Imaging in hepatopulmonary syndrome- case report. A multicenter approach during the coronavirus pandemic

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ABSTRACT

A 60-year-old lady with alcoholic liver disease developed central cyanosis and orthodeoxia. A technetium-99m macro-aggregated albumin lung perfusion scan and contrast echocardiogram were performed. A 13% right to left shunt was calculated from the macro-aggregated albumin scan. There were more bubbles in the left heart than the right at the end of the contrast echocardiogram. Hepatopulmonary syndrome was therefore diagnosed. The patient had a liver transplant five days after these investigations. Further discussion about hepatopulmonary syndrome will be provided.

Normally, macro-aggregated albumin scans are performed in few centers, however as this was at the height of the coronavirus pandemic, the scan needed to be performed locally to reduce the chance of the patient getting coronavirus. Local radiographers were remotely instructed on conducting the macro-aggregated albumin scan by a larger center to provide a timely and important investigation in a logistically difficult scenario.

CASE REPORT

CASE REPORT

A 60-year-old lady with alcohol-related liver disease presented to hospital with a month's history of increased shortness of breath and orthodeoxia- desaturation when in an upright position. She had no pre-existing cardiac or respiratory disease and had not smoked tobacco for 30 years. On examination she had central cyanosis and finger clubbing. There was also an increase in the volume of her ascites accompanying this, which was being drained every 10-14 days at this point. She had developed portal hypertension because of her alcohol-related liver disease and had episodes of hepatic encephalopathy. She was admitted to hospital and during this admission, the clinical team felt that liver transplantation was necessary and workup for transplantation was commenced. Resting oxygen saturations were 92% on air and fell to 82% on walking two flights of stairs. In a supine position on air, her partial pressure of oxygen was 11.1 kPa and decreased to 7.7. kPa on standing.

Initially, a transthoracic echocardiogram was requested to check for raised pulmonary artery pressure. She was noted to have bilateral pleural effusions and a pulmonary artery systolic pressure of 29-34mmHg. There were no obvious atrial septal defects, no right atrium dilatation, no right ventricular hypertrophy, trivial tricuspid regurgitation, and a right atrial pressure estimated at 0-5mmHg.

At the time of the Computed Tomography (CT) thorax being performed, no significant abnormalities were found, however on retrospective review, subpleural telangiectasia were noted (Figures 1A-1C).

A Tc-99m macro-aggregated albumin lung perfusion (Tc-99m MAA) scan was performed to ascertain if there was a right to left shunt. Static anterior and posterior images of the whole body as well as lateral images of the brain were acquired after intravenous technetium-99m injection. There was intense uptake in the lungs, as expected. however, there was also additional moderate abnormal uptake seen in the extrathoracic organs, including the kidneys, stomach, small bowel and minimal uptake in the brain (Figures 2,3), which implies presence of a right to left shunt [1].

To quantify the percentage shunt, comparison of pulmonary and whole body uptake was made [2,3]. Regions of interest (ROIs) were drawn around the lungs and the whole body anteriorly and posteriorly (Figure 4) and the counts of tracer activity were obtained for the images taken immediately after Tc99m administration. The extrapulmonary activity was determined by subtracting the tracer count from the lung ROI from the whole-body ROI. This was then divided by the count obtained for the total body ROI. This was calculated as 13.4%, which is consistent with the presence of a right to left shunt. If

there was extravasation of Tc-99m because of a tissued cannula, the area of tracer activity at the site of the cannula should be subtracted to avoid an artificially raised count of extrapulmonary tracer activity. Otherwise, there would be an overestimation of the percentage shunt and could potentially affect management decisions.

In addition to this, an erect microbubble contrast echocardiogram using agitated saline as the contrast agent was performed on the same day, which showed good right sided opacification after three cardiac cycles (Figure 5A,5B), suggesting absence of an atrial septal defect or patent foramen ovale. Microbubbles were then seen in the left side of the heart (Figure 5C) and gradually increased to opacify the left ventricle. More microbubbles were seen in the left side of the heart compared to right by the end of the study (Figures 5E,5F), which also indicates the presence of a right to left shunt.

Given the symptoms and investigation results, it was concluded that the patient had HPS. Key clinical characteristics are shown in (Table 2). She received her liver transplant five days after investigations finished.

A postoperative haematoma occurred two days after the transplant, for which a laparotomy was performed to evacuate the haematoma and ligate a bleeding vessel at the porta hepatis. She then developed a subphrenic collection six weeks after the transplant, for which she was admitted to hospital and treated with a course of intravenous antibiotics. During the hospital admission, she developed a haemolytic anaemia, which was due to passenger lymphocyte syndrome, a transient immune-mediated haemolytic process that can occur after solid organ or haematopoietic stem cell transplantation when there are minor mismatches in ABO blood group between the transplant donor and recipient [4]. The trigger for developing haemolysis related to passenger lymphocyte syndrome was thought to be infection by the local haematology team, which is consistent with existing literature [5,6]. This was managed with a course of prednisolone starting at 1mg/kg and blood transfusions matched to the transplant donor's blood group. The passenger lymphocyte syndrome had resolved by four months post-transplant.

DISCUSSION

ETIOLOGY AND DEMOGRAPHICS

HPS is characterised by the presence of intrapulmonary vascular dilatations and arterial deoxygenation in the presence of liver disease [7]. Four to forty-seven percent of patients with liver disease develop HPS and estimates are wide ranging because of differences in the cut off arterial oxygen partial pressure and alveolar gradient levels used to define the presence of arterial deoxygenation [7,8]. Children can also develop HPS and has been reported to occur in 6.8% percent of children with biliary atresia [9] and 42.5% of children with liver cirrhosis [10]. HPS is thought to be more prevalent in patients with higher Model for End-stage Liver Disease scores [11]. In two studies of adults with HPS, 58-68% of patients were male and the mean age was 58 years old [8,11]. The median age of HPS onset was 4 years old in a study of paediatric patients with biliary atresia [9].

Current understanding of the etiology of HPS is based mostly on animal studies, however the main mediators are thought to be endothelin-1 and nitric oxide [12]. Endothelin-1 is produced in response to liver injury, which goes on to upregulate pulmonary endothelin B receptors and leads to increased pulmonary endothelial nitric oxide synthase [12]. This gives increased nitric oxide and together with the activated pulmonary endothelin B receptors leads to pulmonary vasodilation [12]. As a result of this abnormal dilatation, oxygen cannot diffuse from the alveolus into all the red blood cells in the capillary, leading to partially oxygenated blood entering the pulmonary veins [12]. This blood travels to the left side of the heart and into the systemic arterial circulation, which leads to arterial deoxygenation.

CLINICAL AND IMAGING FINDINGS

The echocardiogram in this case showed no structural abnormalities, hence cardiac causes for her symptoms were much less likely. To further exclude cardiac causes, the microbubble contrast echocardiogram did not show bubbles in the left heart before the completion of three cardiac cycles, again making a cardiac cause unlikely [13]. The presence of bubbles in the left heart after more than three cardiac cycles indicated presence of intrapulmonary vascular dilatations, which are not present in portopulmonary hypertension [7], therefore excluded portopulmonary hypertension as a differential diagnosis in this case. Whilst microbubble contrast echocardiograms are highly sensitive in identifying intrapulmonary vascular dilatations and can differentiate between intracardiac and intrapulmonary shunts, they are less specific than Tc-99m MAA scans, especially in patients with co-existing intrinsic lung diseases [14].

Tc-99m MAA scans can identify a right to left shunt but can also be used to calculate the percentage of the shunt. However, they are limited by low sensitivity, hence why they are used in conjunction with microbubble contrast echocardiography [15]. At present, there is no gold standard grading system for quantifying right to left shunts identified by Tc-99m MAA scans, or the severity of the shunt. Some studies compare brain uptake with lung uptake whereas others compare lung uptake to whole body uptake to derive the percentage of the right to left shunt [15]. For this patient, whole body uptake was used to determine the percentage shunt and has been shown to be more sensitive than using brain uptake [15]. A normal value for the percentage shunt when calculating using whole body uptake is considered to be less than or equal to 3% [1], therefore based on this, a cut off of 5% extrapulmonary tracer uptake to confirm the presence of a shunt has been adopted by the Royal Free Nuclear Medicine Department in London, United Kingdom, who helped to carry out the scan and are a tertiary referral center for liver transplantation. As such, they have a great deal of experience with pre-operative investigation of patients with suspected HPS and interpreting shunt percentages. Within their centre, it is generally accepted a right to left shunt of over 10% is moderate

and over 15% is severe. The reported cut-offs in adults to confirm the presence of a right to left shunt when comparing lung uptake to brain uptake range from 6-10% [14,16].

There are some associated risks, cost and scan provision considerations to be aware of for both Tc99m-MAA scans and saline microbubble contrast echocardiograms. The provision of contrast echocardiography and Tc-99m MAA scans requires specialist staff, which may not be available in all hospitals. Not all hospitals will have the relevant equipment and facilities to perform Tc99m-MAA scans. Tc-99m MAA scans carry a less than 1 in 10,000 risk of serious allergic reaction [17], have an associated radiation dose and a theoretical risk of cerebral and other visceral microemboli [1]. Costs of a Tc-99m MAA scan are likely to be similar to a ventilation perfusion scan for pulmonary embolus, which in the United States of America is $683 [18], as the Tc-99m MAA scan used to quantify the right to left shunt is the same as the perfusion portion of a ventilation perfusion scan for pulmonary embolus, just that whole body images are taken instead of just the lungs [19]. Saline microbubble contrast echocardiograms do not have radiation associated risks and are not invasive as they are generally performed as transthoracic scans. Saline microbubble contrast echocardiograms are also relatively low cost as consumables for the investigation are common hospital supplies [20]. However, there are rare cases of transient ischaemic attacks and stroke after agitated saline microbubble contrast echocardiograms in those with right to left shunts, none of which were fatal and in most cases symptoms improved or resolved over time [21,22]. Despite these risks and considerations, the benefit of these investigations for this patient was the patient could have quicker curative treatment in the form of an expedited liver transplant, which would have not happened otherwise. Both scans are required as the microbubble contrast echocardiogram will exclude intracardiac shunts and is more sensitive than a Tc99m MAA scan. The Tc99m MAA scan will then demonstrate intrapulmonary vascular dilatations and allow for quantification of the percentage shunt.

Given the patient's presentation occurred at the height of the first wave of the coronavirus pandemic, further consideration needed to be given to where the patient would be investigated to reduce the risk of the patient contracting coronavirus, especially since the patient was clinically vulnerable due to her liver disease. In this instance, advice was sought from the center where the scans were normally performed to then be able to carry out the scan at a local radiology department. The consultant and radiographers liaised with the local team remotely to devise a standard operating procedure to then allow the local department to perform the scans and interpret them appropriately and consistently, not only for this patient, but also for potential future patients. If it was not for such investigations, it may have been assumed the patient's symptoms were related to portopulmonary hypertension, therefore would have not had an expedited liver transplant and may have had a worse outcome.

The patient's local hospital and the advising tertiary referral center already had established working relationships for the multidisciplinary care of liver transplant patients as patients to be considered for liver transplantation from the local hospital are normally discussed with the transplant center. However it was not normal practice for the local hospital nuclear medicine department to perform the Tc-99m MAA scan for right to left shunt quantification. Collaboration between different centers may be possible through multidisciplinary meetings and care pathways to discuss and look after specific groups of patients and the ultilization of professional societies, which may allow networking with other professionals with specific professional interests and also allow for the wider dissemination of knowledge and resources [23].

TREATMENT AND PROGNOSIS

As liver transplantation is the only definitive treatment for HPS and that mortality is twice as high in patients with HPS compared to those with chronic liver disease without HPS, patients are often given a higher priority on transplant waiting lists [7]. However, in portopulmonary hypertension, outcomes after liver transplantation are poor and those with significant portopulmonary hypertension may not be suitable candidates for liver transplantation [7]. Therefore, it is extremely important to differentiate between these two entities in patients awaiting liver transplantation.

Even though liver transplantation can treat the HPS, there are several complications and risks of liver transplantation in itself, including: vascular thromboses, post-operative haemorrhage, biliary leak or stricture, graft rejection, graft failure, cardiovascular disease, renal dysfunction, and complications related to long term immunosuppression such as development of diabetes and increased frequency of infections and malignancy [24,25]. Five year survival rates of patients undergoing liver transplantation for HPS have been reported at 76% for patients with irrespective of etiology of liver disease [26]. Median survival for HPS patients after liver transplantation has been reported as 11.4 years for patients with preoperative partial pressure of oxygen less than 45mmHg and 14.1 years if preoperative partial pressure of oxygen was 45-50mmHg [27].

DIFFERENTIAL DIAGNOSIS

For orthodeoxia to occur, there needs to be shunting of blood from the deoxygenated circulation to the oxygenated circulation, i.e., a right to left shunt. In cases of orthodeoxia, the shunt is made worse by changes in position [28]. This shunt may be intracardiac or intrapulmonary.

Atrial septal defect or patent foramen ovale

Cardiac causes of orthodeoxia include a patent foramen ovale or atrial septal defect, especially if there is concurrent pathology increasing right atrial pressures such as a pericardial effusion [28] or tricuspid regurgitation [29]. The increased right heart pressure would create an increased pressure gradient from the right to left, leading to a clinically significant right to left shunt.

Haemorrhagic hereditary telangiectasia/Osler–Weber–Rendu syndrome

An intrapulmonary shunt may occur due to the presence of pulmonary arteriovenous malformations [28]. Pulmonary arteriovenous malformations could occur congenitally or idiopathically and can be associated with hereditary haemorrhagic telangiectasia (HHT); an autosomal dominant disease also known as Osler–Weber–Rendu syndrome, leading to telangiectasis in the lungs, nasal mucosa, liver, gastrointestinal tract and brain [30]. Pulmonary involvement in HHT is common and is estimated to be present in half of patients with the syndrome [30]. There was no history of epistaxis or other types of bleeding event to suggest this patient had HHT and there was no family history of HHT.

Portopulmonary hypertension

In the context of her advanced liver disease, she may have developed portopulmonary hypertension or hepatopulmonary syndrome (HPS) to cause her symptoms, however it is not essential to have coexisting liver disease to develop portopulmonary hypertension [7].

Portopulmonary hypertension clinically would have features consistent with pulmonary hypertension rather than present with orthodeoxia and platypnea, however low oxygen saturations and central cyanosis are still possible with portopulmonary hypertension, hence it needed to be considered as a differential diagnosis.

Pulmonary embolism

Patients with liver disease are at increased risk of venous thromboembolism [31], despite also being at increased risk of bleeding events because of impaired synthetic function of the liver [31,32]. A clinically significant right to left shunt may occur in pulmonary embolus if there is a concurrent atrial septal defect or patent foramen ovale as the right heart pressure can become raised due to the pulmonary embolism, which then increases shunting through the atrial septal defect or patent foramen ovale [33,34]. It is also possible for right to left shunting to occur transiently In the acute phase of a massive pulmonary embolism because of increased right atrial pressure [35,36]. However, like portopulmonary hypertension, orthodeoxia and platypnea are rare clinical features of pulmonary embolism.

Teaching points

Technetium-99m MAA scans and microbubble contrast echocardiograms are crucial in making a diagnosis of hepatopulmonary syndrome and in identifying the presence and cause of right to left shunts. Cross-center collaboration is possible and necessary in conducting important but uncommon scans for patients in logistically difficult scenarios such as the coronavirus pandemic. This may be facilitated through other pre-existing cross-site working relationships and through professional societies to access professional networks and educational resources to support alternative modes of service delivery where necessary.

AUTHOR CONTRIBUTIONS

Dr Afsara Ahmmed wrote the manuscript, collated images for presentation and obtained informed consent from the patient.

Dr Randeep Kulshrestha came up with the idea for the manuscript, was involved in facilitating investigations for the patient and critically reviewed the manuscript and its revisions.

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DISCLOSURES

Neither author has any interest to declare. No funding was received for this work.

CONSENT

Written informed consent was obtained from the patient to write about their case, publish it in a journal and show pictures of their clinical imaging.

QUESTIONS

1. Which of the following statements are true?

1. Presence of a right to left pulmonary shunt on technetium 99m macro-aggregated albumin lung perfusion scan is characterised by having 5%-10% or greater extrapulmonary tracer uptake (applies)
2. Contrast microbubble echocardiograms are used in conjunction with technetium 99m macro-aggregated albumin lung perfusion scans to improve sensitivity (applies)
3. Contrast microbubble echocardiograms cannot differentiate between intracardiac and intrapulmonary causes of a right to left shunt
4. In hepatopulmonary syndrome, no tracer uptake should be present in the lungs when performing a Technetium 99m macro-aggregated albumin lung perfusion scan
5. Anterior and posterior body views need to be taken in a Technetium 99m macro-aggregated albumin lung perfusion scan (applies)

Explanations for question 1

The cut-off for the presence of a right to left shunt is debated in the literature, but reported figures are 6-10% or greater. Normal whole body uptake should be less than or equal to 3%. [The reported cut-offs in adults for extrapulmonary tracer uptake to confirm the presence of a right to left shunt range from 6-10% in existing literature [14–16].] and [A normal value for the percentage shunt when calculating using whole body uptake is considered to be less than or equal to 3% [1], therefore based

on this, a cut off of 5% extrapulmonary tracer uptake to confirm the presence of a shunt has been adopted by the Royal Free Nuclear Medicine Department in London, United Kingdom].

Contrast microbubble echocardiograms are very sensitive in identifying right to left shunts but are less specific than technetium 99m macro-aggregated albumin lung perfusion scans. [Whilst microbubble contrast echocardiograms are highly sensitive in identifying intrapulmonary vascular dilatations and can differentiate between intracardiac and intrapulmonary shunts, they are less specific than Tc-99m MAA scans, especially in patients with co-existing intrinsic lung diseases (14).]

Contrast microbubble echocardiograms can differentiate between intracardiac and intrapulmonary causes of a right to left shunt. [Whilst microbubble contrast echocardiograms are highly sensitive in identifying intrapulmonary vascular dilatations and can differentiate between intracardiac and intrapulmonary shunts, they are less specific than Tc-99m MAA scans, especially in patients with co-existing intrinsic lung diseases (14).]

Significant tracer uptake should still be expected in hepatopulmonary syndrome. However, in hepatopulmonary syndrome due to the right to left shunt, uptake outside of the lungs is also expected, but to a much lesser extent. [There was intense uptake in the lungs, as expected. however, there was also additional moderate abnormal uptake seen in the extrathoracic organs, including the kidneys, stomach, small bowel and minimal uptake in the brain (figures 2&3) , which implies presence of a shunt [1]]

To quantify the percentage shunt, comparison of pulmonary and whole body uptake was made [2, 3]. Regions of interest (ROIs) were drawn around the lungs and the whole body anteriorly and posteriorly (Figure 4) and the counts of tracer activity were obtained for the images taken immediately after Tc99m administration.

2. Which of the following can cause a right to left shunt?

1. Atrial septal defect (applies)
2. Pulmonary embolism (applies)
3. Hereditary hemorrhagic telangiectasia with pulmonary arteriovenous malformations (applies)
4. Hepatopulmonary syndrome (applies)

Explanations for question 2

Atrial septal defect can cause a right to left shunt as blood from the right side of the heart that is deoxygenated can move through to the left side of the heart and mix with oxygenated blood. This is more likely to happen if there is a concurrent pathology that raises the right atrial pressure to then generate a pressure gradient from right to left for blood to move across. [Cardiac causes of orthodeoxia include a patent foramen ovale or atrial septal defect, especially if there is concurrent pathology increasing right atrial pressures such as a pericardial effusion [28] or tricuspid regurgitation [29].]

Right to left shunting can occur in cases of pulmonary embolism. [A clinically significant right to left shunt may occur in pulmonary embolus if there is a concurrent atrial septal defect or patent foramen ovale as the right heart pressure can become raised due to the pulmonary embolism, which then increases shunting through the atrial septal defect or patent foramen ovale [33,34]. It is also possible for right to left shunting to occur transiently In the acute phase of a massive pulmonary embolism because of increased right atrial pressure [35,36].]

Hereditary hemorrhagic telangiectasia causes right to left shunting due to the presence of pulmonary arteriovenous malformations. [An intrapulmonary shunt may occur due to the presence of pulmonary arteriovenous malformations [28].]

Hepatopulmonary syndrome causes right to left shunting due to intrapulmonary vascular dilatations. [Hepatic disease leads to increases in nitric oxide production, which acts on the alveolar capillaries to form intrapulmonary vascular dilatations. Abnormal gas exchange and right to left shunting then occurs [12].]

3. With regards to imaging findings, which of the following are true?

1. Dilated peripheral arteries may be seen on CT in hereditary haemorrhagic telangiectasia if pulmonary arteriovenous malformations are present (applies)
2. Microbubbles are not expected in the left side of the heart on contrast microbubble echocardiography in hepatopulmonary syndrome
3. Microbubbles are not expected in the left side of the heart on contrast microbubble echocardiography in portopulmonary hypertension (applies)
4. Dilated peripheral arteries may be seen on CT in hepatopulmonary syndrome (applies)
5. Dilated peripheral arteries may be seen on CT in portopulmonary hypertension

Explanations for question 3

When pulmonary arteriovenous malformations are present in a patient with hereditary haemorrhagic telangiectasia, dilated peripheral arteries would be expected but would also be accompanied by the presence of draining veins on CT, unlike hepatopulmonary syndrome. [Dilated peripheral arteries feeding a nodule with draining veins [44].]

Microbubbles are expected in the left side of the heart on contrast microbubble echocardiography in hepatopulmonary syndrome. [Microbubble contrast echocardiography would show passage of microbubbles to the left heart. Dilated pulmonary artery and mild cardiomegaly sometimes seen [37]]

Microbubbles are not expected in the left side of the heart on contrast microbubble echocardiography in portopulmonary hypertension. ["Contrast echo lines stopping in early systole around the pulmonary valve mid-systolic notch" as a result of pulmonary hypertension [40].]

Dilated peripheral arteries may be seen on CT in hepatopulmonary syndrome [Dilated subpleural arteries with abnormally increased number of visible terminal vessels [37].]

Portopulmonary hypertension on CT would show features of pulmonary hypertension, which includes enlargement of the main pulmonary artery, not dilatation of the peripheral arteries. [Increased main pulmonary artery diameter to ascending aorta diameter ratio and enlarged left and right pulmonary arteries [41]]

4. Which of the following are true?

1. In cases of concurrent lung disease, technetium 99m macro-aggregated albumin lung perfusion scans are of higher specificity than contrast microbubble echocardiography (applies)
2. Technetium 99m macro-aggregated albumin lung perfusion scans are performed frequently in many centers
3. Nitric oxide production is thought to be a part of the pathogenesis in hepatopulmonary syndrome (applies)
4. Brain uptake is sometimes used instead of whole-body uptake to derive the percentage shunt in a technetium 99m macro-aggregated albumin lung perfusion scan (applies)
5. Children can also develop hepatopulmonary syndrome (applies)

Explanations for question 4

In cases of concurrent lung disease, technetium 99m macro-aggregated albumin lung perfusion scans are of higher specificity than contrast microbubble echocardiography [Whilst microbubble contrast echocardiograms are highly sensitive in identifying intrapulmonary vascular dilatations and can differentiate between intracardiac and intrapulmonary shunts, they are less specific than Tc-99m MAA scans, especially in patients with co-existing intrinsic lung diseases [14].]

Technetium 99m macro-aggregated albumin lung perfusion scans are a specialist investigation performed in few centers [Normally, macro-aggregated albumin scans are performed in few centers]

Nitric oxide is thought to be involved in the pathogenesis of hepatopulmonary syndrome [Hepatic disease leads to increases in nitric oxide production, which acts on the alveolar capillaries to form intrapulmonary vascular dilatations. Abnormal gas exchange and right to left shunting then occurs [12].]

Brain and whole-body uptake have both been used to compare against lung uptake in technetium 99m macroaggregated albumin lung perfusion scans, but whole-body uptake has been shown to be more sensitive. [whole body uptake was used to determine the percentage shunt and has been shown to be more sensitive than using brain uptake [15]

Children can also develop hepatopulmonary syndrome [Can also occur in children with advanced liver disease [9,10].]

5. Which of the following statements are false?

1. The definite treatment for portpulmonary hypertension is liver transplantation (applies)
2. In orthodeoxia, the degree of shunting increases with changes in position
3. Liver disease must be present to have portopulmonary hypertension (applies)
4. If extravasation of the tracer occurs whilst performing the technetium 99m macro-aggregated albumin lung perfusion scan, this may overestimate the degree of shunt
5. Liver disease must be present to have hepatopulmonary syndrome

Explanations for question 5

Portopulmonary hypertension may worsen after liver transplantation [However, in portopulmonary hypertension, outcomes after liver transplantation are poor and those with significant portopulmonary hypertension may not be suitable candidates for liver transplantation [7].]

Changes in position can cause an increase in the degree of shunting- the shunt is worse when upright. [In cases of orthodeoxia, the shunt is made worse by changes in position [28].]

Liver disease does not need to be present to develop portopulmonary hypertension [In the context of her advanced liver disease, she may have developed portopulmonary hypertension or hepatopulmonary syndrome (HPS) to cause her symptoms, however it is not essential to have coexisting liver disease to develop portopulmonary hypertension [7].]

If an area of extravasation of the tracer is counted when calculating the degree of shunt, it will make the count of extrapulmonary tracer higher, giving a higher value as the percentage shunt and therefore overestimating the degree of shunt. [If there was extravasation of Tc-99m because of a tissued cannula, the area of tracer activity at the site of the cannula should be subtracted to avoid an artificially raised count of extrapulmonary tracer activity.]

Liver disease must be present to have a diagnosis of hepatopulmonary syndrome. [HPS is characterised by the presence of intrapulmonary vascular dilatations and arterial deoxygenation in the presence of liver disease [7]]

REFERENCES

1. MacDonald A, Burrell S. Infrequently performed studies in nuclear medicine: Part 1. *J Nucl Med Technol.* 2008; 36(3): 132-143. PMID: 18703616.

2. Gates GF, Orme HW, Dore EK. Measurement of cardiac shunting with technetium-labeled albumin aggregates. *J Nucl Med.* 1971; 12(11): 746-749. PMID: 5113638.

3. Chokkappan K, Kannivelu A, Srinivasan S, Babut 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(2): 155-160. PMID: 27168866.

4. Romero S, Solves P, Lancharro A, et al. Passenger lymphocyte syndrome in liver transplant recipients: a description of 12 cases. *Blood Transfus.* 2015; 13: 423. PMID: 26057486.

5. de Bruijn S, Philipse E, Couttenye MM, et al. Passenger Lymphocyte Syndrome (PLS): A Single-center Retrospective Analysis of Minor ABO-incompatible Liver Transplants. *J Clin Transl Hepatol.* 2017; 5(1): 9-15. PMID: 28507920.

6. Nadarajah L, Ashman N, Thuraisingham R, Barber C, Allard S, Green L. Literature Review of Passenger Lymphocyte Syndrome Following Renal Transplantation and Two Case Reports. *Am J Transplant.* 2013; 13(6): 1594-1600. PMID: 23617703.

7. Soulaidopoulos S, Goulis I, Cholongitas E. Pulmonary manifestations of chronic liver disease: A comprehensive review. *Ann Gastroenterol.* 2020; 33(3): 237-249. PMID: 32382226.

8. Dahiya DS, Kichloo A, Shaka H, et al. Hepatopulmonary Syndrome: A Nationwide Analysis of Epidemiological Trends and Outcomes From 2012 to 2018. *Gastroenterol Res.* 2021; 14(4): 252-258. PMID: 34527095.

9. Ueno T, Saka R, Takama Y, et al. Onset ages of hepatopulmonary syndrome and pulmonary hypertension in patients with biliary atresia. *Pediatr Surg Int.* 2017; 33(10): 1053-1057. PMID: 28871319.

10. Ceza MR, Garcia E, Anselmi CE, et al. Prevalence and characteristics of hepatopulmonary syndrome in children with cirrhosis in southern Brazil. *Eur J Gastroenterol Hepatol.* 2019; 31(1): 10-15. PMID: 30045096.

11. Ferreira PP, Camara EJ, Paula RL, Zollinger CC, Cavalcanti AR, Bittencourt PL. Prevalence of hepatopulmonary syndrome in patients with decompensated chronic liver disease and its impact on short term survival. *Arq Gastroenterol*. 2008; 45(1): 34-37. PMID: 18425226.

12. Grace JA, Angus PW. Hepatopulmonary syndrome: Update on recent advances in pathophysiology, investigation, and treatment. *J Gastroenterol Hepatol.* 2013; 28(2): 213-219. PMID: 34527095.

13. Soliman OII, Geleijnse ML, Meijboom FJ, et al. The use of contrast echocardiography for the detection of cardiac shunts. *Eur J Echocardiogr*. 2007; 8(3): S2-S12. PMID: 17462958.

14. Abrams GA, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic Utility of Contrast Echocardiography and Lung Perfusion Scan in Patients With Hepatopulmonary Syndrome. *Gastroenterology.* 1995; 109(4): 1283-1288. PMID: 7557096.

15. Zhao H, Tsauo J, Zhang X-W, et al. Technetium-99m-labeled macroaggregated albumin lung perfusion scan for diagnosis of hepatopulmonary syndrome: A prospective study comparing brain uptake and whole-body uptake. *World J Gastroenterol.* 2020; 26(10): 1088-1097. PMID: 32205999.

16. Ito K, Kurihara K, Ishibashi A, et al. Cut-off value for normal versus abnormal right-to-left shunt percentages using 99mTc-macroaggregated albumin. *Nucl Med Commun.* 2011; 32(10): 936-940. PMID: 21876404.

17. Health Products Regulatory Authority. Summary of Product Characteristics PULMOCIS 2 mg kit for radiopharmaceutical preparation, https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0677-003-001_18122019140202.pdf (2019, accessed 26 March 2023).

18. Perrier A, Nendaz MR, Sarasin FP, Howarth N, Bounameaux H. Cost-Effectiveness Analysis of Diagnostic Strategies for Suspected Pulmonary Embolism Including Helical Computed Tomography. *Am J Respir Crit Care Med.* 2012; 167(1): 39-44. PMID: 12502474.

19. Gandhi SJ, Babu S, Subramanyam P, Shanmuga Sundaram P. Tc-99m macro aggregated albumin scintigraphy – indications other than pulmonary embolism: A pictorial essay. *Indian J Nucl Med.* 2013; 28(3): 152-162. PMID: 24250023.

20. Strachinaru M, ten Cate FJ. Microbubble Enhanced Echocardiography in Current Cardiology Practice. *Rev Cardiovasc Med.* 2022; 23: 202.

21. Romero JR, Frey JL, Schwamm LH, et al. Cerebral ischemic events associated with 'bubble study' for identification of right to left shunts. *Stroke.* 2009; 40(7): 2343-2348. PMID: 19498192.

22. Bernard S, Churchill TW, Namasivayam M, Bertrand PB. Agitated Saline Contrast Echocardiography in the Identification of Intra- and Extracardiac Shunts: Connecting the Dots. *J Am Soc Echocardiogr.* 2021; 34: 1-12.

23. European Society of Radiology (ESR). "Role of radiology in a multidisciplinary approach to patient care": summary of the ESR International Forum 2022. *Insights Imaging.* 2023; 14(1): 1-8.

24. Rogal S, Shenai N, Kruckenberg K, Rosenberger E, Dew MA, DiMartini A. Post-transplant Outcomes of Persons Receiving a Liver Graft for Alcoholic Liver Disease. *Alcohol Alcohol.* 2018; 53(2): 157-165. PMID: 29293880.

25. Millson C, Considine A, Cramp ME, et al. Adult liver transplantation: UK clinical guideline - part 2: surgery and post-operation. *Frontline Gastroenterol.* 2020; 11(5): 385-396. PMID: 32879722.

26. Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology.* 2005; 41(5): 1122-1129. PMID: 15828054.

27. Kadry Z, Schaefer E, Krok K, et al. Excellent outcomes with liver transplantation in hepatopulmonary syndrome across pre-transplant PaO2 spectrum. *JHEP Rep.* 2021; 3(5): 100351. PMID: 34604726.

28. Cheng TO. Mechanisms of platypnea-orthodeoxia: what causes water to flow uphill? *Circulation*. 2002; 105(6): e47. PMID: 11839642.

29. Hatani Y, Tanaka H, Kajiura A, et al. Sudden Onset of Platypnea-Orthodeoxia Syndrome Caused by Traumatic Tricuspid Regurgitation With Ruptured Chordae Tendineae After Blunt Chest Trauma. *Can J Cardiol.* 2018; 34(8): 1088. e11-1088.e13. PMID: 29980469.

30. Meier NM, Foster ML, Battaile JT. Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations: clinical aspects. *Cardiovasc Diagn Ther.* 2018; 8(3): 316-324. PMID: 30057878.

31. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. *Am J Gastroenterol*. 2009; 104(1): 96-101. PMID: 19098856

32. Espiritu JD. Pulmonary embolism in a patient with coagulopathy from end-stage liver disease. *Chest.* 2000; 117(3): 924-925. PMID: 10713038.

33. Salvetti M, Zotti D, Bazza A, et al. Platypnea and orthodeoxia in a patient with pulmonary embolism. *Am J Emerg Med.* 2013; 31(4): 760.e1-760.e2. PMID: 23380102.

34. Khauli S, Chauhan S, Mahmoud N. Platypnea. *StatPearls*, https://www.ncbi.nlm.nih.gov/books/NBK534834/ (2022, accessed 27 March 2023). PMID: 30521255.

35. Buffaz P-D, Cracowski J-L, Woodward C, et al. Transient Right-to-Left Shunt in Acute Pulmonary Embolism. *Clin Nucl Med.* 1999; 24: 447-448.

36. Panoutsopoulos G, Ilias I, Christakopoulou I. Transient right-to-left shunt in massive pulmonary embolism. *Ann Nucl Med.* 2000; 14(3): 217-221. PMID: 10921488.

37. McAdams HP, Erasmus J, Crockett R, Mitchell J, Godwin JD, McDermott VG. The hepatopulmonary syndrome: radiologic findings in 10 patients. *AJR Am J Roentgenol.* 1996; 166(6): 1379-1385. PMID: 8633451.

38. Cotton CL, Gandhi S, Vaitkus PT, et al. Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. *Liver Transplant.* 2002; 8(11): 1051-1054. PMID: 12424719.

39. Kuo PC, Plotkin JS, Johnson LB, et al. Distinctive Clinical Features of Portopulmonary Hypertension. *Chest.* 1997; 112(4): 980-986. PMID: 9377962.

40. Gullace G, Savoia MT, Ravizza P, et al. Contrast echocardiographic features of pulmonary hypertension and regurgitation. *Heart.* 1981; 46: 369-373. PMID: 7295432.

41. Devaraj A, Loveridge R, Bosanac D, et al. Portopulmonary hypertension: Improved detection using CT and echocardiography in combination. *Eur Radiol.* 2014; 24(10): 2385-2393. PMID: 25052075.

42. Webb G, Gatzoulis MA. Atrial septal defects in the adult: Recent progress and overview. *Circulation.* 2006; 114(15): 1645-1653. PMID: 17030704.

43. Parra JA, Bueno J, Zarauza J, et al. Graded contrast echocardiography in pulmonary arteriovenous malformations. *Eur Respir J.* 2010; 35(6): 1279-1285. PMID: 19996192.

44. Carette MF, Nedelcu C, Tassart M, Grange JD, Wislez M, Khalil A. Imaging of Hereditary Hemorrhagic Telangiectasia. *Cardiovasc Intervent Radiol.* 2009; 32: 745-757. PMID: 18972161.

45. Hritani R, Alrifai A, Soud M, Moussa Pacha H, Alraies MC. Which patients with pulmonary embolism need echocardiography? *Cleve Clin J Med.* 2018; 85(11): 826-828. PMID: 30395521.

46. Ronny C, Pablo L, Victor N, et al. Echocardiographic findings in pulmonary embolism: An important guide for the management of the patient. *World J Cardiovasc Dis.* 2012; 2012: 161-164.

47. Moore AJE, Wachsmann J, Chamarthy MR, Panjikaran L, Tanabe Y, Rajiah P. Imaging of acute pulmonary embolism: an update. *Cardiovasc Diagn Ther.* 2018; 8(3): 225-243. PMID: 30057872.

48. Roberts KE, Kawut SM, Krowka MJ, et al. Genetic risk factors for hepatopulmonary syndrome in patients with advanced liver disease. *Gastroenterology.* 2010; 139(1): 130-9. e24. PMID: 20346360.

FIGURES

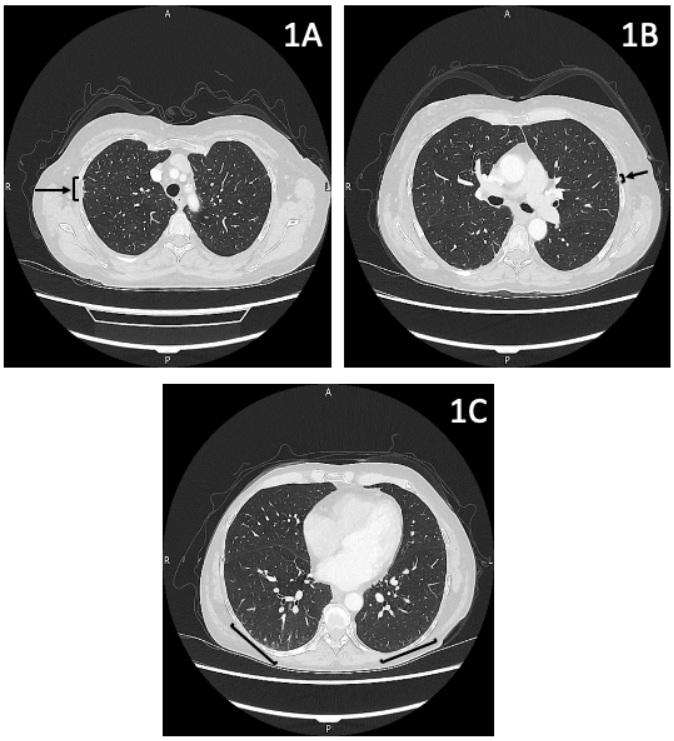

Figure 1: 60-year-old lady with hepatopulmonary syndrome.
Findings: Axial contrast enhanced CT (1A-1C) of the thorax shows subpleural telangiectasis (marked with arrow and/or square bracket) throughout the thorax.
Technique: Axial Post contrast CT taken using Canon Aquilon one Genesis volumetric CT scanner, 120kV, 0.5mm slice thickness, 60ml Iomeron 400 contrast administered intravenously.

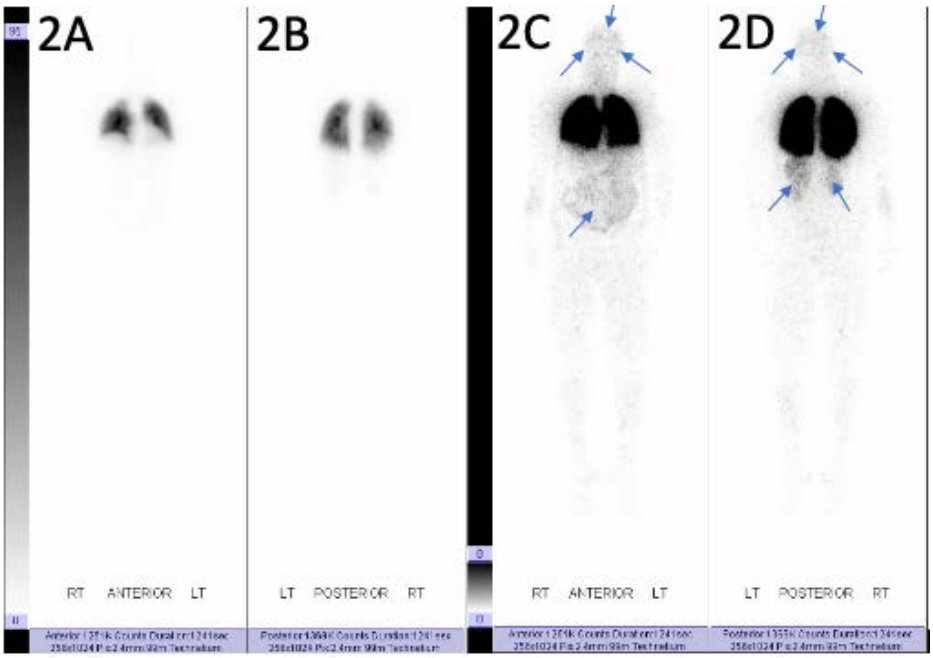

Figure 2: 60-year-old lady with hepatopulmonary syndrome.

Findings: Anterior and posterior heat maps from Tc-99m MAA lung perfusion scan- immediately after Tc-99m MAA administration (2A and 2B) and after three hours (2C and 2D) showing evidence of activity outside of the lungs as marked by arrows.

Technique: 0.4ml of 158Mbq Tc99m (Pulmocis) was administered intravenously. Static images of the whole body anteriorly and posteriorly, lateral brain and anterior and posterior views of the kidneys and brain were taken on Symbia T16 SPECT/CT gamma camera immediately after Tc99m administration and three hours post Tc99m administration.

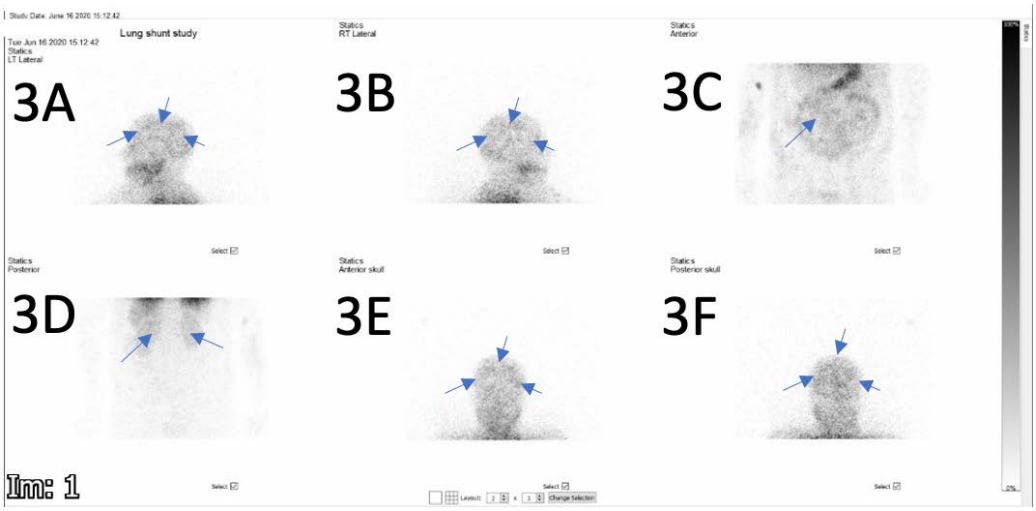

Figure 3: 60-year-old lady with hepatopulmonary syndrome.

Findings: Static images of right (3A) and left lateral brain (3B), anterior (3C) and posterior (3D) abdomen and anterior (3E) and posterior brain (3F) showing the presence of tracer outside of the lungs as marked by the arrows.

Technique: 0.4ml of 158Mbq Tc99m (Pulmocis) was administered intravenously. Static images of the whole body anteriorly and posteriorly, lateral brain and anterior and posterior views of the kidneys and brain were taken on Symbia T16 SPECT/CT gamma camera immediately after Tc99m administration and three hours post Tc99m administration.

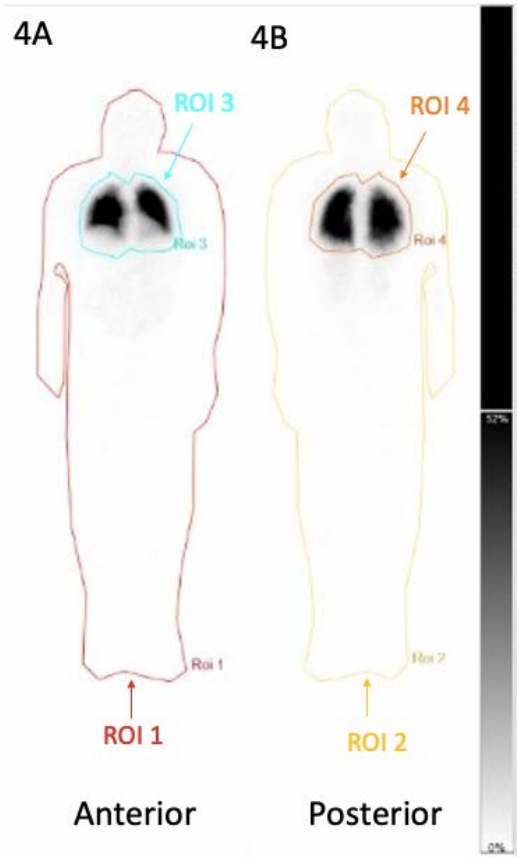

Figure 4: 60-year-old lady with hepatopulmonary syndrome.

Findings: Image showing anterior (4A) and posterior (4B) regions of interest used to calculate percentage shunt. ROI 1 (4A, red outline) gave the anterior whole body tracer count, ROI 2 (4B, yellow outline) gave the posterior whole body tracer count, ROI 3 (4A, cyan outline) gave the anterior tracer count for the lungs, ROI 4 (4B, orange outline) gave the posterior tracer count for the lungs.

0.4ml of 158Mbq Tc99m (Pulmocis) was administered intravenously. Static images of the whole body anteriorly and posteriorly, lateral brain and anterior and posterior views of the kidneys and brain were taken on Symbia T16 SPECT/CT gamma camera immediately after Tc99m administration and three hours post Tc99m administration. Calculations to determine the percentage shunt were performed using the images taken immediately after Tc99m administration, with the three-hour post Tc99m images acting as visual confirmation.

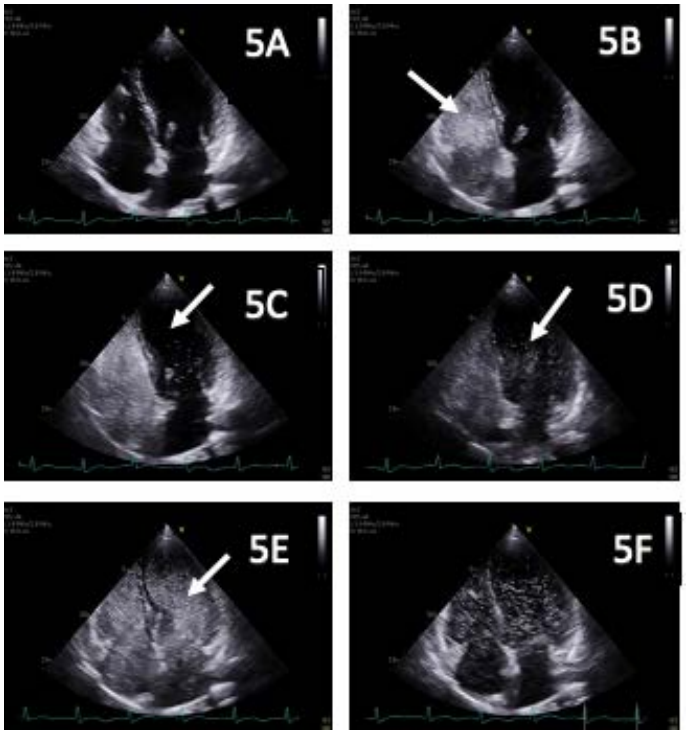

Figure 5: 60 year old lady with hepatopulmonary syndrome.

Findings: Still images from microbubble contrast echocardiogram. 5A) start,5 B) opacification of right heart after three cardiac cycles as marked by arrow, 5C) bubbles in left side of heart start to appear as marked by arrow, 5D) Increase in bubbles in left heart as marked by arrow, 5E) Filled left ventricle as marked by arrow, 5F) End of series showing a greater number of bubbles in the left heart than the right (left ventricle marked by arrow).

Technique: Contrast microbubble echocardiogram in erect position using approximately 6ml intravenous agitated saline as contrast agent. Frame rate = 48 frames per second. Frequency 1.4MHz- 2.8 MHz. Depth = 16cm. Images taken on GE Vivid E95 ultrasound machine.

Differential diagnosis	Echocardiography	CT	Tc-99mm MAA lung perfusion scan
Hepatopulmonary syndrome	Microbubble contrast: passage of microbubbles to the left heart. Dilated pulmonary artery and mild cardiomegaly sometimes seen [37]	Dilated subpleural arteries with abnormally increased number of visible terminal vessels [37].	Extrapulmonary tracer uptake [37]
Portopulmonary hypertension	Elevated pulmonary artery systolic pressure, tricuspid regurgitation and dilated right atrium and ventricle [38,39]. "Contrast echo lines stopping in early systole around the pulmonary valve mid-systolic notch" as a result of pulmonary hypertension [40].	Increased main pulmonary artery diameter to ascending aorta diameter ratio and enlarged left and right pulmonary arteries [41]	Tracer uptake limited to the lungs.
Atrial septal defect / Patent foramen ovale	Microbubble contrast: passage of microbubbles through interatrial septum to the left atrium [13].	Enlarged right atrium and right ventricle [42]	Extrapulmonary tracer uptake [19]
Hereditary haemorrhagic telangiectasia/ Osler-Weber-Rendu Syndrome (with pulmonary arteriovenous malformations)	Microbubble contrast echocardiography: passage of bubbles to left heart [43].	Dilated peripheral arteries feeding a nodule with draining veins [44].	Extrapulmonary tracer uptake [3].
Pulmonary embolism	In higher risk cases, may have raised right atrium and pulmonary artery pressures and right ventricular dysfunction that spares the right ventricle apex [45]. May also see right heart emboli and right ventricle dilatation [46]. In the unlikely scenario that platypnea and orthodeoxia are present, there may be a concurrent atrial septal defect or patent foramen ovale (see Atrial septal defect / Patent foramen ovale row of this table)	Acutely, pulmonary arterial filling defects are central. Chronically, filling defects are adherent to vessel walls. Features of right heart strain may also be present such as interventricular septum flattening, increased right ventricle to left ventricle ratio and reflux of contrast into the inferior vena cava [47].	Usually, uptake is restricted to the lungs, however in the unlikely scenario that platypnea and orthodeoxia are present, there may be extrapulmonary tracer uptake secondary to atrial septal defect or patent foramen ovale.

Table 1: Differential diagnosis table

Etiology	Hepatic disease leads to increases in nitric oxide production, which acts on the alveolar capillaries to form intrapulmonary vascular dilatations. Abnormal gas exchange and right to left shunting then occurs [12].
Prevalence	4-47% of patients with liver cirrhosis [8]
Gender ratio	58-68% male in adult inpatients with HPS [8,11]
Age predilection	Mean age for adult inpatients 58 years [8,11]. Can also occur in children with advanced liver disease [9,10].
Risk factors	Not well defined, however increased severity of liver disease as determined by Model for End-stage Liver Disease score [11] and polymorphisms in genes regulating angiogenesis [48] have been associated with development of HPS
Treatment	Liver transplantation [7]
Prognosis	5-year survival of 76% after liver transplantation, 23% without liver transplantation [26]

Table 2: Summary table describing key characteristics of hepatopulmonary syndrome

ABBREVIATIONS

CT = Computed Tomography
HHT = Haemorrhagic Hereditary Telangiectasia
HPS = Hepatopulmonary Syndrome
ROIs = Regions of Interest
Tc-99mm MAA = Technetium 99m macroaggregated albumin

KEYWORDS

Hepatopulmonary Syndrome; Technetium Tc 99m Aggregated Albumin; Nuclear Medicine; Lungs; Liver; Right-to-Left Shunt; Contrast Echocardiography; COVID-19 Pandemic; Interdepartmental Relations