstruction and angioplasty procedures.[4] Nuclear lung perfusion scans can also be used as a noninvasive alternate of transoesophageal echocardiography (TEE) to identify and grade patent foramen of ovale (PFO). Moreover, the perfusion scan results are comparable to TEE in following-up after treatment of conditions such as PFO and atrial septal defects.

Possible areas of pitfalls in technetium-99m macroaggregated albumin perfusion scans

- Disintegrated MAA particles: When performing a semi-quantitative lung perfusion scans, meticulous quality control checks cannot be overemphasized. For the purpose of clinical usage, more than 90% of injected MAA particles should of size 10–60 μm. If a significant proportion of particles are smaller than desirable size (either due to faulty preparation or undue delay in image acquisition after initial injection), it is likely that those particles would escape from getting filtered in pulmonary capillaries and reach systemic circulation. This would result in false overestimation of the R-L shunt fraction. Most of the times, planar acquisition starts immediately after intravenous administration of Tc-99m MAA, as the injection is usually done in the gamma camera/SPECT-CT suit. However, while planning for Y-90 treatment, the injection is performed after selective catheterization of hepatic artery by the interventional radiologist, wherein there could be a formidable time

spent shifting the patient from the fluoroscopic table to gamma camera/SPECT-CT. Evidences suggest that in those settings, the injection to image acquisition time should be preferably kept under 1 h, in order to avoid false overestimation of lung shunt fraction that can potentially preclude the option of Y-90 treatment in an eligible patient[15]

- Free technetium and contamination with Tc-99m-pertechnetate: Ideally more than 95% of technetium should be bound to the MAA in order to serve the purpose. This can be assessed by means of quality checking measures like chromatography. The presence of unbound technetium or pertechnetate contaminants would again result in extrapulmonary tracer accumulation in the absence of R-L shunt. One clue is to look at the brain activity. These radiopharmaceutical contaminants do not cross the blood-brain barrier and present as activity in the dural venous sinuses than activity in the brain itself. On the contrary, the Tc-99 MAA particles are localized as activity in the brain parenchyma.[16] Moreover, free pertechnetate shows preferential uptake in the thyroid, salivary glands and stomach, whereas Tc-99 MAA activity is observed mainly in the kidneys, liver, spleen, and brain
- The problem of misregistration: Excessive breathing movements may lead to this complication, especially in pretreatment workup of patients for Y-90 radio-embolization, as we mentioned earlier. When there is misregistration of activity in the liver for that in the lung, calculated lung shunt fraction would be incorrectly high. Three-dimensional volume data offered by SPECT-CT allows for making necessary corrections to solve the problem.

Conclusion

Tc-99m MAA nuclear lung scan is a simple, noninvasive, and nonoperator dependent imaging tool in nuclear medicine which gives a reproducible method of calculating lung perfusion, in a semi-quantitative manner. Other than its most frequent use as a part of ventilation/perfusion scan to rule out pulmonary thromboembolism, the nuclear perfusion scan has several well-established roles in the current state of the art practice of clinical nuclear medicine. Due caution should be taken while performing nuclear lung perfusion scan for shunt estimation, so as to avoid potential miscalculation that may result in improper patient management. New developments in the image acquisition including the advent of SPECT/CT and count calculation algorithms are likely to improve the precision of the results, making the imaging modality a reliable tool for posttreatment follow-ups.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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