STATE-OF-THE-ART REVIEW ARTICLE

Clinical Implications of Pulmonary Shunting on Saline Contrast Echocardiography

Sebastiaan Velthuis, MD, PhD, Elisabetta Buscarini, MD, PhD, James R. Gossage, MD, PhD, Repke J. Snijder, MD, Johannes J. Mager, MD, PhD, and Martijn C. Post, MD, PhD, *Nieuwegein, The Netherlands; Crema, Italy; and Augusta, Georgia*

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.

From the Department of Cardiology (S.V., M.C.P.) and the Department of Pulmonology (R.J.S., J.J.M.), St Antonius Hospital, Nieuwegein, The Netherlands; the Department of Gastroenterology, Maggiore Hospital, Crema, Italy (E.B.); and the Department of Medicine, Georgia Regents University, Augusta, Georgia (J.R.G.).

Reprint requests: Sebastiaan Velthuis, MD, PhD, Department of Cardiology, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands (E-mail: s.velthuis@antoniusziekenhuis.nl).

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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