International Journal of Cardiology 218 (2016) 240–245

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Screening pulmonary arteriovenous malformations in a large cohort of Spanish patients with hemorrhagic hereditary telangiectasia☆,☆☆

José Antonio Parra [a,*,1], José María Cuesta [b], Roberto Zarrabeitia [c], Concepción Fariñas-Álvarez [d], Jesús Bueno [e], Sarah Marqués [e], Carmen Parra-Fariñas [f], María Luisa Botella [g], Carmelo Bernabéu [g], Jesús Zarauza [h]

[a] Department of Radiology Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain
[b] Department of Cardiology, Hospital Sierrallana, Torrelavega, Cantabria, Spain
[c] Department of Internal Medicine, Hospital Sierrallana and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Torrelavega, Cantabria, Spain
[d] Quality Unit, Hospital Universitario Marques de Valdecilla, Santander, Cantabria, Spain
[e] Department of Radiology, Hospital Sierrallana, Torrelavega, Cantabria, Spain
[f] Department of Radiology, Hospital Universitari Vall d´Hebron, Barcelona, Catalonia, Spain
[g] Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain
[h] Department of Cardiology, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain

ARTICLE INFO

Article history:
Received 29 December 2015
Received in revised form 6 April 2016
Accepted 12 May 2016
Available online 14 May 2016

Keywords:
Hereditary hemorrhagic telangiectasia
Pulmonary arteriovenous malformations
Transthoracic contrast echocardiography
Computed tomography
Ultrasound contrast agents

ABSTRACT

Background and objectives: Because of the serious nature of potential complications, screening for pulmonary arteriovenous malformations is required in patients with hereditary hemorrhagic telangiectasia. The aim of this study was to evaluate the utility of contrast echocardiography and compare the performance of two contrast agents: agitated saline and Gelofusine.

Material and methods: Two hundred and five patients screened for PAVMs using TTCE and computed tomography (CT) performed with an interval of less than 180 days. Contrast echocardiography studies were graded on a 4-point semiquantitative scale based on the amount of microbubbles seen in left heart chambers.

Results: Positive TTCE findings were seen in 137 (66.8%) patients, whereas CT confirmed PAVMs in 59 (43.1%). Two of 67 grade 1 patients; 18 of 42 grade 2; 17 of 22 grade 3 and all grade 4 had PAVMs on CT. Embolotherapy was feasible in 38.9% patients in grade 2 and 82.3% and 95.2% in grades 3–4. No patients in grade 1 were embolized. The mean cardiac cycle in which bubbles were first seen in the left heart in patients without and with PAVMs on CT was 6.1 and 3.9 ($p < 0.0001$). Compared to saline, Gelofusine produced an overall increase in grade.

Conclusions: No grade 1 patients had treatable PAVMs. There is a need for improvement in the selection of patients for CT in grade 2, where less than half have PAVMs on CT. The cardiac cycle may help to differentiate between patients with and without PAVMs. Gelofusine was not better than saline for PAVM screening.

1. Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a rare (1 in 5000 to 8000 people) disorder, transmitted in an autosomal dominant trait; with more than 90% of the cases caused by mutations in Endoglin (*ENG*; HHT1), activin A receptor type II-like 1 (*ACVRL1*/*ALK1*; HHT2), or SMAD4 (Hereditary hemorrhagic telangiectasia and Juvenile polyposis; HTJP) genes [1,2]. These mutations, together with other environmental factors promote the development of small (telangiectasia) or large arteriovenous malformations (AVMs) in almost all organs of the economy [1,2]; including the lung, where pulmonary arteriovenous malformations (PAVMs) are a common finding. This is especially true among HHT1 patients in whom pulmonary shunts are seen in up to 85% of these patients [3–7]. PAVMs create a right-to-left shunt between the pulmonary arterial and venous circulation that can lead to hypoxemia, paradoxical embolism, or rupture and, as a consequence, not

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

☆☆ This study has been supported by grants from *Instituto de Salud Carlos III* (ISCIII; PI11/0246 to JAP), FEDER (to JAP), *Ministerio de Economía y Competitividad* of Spain (SAF2011-23475 to LMB and SAF2013-43421-R to CB), and *Centro de Investigación Biomédica en Red de Enfermedades Raras* (CIBERER; ISCIII-CB06/07/0038 to CB). CIBERER is an initiative of the *Instituto de Salud Carlos III* (ISCIII) of Spain supported by FEDER funds.

* Corresponding author at: Department of Radiology, Hospital Universitario Marqués de Valdecilla, Avd. Valdecilla s/n, Santander, 39008, Cantabria, Spain.
E-mail addresses: japarra@humv.es (J.A. Parra), jmccbuelna@hotmail.com (J.M. Cuesta), roberto.zarrabeitia@scsalud.es (R. Zarrabeitia), cfarinas@humv.es (C. Fariñas-Álvarez), jesus.bueno@scsalud.es (J. Bueno), sarah.marques@scsalud.es (S. Marqués), carmenparrafarinas@gmail.com (C. Parra-Fariñas), cibluisa@cib.csic.es (M.L. Botella), bernabeu.c@cib.csic.es (C. Bernabéu), manuel.zarauza@humv.es (J. Zarauza).
[1] Associate professor, University of Cantabria.

http://dx.doi.org/10.1016/j.ijcard.2016.05.065
0167-5273/

infrequently a brain abscess, stroke, or hemoptysis is seen in individuals with a previously undiagnosed PAVM [2–4]. Recent data also, highlight that reduced oxygenation of blood due to pulmonary AVMs results in a graded erythrocytotic response to maintain arterial oxygen content, and higher stroke volumes and/or heart rates to maintain oxygen delivery [8]. This latter situation can also be aggravated in HHT patients by the anemia resulting from iron losses due to bleeding from nasal and gastrointestinal telangiectasies [8]. Anatomic resolution of PAVMs through embolization, has been shown to reduce strokes, migraines, and hematologic, cardiac and ventilatory demands [2].

Because of the serious nature of these potential complications and benefits for embolization screening for PAVMs is recommended in HHT patients [9]. Transthoracic contrast echocardiography (TTCE) followed by CT in patients testing positive with this technique is the recommended imaging method in the last 2010 clinical guideline [9]. Nonetheless, positive TTCE findings are relatively common in patients with HHT (60% to 85% of patients tested) [3,10,11], whereas a much smaller percentage of between 21% and 52.3% actually shows PAVMs on CT [12]. Therefore, adherence to clinical guideline recommendations would result in a large number of unwarranted CT studies, implying unnecessary radiation exposure and healthcare expenditure [2,13–15]. The results of a previous study by our group [13] and those of other authors [10,14,16] have indicated that use of a system to grade the passage of contrast material on TTCE to estimate the size of pulmonary shunts is of value for selecting patients who should subsequently undergo CT evaluation. Two TTCE grading systems have been proposed: a 4-grade scale [10,13,17] and a 3-grade scale [7,14,16]. The main difference between the two options is that grades 3 and 4 in the 4-grade scale correspond to grade 3 in the 3-grade scale. At present, the indication for CT seems clear in patients showing moderate or extensive contrast passage using these scales (grades 2, 3, and 4). In patients with a pulmonary shunt grade 1, according to the work of Velthuis et al. [18], a conservative management strategy (without CT and antibiotic prophylaxis) is probably justified considering the absence of treatable PAVMs and the negligible risk of cerebral paradoxical embolism in this subset of patients. An interesting question in TTCE grade 1 is to know if these positive results are a consequence of very small PAVMs or the results of normally present intrapulmonary arteriovenous anastomosis [19]. An increase in cardiac output has been shown to produce an increase of blood flow through to this normally present intrapulmonary arteriovenous anastomosis in healthy patients [20].

Most echocardiography studies carried out in HHT patients use an agitated saline solution as the contrast agent. However, other contrast options are available, such as the colloid solution, Gelofusine (Braun Medical, Melsungen, Germany). Gelofusine is reported to provide better opacification of the heart chambers than agitated saline solution [21], as the bubbles formed are smaller [22,23] and more stable [24]. Use of Gelofusine may result in a smaller number of suboptimal studies relative to saline contrast [21,24].

Based on this background, the aim of this study was to assess the use of graded contrast echocardiography for selecting Spanish HHT patients to undergo CT, and evaluate the performance of agitated saline solution versus Gelofusine as contrast media. To the best of our knowledge, this is the first study comparing these two contrast agents in the screening of PAVMs of HHT patients.

2. Materials and methods

From January 2003 to December 2014, 664 patients with suspected HHT were seen in our HHT unit through one of the following channels: ambulatory visit, hospital admittance, or genetic testing alone. Patients seen through either of the first 2 channels underwent a hospital protocol that included a clinical history-taking, physical examination, laboratory testing, genetic testing, TTCE, chest or abdominal CT, abdominal ultrasound, and brain or lumbar MRI, when clinically justified. Only patients who underwent TTCE and CT within an interval of ≤180 days between the two techniques were included in the study. Patients in whom a persistent foramen ovale was detected were excluded. The hospital ethics committee for clinical research of the Autonomous Community of Cantabria approved the study protocol. All patients provided written consent for participation. The presence or absence of anemia was considered in women and men when hemoglobin (Hb) levels were lower than 12 g/dL, and 13,5 g/dL, respectively.

The TTCE technique, previously used by our team and described by others [13,14], was performed by 3 experienced echocardiographers, following intravenous line placement in an antecubital vein. The two contrast agents, agitated saline (9 mL saline solution mixed with 0.5 mL room air and 0.5 mL of blood from the patient) and Gelofusine (10 mL), were administered with the patient in left lateral decubitus. A four-chamber view was used, and TTCE was considered positive for pulmonary shunting when bubbles were observed in the left atrium without application of the Valsalva maneuver. The number of cardiac cycles that occurred before bubbles appeared in the left atrium was recorded and a delay of >3 cycles was established to differentiate PAVMs from intracardiac shunt [25]. Shunts visualized through a pulmonary vein were classified as pulmonary shunts regardless of the cardiac cycle [12]. A second study with the Valsalva maneuver was performed when contrast was present in the left atrium in less than four cardiac cycles. The study was considered positive for PAVM if intracardiac shunts were not visualized by color Doppler and the pattern of appearance of bubbles was not modified by Valsalva. Based on the amount of bubbles visible in the left ventricle, TTCE findings were rated according to the grading system of Barzilai et al. [17], modified by Zukotynski et al. [10] and used in our previous study [13] into ×4 grades: grade 1, minimal left ventricular opacity (up to 20 bubbles); grade 2, moderate opacity; grade 3, extensive opacity without outlining the endocardium; and grade 4, extensive opacity with endocardial definition.

TTCE with agitated saline contrast was performed in all patients. Between 2008 and 2014, patients additionally underwent TTCE using Gelofusine to determine whether there were differences in screening outcomes versus saline. The same protocol described above was used, and the Gelofusine study was performed a few minutes after the saline study in the same session after making sure that there were no bubbles from the previous study.

Chest CT was carried out on 3 different multidetector systems over the study period: a 2-row Somatom AR.T scanner (Siemens, Erlangen, Germany), a 32-row LightSpeed scanner (General Electric, New York, USA), and an 80-row Aquilion Prime TSX-303A scanner (Toshiba Medical Systems Corporation, Japan), using ≤3 mm slice thickness [9]. Nonionic contrast agent (300 mg/mL iodine at a rate of 3 mL/s and maximum dose of 2 mL/kg) was routinely administered because in most of these patients the liver was included in the study in order to rule out hepatic arteriovenous malformations (HAVMs). These studies were performed in a caudo-cranial direction and always included an image acquisition in an early arterial phase [5,26]. The images obtained were evaluated by 3 radiologists with experience in HHT. Visualization of a nodule with an afferent artery and efferent vein was considered diagnostic for PAVM [5]. The presence of telangiectasies, perfusion disorders, vascular confluent masses or arteriovenous or veno-venous shunts was considered diagnostic for HAVMs [27]. In the assessments of TTCE and CT features, readers were blinded to the results of the other imaging study.

Revascularization of a previously treated PAVM was defined based on CT findings of a persistent aneurysmal sac with prominent afferent arteries and drainage veins [28,29]. Patients with an afferent artery measuring ≥3 mm, a PAVM with less size but suitable for embolization and those with CT criteria indicating revascularization [30] were sent to the angiography suite to plan embolotherapy.

2.1. Statistical analysis

Baseline characteristics of the patients were compared using a Mann–Whitney U test or Kruskal–Wallis test for continuous variables.