STATE-OF-THE-ART REVIEW ARTICLE

Clinical Implications of Pulmonary Shunting on Saline Contrast Echocardiography

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Pulmonary right-to-left shunting can be encountered using transthoracic contrast echocardiography (TTCE) with agitated saline. Diseases associated with pulmonary shunting on saline TTCE include hereditary hemorrhagic telangiectasia (HHT), hepatopulmonary syndrome, and some congenital heart defects after partial or complete cavopulmonary anastomosis. Furthermore, small pulmonary shunts on saline TTCE are also documented in a proportion of healthy individuals. Pulmonary shunting carries the risk for severe neurologic complications due to paradoxical embolization. In HHT, additional chest computed tomography is recommended in case of any pulmonary shunt detected on saline TTCE, to evaluate the feasibility for transcatheter embolotherapy of pulmonary arteriovenous malformations. Furthermore, antibiotic prophylaxis is advised in case of any pulmonary shunt on saline TTCE to prevent brain abscesses after procedures with risk for bacteremia. The present review provides an overview of important aspects of pulmonary shunting and its detection using saline TTCE. Furthermore, advances in understanding the clinical implications of different pulmonary shunt grades on saline TTCE are described. It appears that small pulmonary shunts on saline TTCE (grade 1) lack any clinical implication, as these shunts cannot be used as a diagnostic criterion for HHT, are not associated with an increased risk for neurologic complications, and represent pulmonary arteriovenous malformations too small for subsequent endovascular treatment. This implies that additional chest computed tomography could be safely withheld in all persons with only small pulmonary shunts on saline TTCE and sets the stage for further discussion about the need for antibiotic prophylaxis in these subjects. Besides further optimization of the current screening algorithm for the detection of pulmonary arteriovenous malformations in HHT, these observations can be of additional clinical importance in other diseases associated with pulmonary shunting and in those healthy individuals with documented small pulmonary shunts on saline TTCE. (J Am Soc Echocardiogr 2015;28:255-63.)

Keywords: Saline contrast echocardiography, Pulmonary right-to-left shunt, Pulmonary arteriovenous malformation, Hereditary hemorrhagic telangiectasia, Hepatopulmonary syndrome

Abnormal pulmonary right-to-left shunting is occasionally encountered on transthoracic contrast echocardiography (TTCE) using agitated saline, which was originally described by Shub *et al.*[1] in 1976. Although saline TTCE is most frequently used for the detection of intracardiac (interatrial) shunting, it is important to be aware of other potential explanations for right-to-left shunting. Diseases associated with pulmonary shunting on saline TTCE include hereditary hemorrhagic telangiectasia (HHT), hepatopulmonary syndrome (HPS), and some congenital heart defects after partial or complete cavopulmonary anastomosis. Furthermore, small pulmonary shunts on saline TTCE are also documented in a proportion of healthy individuals. In the present review, we provide an overview of important aspects of pulmonary shunting and its detection using saline TTCE. Furthermore, we discuss advances in understanding the clinical implications of different pulmonary shunt grades on saline TTCE, based mainly on recent studies in patients with HHT.

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Pulmonary Shunting in HHT

HHT, also known as Rendu-Osler-Weber syndrome, is an autosomal-dominant inherited vascular disorder with an estimated prevalence of 1 in 5,000 individuals.[2] The disease is characterized by the presence of abnormal direct artery-to-vein communications, ranging from dilated microvessels in skin and mucosal membranes (so-called telangiectasias) to large arteriovenous malformations in predominantly pulmonary, hepatic, and cerebral circulation.[3] Pulmonary arteriovenous malformations (PAVMs) are frequently encountered in HHT and lead to permanent pulmonary right-to-left shunting. Pulmonary shunting predisposes to complications from paradoxical systemic embolization of both thrombotic and septic origin, including ischemic stroke and brain abscess.[4-7] Pulmonary shunting is also associated with an increased prevalence of migraine with aura and may result in hypoxemia, as blood flows directly from the pulmonary artery to the pulmonary vein without effective gas exchange.[8,9] On the basis of theoretical arguments, patients with PAVMs are advised to avoid scuba diving, as there may be an increased risk for complications

Abbreviations

CT = Computed tomography

HHT = Hereditary hemorrhagic telangiectasia

HHT1 = Hereditary hemorrhagic telangiectasia type 1

HHT2 = Hereditary hemorrhagic telangiectasia type 2

HPS = Hepatopulmonary syndrome

PAVM = Pulmonary arteriovenous malformation

TTCE = Transthoracic contrast echocardiography

from decompression illness.[10] Furthermore, the abnormal segment of a PAVM between the pulmonary artery and vein is fragile and may rupture, which then results in hemoptysis or hemothorax.[11] PAVMs can be treated with percutaneous transcatheter embolotherapy, which is an endovascular intervention that occludes the PAVM feeding artery with a coil or plug, to reduce the risk for PAVM-related complications.[12]

HHT consists of two main subtypes, HHT type 1 (HHT1) and HHT type 2 (HHT2). HHT1 results from mutations in the *ENG* gene on chromosome 9, encoding the protein endoglin,[13] whereas HHT2 results from mutations in the activin receptor–like kinase (*ACVRL1*) gene on chromosome 12, encoding the protein ALK-1.[14] A third disease-causing mutation has been shown in the *SMAD4* gene, which causes a combined syndrome of juvenile intestinal polyposis and HHT.[15] In addition, two more loci causing HHT have been mapped to chromosome 5 (HHT type 3) and 7 (HHT type 4), although the exact causative genes have not been identified yet.[16,17] Most families with HHT have unique mutations, and >600 types of mutations have been reported (http://www.hhtmutation.org). The majority of patients with HHT (>80%) have mutations in either *ENG* (HHT1) or *ACVRL1* (HHT2), with *ENG* mutations being more common than *ACVRL1* mutations,[15] but geographic variations exist.[18,19] The most important clinical difference between HHT1 and HHT2 is the prevalence and size of pulmonary right-to-left shunting on TTCE; TTCE documents pulmonary shunting in 91% of patients with HHT1, compared with 61% of those with HHT2. Small, moderate, or large pulmonary shunts (grade 1, 2, or 3) are found in 17%, 25%, and 48%, respectively, of patients with HHT1 patients, compared with 34, 13%, and 6% of those with HHT2.[20] Hepatic arteriovenous malformations are more frequently seen in patients with HHT2, which makes these patients more prone to high-output heart failure and pulmonary hypertension.[21]

Because of the high prevalence of PAVM-related pulmonary shunting in HHT, its associated severe complications, and effective transcatheter treatment options, screening for pulmonary shunting is recommended in all persons with possible or confirmed HHT.[10] The screening algorithm traditionally consisted of chest x-ray, arterial blood gas analysis, and pulmonary shunt fraction measurements (using the 100% oxygen method or ^{99m}Tc-labeled albumin microspheres or macroaggregates of albumin radionuclide scanning), followed by chest computed tomography (CT) and/or pulmonary angiography in case of high suspicion for PAVMs.[22] However, during the past few years, TTCE using agitated saline has evolved as new first-line screening technique for the detection of PAVM-related pulmonary shunting, on the basis of excellent sensitivity and negative predictive value (97%–100%), with lower risks and costs.[10,20,23-27]

Pulmonary Shunting in HPS

Pulmonary right-to-left shunting is also described in patients with the HPS. This syndrome is associated with hepatic disease and defined as an arterial oxygenation defect induced by structural vascular remodeling with a physical change in pulmonary capillary dimension and angiogenesis.[28] It is most often due to liver cirrhosis of any cause, with about 10% to 30% of patients with cirrhosis having the syndrome,[29] but any form of acute or chronic liver disease has been associated with HPS. HPS is also described in the presence of an Abernathy malformation, which is a congenital anomaly of the splanchnic vasculature in which portal venous blood is diverted into the inferior caval vein.[30] The pathologic finding in HPS is widespread dilatation of pulmonary microvessels encompassing the pulmonary precapillary and alveolar capillary beds.[31] Less commonly, HPS may also result in macroscopic PAVMs.[32] HPS results in impaired gas exchange due to a ventilation-perfusion mismatch, a diffusion limitation, and the presence of pulmonary shunting. The related hypoxemia is often refractory to supplemental oxygen. The true mechanisms responsible for the vascular changes in HPS remain incompletely understood. Because HPS represents a relatively common and important cause of pulmonary disease in cirrhosis, its presence should be considered in all patients with liver disease who complain of dyspnea. Patients with HPS can experience platypnea (hypoxemia exacerbated in the upright position), because of the predominance of structural vascular remodeling in the lung bases and increased blood flow through these regions in the upright position. HPS is associated with left atrial enlargement and increased cardiac output. Furthermore, neurologic complications such as ischemic stroke and cerebral abscess have been described in HPS, because of embolic material from the venous to systemic arterial circulation via the abnormal dilated pulmonary vessels.[33,34] Patients with HPS have an increased mortality. Liver transplantation, or correction of portacaval shunt in the case of an Abernathy malformation, remains the only effective treatment at present. After these interventions, the acquired pulmonary shunting might be reversible.[32,35,36] Saline TTCE is the most sensitive and commonly used test for the detection of HPS[37] and is performed in every analysis for liver transplantation. Prompt recognition of this syndrome with pulmonary shunting and timely referral are important to improve outcomes in patients with severe liver disease.

Pulmonary Shunting after Cavopulmonary Anastomosis

The occurrence of pulmonary right-to-left shunting has also been described years after correction of some congenital heart defects with cavopulmonary anastomosis (the Glenn procedure),[38] which can be a major factor for late clinical deterioration in these patients.[39] For example, in patients with single-ventricle hearts, the pulmonary artery can be transected and anastomosed end to end to the superior caval vein so that blood returning from the upper body is oxygenated in both lungs (the bidirectional Glenn procedure). It has been reported that PAVMs with pulmonary shunting on saline TTCE develop in up to 71% of these patients.[40] Miscellaneous forms of other congenital heart disease with direct drainage of hepatic veins into the left atrium have also been associated with pulmonary shunting.[41,42]

TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY USING AGITATED SALINE

Technique

Saline TTCE is an excellent technique for the evaluation of pulmonary right-to-left shunting. The procedure can be performed by placing an intravenous line to which two 10-mL syringes are

connected, one filled with 8 mL physiologic saline solution and the other with 1 mL air. Subsequently, 1 mL blood is drawn in the air-filled syringe and mixed with the saline-filled syringe by reverse flushing between both syringes, creating agitated saline with microbubbles. The patient is then positioned in the left lateral position, and 5 mL fresh agitated saline is injected within 3 sec in the right antecubital vein, while simultaneously projecting the four-chamber apical view with two-dimensional echocardiography. The agitated saline contains microbubbles that are easily visualized as contrast in the right-sided heart chambers, compared with the normally echolucent blood. In persons without right-to-left shunting, the contrast appearing in the right-sided heart chambers gradually dissipates as the microbubbles become trapped in the pulmonary circulation. The agitated saline should not be injected through an intrapulmonary catheter in wedge position, as microbubbles may then cross the pulmonary capillary bed. Saline TTCE is preferably performed at specialized centers using a standard protocol, such that it can be performed by a constant group of trained echocardiographers and interpreted by cardiologists with expertise in both pulmonary and intracardiac right-to-left shunting, to achieve the accuracy reported in literature.

Pulmonary versus Cardiac Right-to-Left Shunting on Saline TTCE

After contrast injection, the left-sided heart chambers should be closely observed for the potential appearance of microbubbles, its timing, and especially shunt origin. All right-to-left shunts visualized through pulmonary veins should be classified as pulmonary shunting. Only in the case of poor visualization of shunt origin, saline TTCE has been variably defined as positive for pulmonary shunting on the basis of a delay of more than three or four cardiac cycles before microbubbles appear in the left atrium after their first appearance in the right atrium, but there is no clear scientific evidence for a precise delay of three or four cardiac cycles to distinguish intracardiac from pulmonary shunting.[43] In the case of PAVMs, the delay of contrast appearance in the left atrium depends on the quantity, anatomic locations, and sizes of PAVMs, and a delay of two to eight cardiac cycles has been previously described for pulmonary shunting.[1,25,26,44-47] However, one should remain cautious about depending solely on the timing of appearance of microbubbles as proof of their route of transmission between the right and left heart chambers. Detailed echocardiographic parameters such as left ventricular function, valvular heart disease, right ventricular systolic pressure, heart rate, cardiac output, anemia, imaging depth, different acoustic views, and positioning of the acoustic focus may in theory also influence the timing and amount of left-sided microbubbles but are not recorded in a standard manner in most literature. In our opinion, a delay of more than three cardiac cycles should be accepted as the low threshold for pulmonary shunting on saline TTCE, when shunt origin cannot be visualized. In daily practice, microbubbles appearing in the left atrium with a delay of two to three cardiac cycles and no clear shunt origin can be considered indeterminate right-to-left shunts, and additional transesophageal echocardiography or chest CT can be performed.[48,49] At experienced centers, this scenario occurs in only 4.0% of patients screened for HHT.[20]

Respiratory maneuvers such as the Valsalva maneuver may induce transient appearance of mild contrast in the left atrium, independent of venous injection of saline contrast. This is called the rouleaux phenomenon (or nonsmoke spontaneous individual contrast).[50] This rouleaux formation is caused by blood flow stasis in the pulmonary vein during the respiratory maneuver and is dependent on red blood cell interactions with plasma protein components.[51] The echo density of this rouleaux formation is lower than that of the saline contrast and is not indicative of true right-to-left shunting. To allow better distinction between rouleaux formation and true (intracardiac) right-to-left shunting, the Valsalva maneuver should ideally also be performed before saline contrast injection. The diagnosis of PAVM-related pulmonary shunting depends on a saline contrast injection without the Valsalva maneuver and is therefore not hindered by the rouleaux phenomenon.

In addition, respiration induces cyclic physiologic modifications of intracardiac hemodynamics. These changes are related to variations in intrathoracic pressure, systemic and pulmonary venous return, and the interdependence among the four cardiac chambers. With inspiration, intrathoracic pressure decreases, which results in augmented flow into the right atrium and ventricle, with decreased flow out of the pulmonary veins into the left atrium and ventricle. With expiration, intrathoracic pressure increases, resulting in mild decrease in right ventricular diastolic filling and subsequent increase in left ventricular filling. Under normal circumstances, the peak velocity of mitral inflow varies by $\leq$15% with respiration and tricuspid inflow by $\leq$25%.[52] These respiration-related normal variations of cardiac hemodynamics may therefore influence the timing of both intracardiac and pulmonary shunting on saline TTCE. Without a Valsalva maneuver, it is possible that the pressure gradient between the right and left atria becomes high enough for intracardiac shunting during certain parts of the normal respiratory cycle, which may then lead to a marked delay in the appearance of microbubbles in the left ventricle, mimicking pulmonary shunting. Therefore, it is important to perform saline TTCE both with and without the Valsalva maneuver during normal respiration.

Different Pulmonary Shunt Grades on Saline TTCE

To increase the usefulness of saline TTCE as a first-line screening technique for the detection of pulmonary right-to-left shunting, an echocardiographic pulmonary shunt grading system was proposed by Barzilai *et al.*[44] Their classification relied on the relative opacification of the left ventricle with microbubbles on a scale ranging from 1 to 4, representing, respectively, minimal, moderate, and extensive opacification without or with outlining of the endocardial definition. Because this classification lacks objective characteristics to differentiate between shunt sizes, it might be susceptible to subjective interpretation. Furthermore, the distinction between grade 3 and 4 pulmonary shunts can be rather difficult in clinical practice, as the cutoff point between presence and absence of endocardial outlining is not always clear. Therefore, we[7,23,53] choose to use a quantitative grading system, based on the maximum number of microbubbles counted in the left ventricle in one still frame. With this system, a pulmonary shunt can be graded as 1 ($\leq$29 microbubbles), 2 (30–100 microbubbles), or 3 ($>$100 microbubbles), meaning that the grade 4 shunt described by Barzilai *et al.* is included in our grade 3 pulmonary shunt on saline TTCE (Figure 1, Videos 1A–1D; available at www.onlinejase.com). High interobserver agreement with κ coefficients of 0.85 to 0.94 has been reported for this quantitative echocardiographic pulmonary shunt grading system.[23,54] This illustrates that pulmonary shunt grading on saline TTCE can be very reliable at clinics with specific expertise in TTCE, but it remains uncertain whether this also applies to centers without this experience. One important element is a standardized method of saline contrast preparation and injection, to ensure that the number of microbubbles injected from patient to patient is relatively uniform. There have been concerns that quantification of pulmonary shunt grade on saline TTCE may become difficult in the gray zone between grades 1 and 2. However, in a previous study,

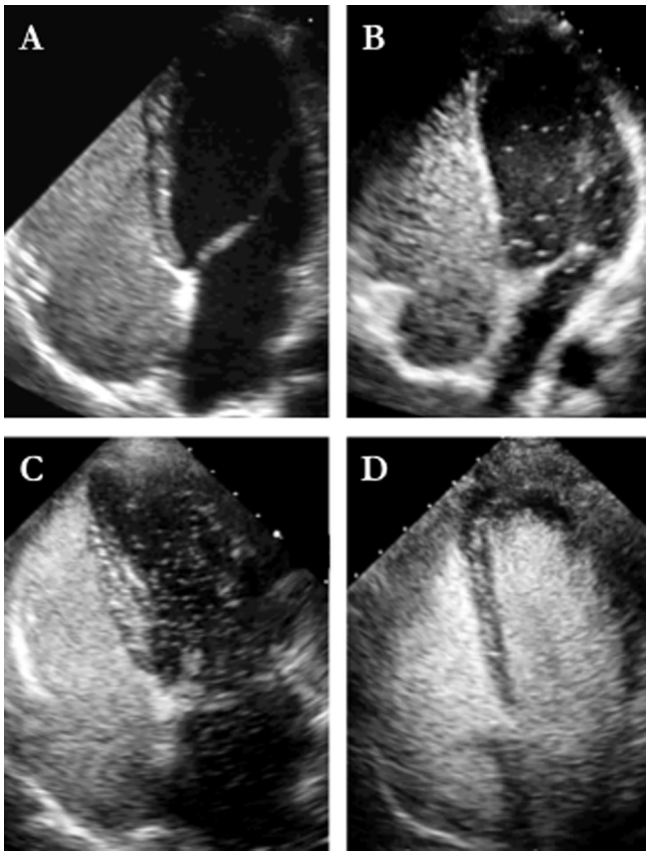

Figure 1 Different pulmonary shunt grades on saline TTCE. Apical four-chamber view, using saline TTCE. **(A)** No shunt; **(B)** grade 1; **(C)** grade 2; **(D)** grade 3. Adapted from Velthuis *et al*.[20] and reproduced with permission of the European Respiratory Society. *TTCE*, Transthoracic contrast echocardiography.

investigators analyzed all saline transthoracic contrast echocardiograms with pulmonary shunt grades of 1 and 2 and observed that this scenario was not frequently seen; a bubble range between a maximum of 27 and 32 bubbles was encountered in only 3.7% of patients with a pulmonary shunt of either grade 1 or 2.[55] The mean numbers of microbubbles in the left ventricle in that study[55] were 10 and 49 for grades 1 and 2 pulmonary shunt grade, respectively, on saline TTCE.

CLINICAL IMPLICATIONS OF PULMONARY SHUNTING ON SALINE TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY

Pulmonary Shunt Grade on Saline TTCE and Clinical Diagnosis of HHT

Although genetic testing for HHT-causing gene mutations has improved in the past few years and become more widely available, deoxyribonucleic acid analysis per se is not always sufficient in diagnosing HHT. Previous studies have described mutation detection rates of 72% to 93% in patients with clinically confirmed HHT,[56-59] and underuse of genetic testing has been reported in first-degree relatives at risk for HHT.[60] Therefore, an accurate clinical evaluation remains essential in all persons with suspected HHT. This clinical diagnosis of HHT is established according to the four Curaçao criteria, consisting of spontaneous and recurrent epistaxis, telangiectasias at characteristic sites, a first-degree relative with HHT, and the presence of visceral arteriovenous malformations. Three criteria suffice for a definite diagnosis of HHT, two criteria are considered to suggest possible HHT, and one or no criteria make the diagnosis unlikely.[61] The current clinical Curaçao criteria, based on chest CT for the detection of PAVMs, already offer good diagnostic performance compared with genetic testing.[62] A recent study specifically evaluated the new role of pulmonary shunting on saline TTCE as a clinical Curaçao criterion.[55] Although a grade 1 pulmonary shunt on saline TTCE is found significantly more often in patients with HHT compared with a control population,[23] it has been demonstrated that only the addition of grade ≥2 pulmonary shunts on saline TTCE to the current Curaçao criteria further increases their sensitivity to 90%, without affecting specificity (74%).[55] Grade 1 pulmonary shunts on saline TTCE are also documented in 6% to 28% of healthy individuals without HHT,[23,27,63] and accepting these small pulmonary shunts as a positive Curaçao criterion therefore leads to more false-positive clinical diagnoses of HHT,[55] which should be prevented. In our own experience, the presence of a grade 1 pulmonary shunt on saline TTCE in healthy individuals (without HHT) is closer to 8% than 28%.[23,55] Respiratory variations with potential delayed appearance of microbubbles in the left ventricle may have mimicked pulmonary shunting in a study by Woods *et al*.,[63] who described a relatively high prevalence of small pulmonary shunts in healthy subjects. Furthermore, that study could have been biased toward volunteers with migraine (as the study advertisements described a research study investigating shunts and migraine), in whom a higher prevalence of pulmonary shunting has been reported.[9]

Pulmonary Shunt Grade on Saline TTCE and Risk for Neurologic Complications

A paradoxical embolization is considered the likely predominant mechanism of stroke and/or brain abscess in patients with HHT and PAVMs.[64] Pulmonary shunting may also be a potentially unrecognized facilitator of otherwise cryptogenic stroke, transient ischemic attack, or brain abscess.[65] Recognizing patients at risk is important to facilitate appropriate management strategies. In patients with patent foramen ovales, larger diameter and more extensive or permanent interatrial right-to-left shunts on saline TTCE are associated with a significantly higher prevalence of cerebral ischemic stroke.[66] Therefore, it has been hypothesized that the risk for paradoxical embolization in patients with pulmonary shunting also depends on the relative perfusion of PAVMs, but evidence has remained conflicting. Moussouttas *et al*.[5] previously included 75 patients with PAVM-feeding artery diameters of ≥3 mm on pulmonary angiography and evaluated the presence of cerebral paradoxical embolization. The prevalence of ischemic stroke in that study increased from 14% in patients with single PAVMs to 27% in those with multiple PAVMs on pulmonary angiography, and the prevalence of brain abscess also increased twofold in patients with multiple PAVMs, suggesting an increased predisposition to neurologic complications in patients with greater numbers of PAVMs.[5] However, in another cohort of 219 patients with PAVMs on chest CT, investigators could not find an association between PAVM-feeding artery diameter on chest CT and risk for stroke or brain abscess.[6] Gazzaniga *et al*.[23] was the first to suggest a potential relation between pulmonary shunt size on saline TTCE and neurologic complications. Saline TTCE represents a functional measurement of pulmonary shunting, instead of

the anatomic shunt measurement by chest CT, which may explain their different findings. More recently, the study by Gazzaniga *et al.* was confirmed in a large, two-center, retrospective study, which demonstrated a striking association between pulmonary shunt size on saline TTCE and prevalence of neurologic complications in 1,038 subjects with (suspected) HHT.[7] Neurologic complications were found in 0.4%, 6.5%, and 20.9% of patients with grades 1, 2, and 3 pulmonary shunts, respectively, on saline TTCE.[7] A grade 1 pulmonary shunt on saline TTCE was not significantly associated with an increased prevalence of neurologic complications (0.4%), compared with patients with negative results on TTCE (1.4%).[7]

Pulmonary Shunt Grade on Saline TTCE and Feasibility for Transcatheter Embolotherapy

It has been demonstrated that the probability of detecting PAVMs on chest CT increases with higher pulmonary shunt grade on saline TTCE.[20,23,46,47,54] A recent study confirmed that the positive predictive value of grades 1, 2, and 3 pulmonary shunts on saline TTCE for the presence of PAVMs on chest CT is 13%, 45%, and 93%, respectively.[20] Interestingly, recent studies have also revealed that the feasibility of transcatheter embolotherapy of PAVMs on chest CT is strongly related to pulmonary shunt grade on saline TTCE.[20,23,46,47,54] Persons with grade 1 pulmonary shunts on saline TTCE do not have treatable PAVMs on chest CT, whereas transcatheter embolotherapy of PAVMs can be performed in 25% and 77% of patients with grades 2 and 3 pulmonary shunts, respectively, on saline TTCE.[20]

Is It Safe (Not) to Perform Saline TTCE?

There have been concerns about the safety of saline TTCE, and screening for pulmonary shunting therefore still takes place with only chest CT at some centers. Potential complications of saline TTCE might be related to the injection of a small amount of air (0.5–1.0 mL) in combination with the presence of possible right-to-left shunting and subsequent risk for systemic air emboli. However, the safety of saline TTCE was well documented in a large retrospective survey of 363 physicians regularly performing contrast echocardiography conducted by the American Society of Echocardiography.[67] In that survey, an estimated total of 27,000 contrast echocardiographic procedures were performed over a 16-year period. Saline TTCE indeed appeared to carry some risk for side effects (transient neurologic deficits, lightheadedness, visual sparks, flashing lights, scotomata, central and peripheral numbness, nausea, vagal symptoms, and anxiety), but this risk was low (prevalence, 0.062%), and, importantly, no residual side effects or complications were reported. These observations by Bommer *et al.*[67] are supported by a very low incidence of minimal and self-resolving side effects in more recent studies.[23,46,68] However, it remains important to stress that only a small amount of air is needed for the detection of right-to-left shunting with saline TTCE, and even simple vigorous reverse flushing of saline between syringes may suffice in some cases. However, microbubbles created by vigorous shaking alone (with no air) have a shorter life and may not reach the heart in sufficient numbers and can therefore influence the TTCE grading system of pulmonary shunting presented in this review.

One could also reverse the question to "Is it safe not to perform saline TTCE?" as it has been demonstrated that chest CT produces negative results in 55% and 8% of patients with grades 2 and 3 pulmonary shunts, respectively, on saline TTCE.[20] This enhances the importance of saline TTCE compared with chest CT in the detection of pulmonary shunting. In some cases, chest CT might only suggest the presence of significant pulmonary shunting by a more rapid transit of blood across the pulmonary vasculature. These pulmonary shunts probably represent diffuse microscopic PAVMs below the detection limit of chest CT, but should be regarded as a positive Curaçao criterion in the clinical diagnosis of HHT[55] and appear to confer increased risk for neurologic complications[7] where antibiotic prophylaxis is advised before procedures with high risk for bacteremia to prevent brain abscesses, according to the international guideline for the diagnosis and management of HHT.[10]

How to Handle Small Pulmonary Shunts on Saline TTCE: Does Any Bubble Matter?

Additional chest CT and antibiotic prophylaxis is already deferred in patients with HHT with negative results on TTCE,[10] but whether this strategy is also safe in all persons with only grade 1 pulmonary shunts on saline TTCE is currently unknown. This question is of additional interest, because the presence of small pulmonary shunts on saline TTCE has also been reported in a significant proportion of healthy individuals without HHT.[23,27,63] The common opinion is that the appearance of microbubbles in the left-sided heart chamber is pathologic, in the absence of intracardiac shunting. The normal pulmonary capillary diameter is about 5 to 10 μm and does not exceed 13 μm, even under high nonphysiologic perfusion pressures.[69] The estimated size of microbubbles entering the pulmonary circulation is 60 to 90 μm,[70] so most saline microbubbles are filtered out in the pulmonary capillary network. However, it has also been demonstrated that microspheres 25 to 50 μm in size are able to traverse the pulmonary vasculature of human lungs under physiologic perfusion and ventilation pressures,[70] and microbubbles can shrink or fracture into smaller ones that can traverse the pulmonary capillary network.[71] Furthermore, microbubbles that are trapped in a capillary may eventually be released to the venous pulmonary circulation once enough gas has diffused out to enable reversal of entrapment. These small saline microbubbles have a high internal pressure because of surface tension effects. The gas inside (nitrogen and oxygen) will therefore rapidly diffuse down its concentration gradient into blood, which decreases bubble size and accelerates total dissolution.[71] The mean pulmonary capillary transit time of red blood cells is $\geq$750 msec, and this does not fall below 450 msec, even with nonphysiologic cardiac output of 30 L/min.[72,73] A transit time from the main pulmonary artery to the left atrium of $\geq$6 sec has also been reported.[72] For example, an 8-μm bubble will completely dissolve in 190 to 550 msec, which is clearly shorter than the time needed for a microbubble to pass from a pulmonary capillary to the left atrium.[74] Therefore, almost all injected saline microbubbles are usually undetectable in the left-sided heart by echocardiography.

The current guidelines on the diagnosis and management of PAVMs and HHT advise additional chest CT in case of any pulmonary shunt on saline TTCE,[10] to confirm the necessity of transcatheter embolotherapy of PAVMs. We believe that chest CT can be safely withheld in the presence of a grade 1 pulmonary shunt on saline TTCE, as any PAVM found on chest CT will be too small for subsequent transcatheter embolotherapy,[20,23,46,47,54] and these small echocardiographic shunts do not appear to be associated with an increased risk for neurologic complications.[7]

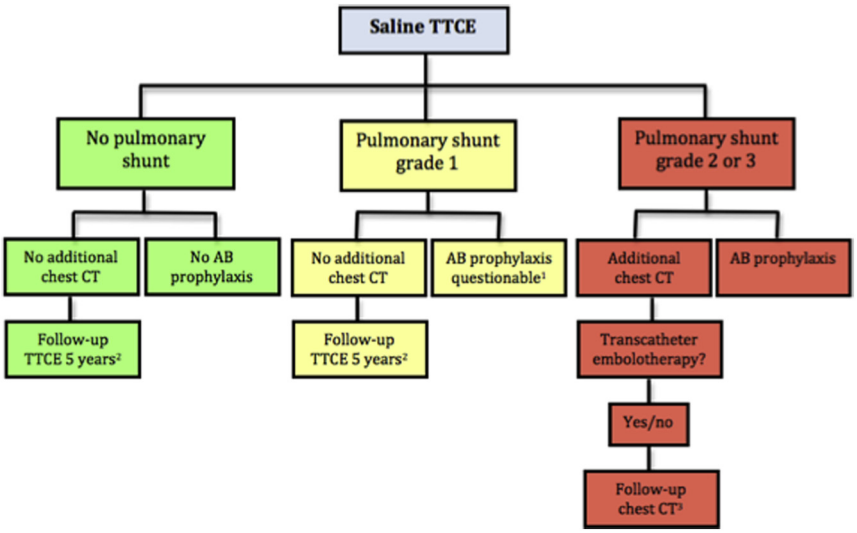

Figure 2 Suggested new screening algorithm for the detection of PAVMs in HHT. [1]Although still advised by the present guideline, the true role of antibiotic (AB) prophylaxis for patients with only grade 1 pulmonary shunts on saline TTCE is currently unclear and needs to be reconsidered. [2]Only in case of proven HHT. [3]Chest CT 4 to 6 months after embolization, followed by every 3 years. Chest CT every 5 years in case of no treatable PAVM. The suggested algorithm is based partly on common clinical practice, and reduction in neurologic or other outcomes by following this algorithm has not been established. *CT*, Computed tomography; *HHT*, hereditary hemorrhagic telangiectasia; *PAVM*, pulmonary arteriovenous malformation; *TTCE*, transthoracic contrast echocardiography.

Deferring chest CT in all such patients could result in a tremendous cost saving and a reduction in radiation exposure in mainly young adults.[53] This strategy would be in line with a recently published position paper from the European Society of Cardiology that cautions against inappropriate radiation exposure if the needed information can also be obtained with nonionizing tests of comparable accuracy.[75]

In addition, the current guidelines on the diagnosis and management of PAVMs and HHT also recommend the prescription of antibiotic prophylaxis before procedures with risk for bacteremia in patients with HHT with any pulmonary shunting on saline TTCE, to prevent brain abscesses.[10] Our present review now sets the stage for further discussion about the need for antibiotic prophylaxis in all persons with only grade 1 pulmonary shunts on saline TTCE, as these shunts are not associated with an increased prevalence of neurologic complications in a recent large retrospective study,[7] and there are no other data to support the use of antibiotic prophylaxis in these subjects. It may be interesting to extrapolate this question to the previous discussion about antibiotic prophylaxis in the prevention of infective endocarditis, which, like brain abscesses in patients with HHT, is also an uncommon but a serious and often life-threatening condition. The lack of solid epidemiologic evidence for benefit of antibiotic prophylaxis, together with the more frequent occurrence of antibiotic resistance and side effects as significant public health problems, lead to the extensive revised international guideline on the prevention of endocarditis.[76] It is striking that the restricted indications for antibiotic prophylaxis to prevent endocarditis were not based on new data but more on a change in philosophy. The aim to narrow the indication for antibiotic prophylaxis seems to be a healthy trend, and the true role of antibiotic prophylaxis in all patients with only grade 1 pulmonary shunts on saline TTCE is questionable and needs to be reconsidered. However, we realize that a prior brain abscess in a patient with a grade 1 pulmonary shunt on saline TTCE may pragmatically lead to antibiotic prophylaxis in the future.

Follow-Up of Pulmonary Shunts on Saline TTCE

The current guidelines on the diagnosis and management of PAVMS and HHT recommend long-term follow-up for patients with PAVM-related pulmonary shunting, to detect growth of untreated PAVMs and also reperfusion of treated PAVMs.[10] In patients with pulmonary shunting on saline TTCE without (treatable) PAVMs on chest CT, follow-up is currently advised with chest CT approximately every 1 to 5 years on a case-by case basis, with consideration for limiting radiation exposure.[10] Although we do not yet have sufficient long-term data on potential growth of PAVMs, it seems conceivable that follow-up of patients with HHT with no or grade 1 pulmonary shunts on saline TTCE could be performed by TTCE every 5 years, also depending on age. Additional chest CT would then be indicated only if the echocardiographic pulmonary shunt size increases to ≥grade 2. Grades 2 and 3 pulmonary shunts on initial saline TTCE can be followed by chest CT every 5 years, as can patients with treated PAVMs, because saline TTCE continues to produce positive results in 90% of cases after transcatheter embolotherapy.[77]

Potential New Screening Algorithm for the Detection of PAVMs in Patients with (Suspected) HHT

Considering the recent advances in understanding the clinical implications of pulmonary shunting on saline TTCE described in this review, we can suggest an adjusted screening algorithm for the detection of PAVMs in patients with (suspected) HHT (Figure 2). One should keep in mind that this algorithm is based partly on common clinical practice, as much supporting data other than presented in the present review are lacking. Using our suggested strategy, however, additional chest CT and antibiotic prophylaxis may be prevented in about 22% of individuals screened for HHT.[7] The recent advances in understanding the clinical implications of pulmonary shunting on saline TTCE described in this review will be discussed at the next consensus conference on PAVMs and HHT.

CONCLUSIONS

Abnormal pulmonary right-to-left shunting can be present in case of HHT or HPS or after correction of specific heart defects using cavopulmonary anastomosis. Saline TTCE is safe and is the preferred technique for the detection of pulmonary shunting in these patients. Subsequent quantification of different pulmonary shunt grades on saline TTCE further enhances its clinical value. Small pulmonary shunts on saline TTCE (grade 1) lack any clinical implication, as these shunts cannot be used as a diagnostic criterion for HHT, are not associated with increased risk for neurologic complications due to paradoxical embolization, and represent PAVMs that are too small for endovascular embolotherapy. This suggests that additional chest CT can be safely withheld in all patients with only small pulmonary shunts on saline TTCE (grade 1) and sets the stage for further discussion about their need for antibiotic prophylaxis. Besides further optimization of the current screening algorithm for the detection of PAVMs in HHT and better understanding of pulmonary shunting in other pathologic conditions, these observations can be of additional clinical importance, because small pulmonary shunts on saline TTCE (grade 1) are also documented in a significant proportion of healthy individuals.

Not any bubble matters!

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SUPPLEMENTARY DATA

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