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Graded contrast echocardiography in pulmonary arteriovenous malformations

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ABSTRACT: To compare the results of transthoracic contrast echocardiography (TTCE) adding a grading scale with the results of thoracic computed tomography (CT) in order to optimise the use of both techniques.

95 patients with hereditary haemorrhagic telangiectasia (HHT) were examined with TTCE and thoracic CT to detect pulmonary arteriovenous malformations (PAVMs). According to previous studies, TTCE was divided into a four grade scale depending on the degree of opacification of the left ventricle after the administration of a contrast agent.

Of the 95 patients (50.5% female; mean age 46 yrs), none with normal or grade 1 TTCE had detectable PAVMs on thoracic CT. Shunts of grades 2, 3 and 4 were associated with PAVMs according to thoracic CT in 25, 80, and 100% of the cases. There was a statistically significant association between the TTCE grade and the detection of a PAVM by thoracic CT. There were also statistically significant associations between TTCE grade and the cardiac cycle when the contrast was first visible in the left atrium, and size of the feeding artery.

Graded TTCE and timing of left atrium opacification may be useful techniques in selecting HHT patients for PAVM screening with thoracic CT scans.

KEYWORDS: Hereditary haemorrhagic telangiectasia, Osler–Weber–Rendu syndrome, pulmonary angiography, pulmonary arteriovenous malformations, thoracic computed tomography, transthoracic contrast echocardiography

Hereditary haemorrhagic telangiectasia (HHT) or Osler–Weber–Rendu syndrome is a rare disorder (one in 5,000/8,000) [1, 2] transmitted in an autosomal dominant pattern and characterised by the progressive onset of epistaxis, mucocutaneous telangiectasias and vascular malformations that can develop in many organs, particularly the lung, where pulmonary arteriovenous malformations (PAVMs) are described in up to 48% of HHT patients [3]. According to the Curaçao criteria, the diagnosis of HHT is considered definite when three or more of the following criteria are present: spontaneous or recurrent epistaxis, multiple mucocutaneous telangiectasias, visceral vascular malformations or a first-degree relative with HHT [4]. The condition is suspected when only two of these features are present. Epistaxis is usually the earliest and most common manifestation of the disease.

Molecular genetic analysis has led to the identification of multiple HHT loci, with two genes (*ENG* and *ACRVL1*) being responsible for 90% of the described cases: *ENG* on the long arm of the chromosome 9 encoding for endoglin (type I HHT) and *ACVRL1* on the long arm of the chromosome 12 coding for the activin receptor like kinase (ALK-1) (type II HHT) giving rise to haploinsufficiency, the proposed origin for the pathogenicity of the disease [5–7]. In addition, other genetic and environmental influences probably participate in the HHT phenotype [8]. Type I HHT has been associated with an increased risk of PAVMs while type II HHT with hepatic vascular malformations [8–10].

Patients with PAVMs are particularly at risk of severe local complications (spontaneous haemothorax or massive haemoptysis, especially in pregnancy) [11], dyspnoea and neurological complications, such as transient ischaemic attack (6–37%), stroke (10–19%) or cerebral abscess (5–19%), due to the right to left shunt (RLS) that facilitates the passage of emboli into the cerebral circulation [12, 13]. Since these complications occur in asymptomatic individuals and can be effectively prevented by the safe procedure of embolotherapy, screening of asymptomatic HHT patients is recommended [14].

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Several screening tests have been proposed alone or in combination (chest radiography, arterial oxygen measurements, radionuclide studies or transthoracic contrast echocardiography (TTCE)) [3, 15, 16]. The current recommendation is to use TTCE as the initial screening test for PAVMs [14]. TTCE has, however, two main drawbacks; the first is the high false positive rate when compared to computed tomography (CT), probably in relationship with its ability to detect very small lesions [16, 17], and the second being from its incapacity to discriminate the size and localisation of the PAVMs, making it necessary to perform complementary tests.

For many years, pulmonary arteriography has been the gold standard for the study of patients under suspicion of having PAVMs. However, the development of multidetector technology, which allows the acquisition of multiple images in a short period of time, the possibility of image reconstruction in different planes and image analysis with different techniques (such us multiplanar reconstruction, maximum intensity projection or three-dimensional reconstructions), has converted CT to a powerful, sensitive and specific technique with a performance similar, or even superior, to angiography for the detection of pulmonary vascular disorders [18–21]. CT has, however, the drawback of using ionising radiation, which is recommended to be restricted, especially in young people.

Three recent articles [22–24] have emphasised the usefulness of a TTCE grading scale as a complementary tool to improve the selection of patients considered for a thoracic CT after TTCE in order to avoid unnecessary radiation exposure. Shunt grade on TTCE appears to be correlated with the presence of PAVMs on thoracic CT [24].

The purpose of this study was to compare the results of TTCE employing a graded scale with the results of thoracic CT in order to rationalise the utilisation of both techniques.

MATERIALS AND METHODS

A total of 125 HHT patients and their relatives were evaluated in the Sierrallana Hospital (Torrelavega, Spain) from June 2003 to June 2008. All patients were screened as part of the study protocol with a TTCE, thoracic CT and a genetic test. This study protocol was approved by the institutional review board.

TTCE

According to the established protocol, TTCE was performed by three experienced echocardiographers, by placing an intravenous line with a three-way stopcock to which two 10 mL syringes were connected. In the first studies, agitated saline solution was used (9 mL of saline solution mixed with 0.5 mL of air and 0.5 mL of blood), and in the rest, 10 mL agitated fluid gelatine, without mixed air (Gelofusine®; Braun Medical AG, Emmenbrücke, Switzerland). With the patients in left lateral decubitus position, and using a four-chamber view, TTCE results were defined as positive for RLS if contrast solution was observed in the left atrium after injection without a Valsalva manoeuvre. The number of cardiac cycles before the appearance of bubbles in the left atrium, after their first appearance in the right atrium, was measured. The presence of bubbles after three cardiac cycles was considered a sign of PAVM as opposed to intracardiac shunt [15]. A second study with Valsalva manoeuvre 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 shunt were not visualised by colour Doppler, and the pattern of appearance of bubbles was not modified by Valsalva. For each type of study, the amount of contrast visible in the left ventricle was graded according to the grading system proposed by BARZILAI *et al.* [25] in four grades: grade 1 indicates minimal left ventricular opacity (<20 bubbles), grade 2 indicates moderate opacity, grade 3 extensive opacity without outlining the endocardium and grade 4 extensive opacity with endocardial definition (fig. 1).

Thoracic CT

After performing an abdominal CT, a thoracic CT was made in a two detector CT with a section thickness of 3 mm, and a reconstruction thickness of 1.5 mm; 120 kV and 100 mAs. A nonionic contrast agent (300 mg of iodine per mL with a rate of 3 $mL \cdot s^{-1}$ and a maximum dose of 2 mL per kg) was administered routinely. In children, in whom abdominal CT was not performed, the study was made without the administration of a contrast agent with the kV and mAs adapted to the body habitus. Once the study was completed, it was evaluated by two experienced radiologists in interpreting thoracic CT for the presence of PAVMs, and the final diagnosis was reached by consensus. In all cases, the studies were evaluated in a work station in axial, multiplanar, maximum intensity projection and volume rendering reformations. The presence of a nodule with an afferent artery and efferent vein was considered diagnostic for lung PAVM on CT [18, 20]. In all of these positive cases, the number of the PAVMs, the location in the lung (central or peripheral) [20] and the size of the feeding artery were recorded. Both TTCE and thoracic CT were performed and interpreted blinded to the results of the other study.

Angiography

After a preliminary study of the main, right and left pulmonary arteries, embolisation of the PAVM was performed, when possible, by positioning a microcatheter (Rebar-18 microcatheter, eV3; Microtherapeutics Inc., Irvine, CA, USA) in the feeding artery. Embolisation was performed with electrodetachable coils (GDC 360, 3D and Vortex microcoils; Boston Scientific Corporation, Natick, MA, USA).

Statistical analysis

The positive predictive value (PPV) of TTCE was calculated using thoracic CT as the reference standard. The PPV represents the percentage of the sample with a given TTCE grade that was determined to have PAVMs on CT. A Pearson Chi-squared test for association was performed for variables not following a normal distribution, and unpaired t-tests were used to evaluate the association between the amount of contrast visualized in the left ventricle, the cardiac cycle where the contrast was first visualised in the left atrium with TTCE, and the presence of PAVMs on CT.

Linear regression analysis was performed to determine if there was an association between the TTCE grade and the size of the feeding artery and efferent vein. All tests were two-tailed, and p-values <0.05 were considered significant. Statistical analyses were performed using SPSS v15.0 (SPSS Inc., Chicago, IL, USA).

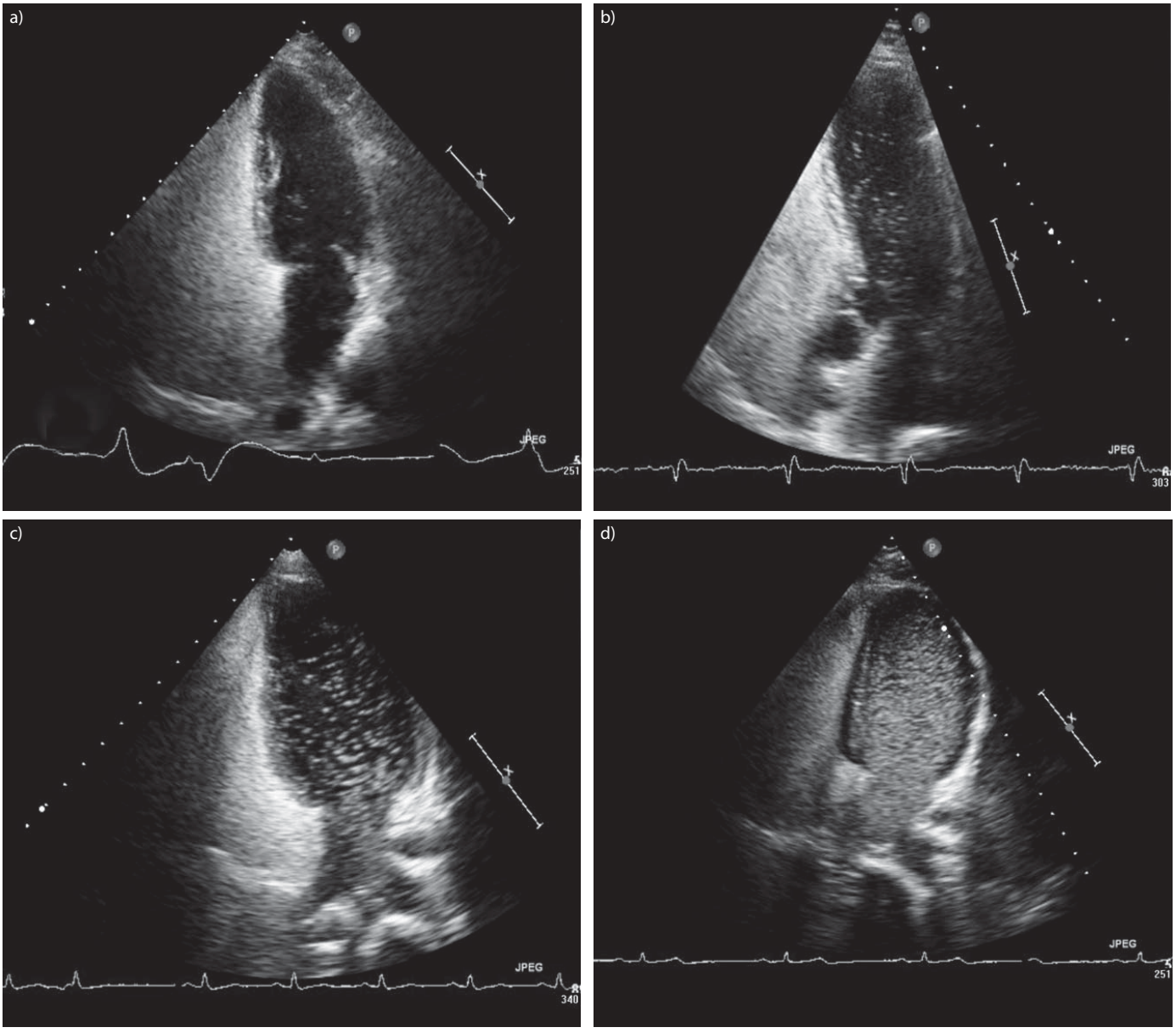

FIGURE 1. Transthoracic contrast echocardiography grades 1 to 4 with minimal (a), moderate (b), extensive (c) and extensive with endocardial definition (d) amount of contrast in left heart cavities.

RESULTS

Out of the 125 patients evaluated for suspected HHT, only those patients with three or four Curaçao criteria, and a TTCE, thoracic CT and angiography performed within an 180-day period were included in the study. Three patients with HHT (two type I HHT and one type II HHT) and with a TTCE diagnosis of patent foramen ovale (PFO) were also excluded. None of these patients with PFO have PAVMs on thoracic CT. 95 patients met all the criteria (table 1).

According to the thoracic CT findings 20 (21%) of the 95 patients studied had PAVMs (fig. 2); 10 females, mean $\pm$SD age 41.1 $\pm$ 14.4 yrs (range 11–67 yrs). All 20 patients underwent a genetic study and 13 (65%) were type I (table 2).

In 15 patients we measured the size of the feeding artery in the thoracic CT (table 2). The mean $\pm$SD size of the feeding artery was of 3.78 $\pm$ 1.08 mm (range 2.4–6.6 mm). When we compared the size of the feeding artery with the TTCE grade, we found an association between both parameters that was statistically significant exclusively in the case of patients with a single PAVM. In these 12 patients, we found a significant relationship between the TTCE grade and the size of the feeding artery in a linear regression analysis, so that the bigger the size of the artery, the higher the TTCE grade, being significant according to the Pearson correlation (0.6; $p=0.035$) (table 3).

TTCE was considered positive for extracardiac RLS in 71 (74.7%) of the 95 patients. Of these 71 patients, 34 patients were considered grade 1, 20 grade 2, 10 grade 3 and seven grade 4 (table 4).

None of the patients with negative TTCE or grade 1 TTCE showed images compatible with PAVMs on thoracic CT. Five

TABLE 1 Characteristics of the study population

Age yrs	46.4 (6–78)
Sex	
Female	48/95 (50.5)
Male	47/95 (49.5)
Curaçao criteria	
Three	54/95 (56.8)
Four	41/95 (43.2)
Genetic test#	
Type I HHT	33/90 (36.7)
Type II HHT	55/90 (61.1)
No type I or type II HHT	2/90 (2.2)
Time between *i.v.* contrast injection and thoracic CT image acquisition s	103.0 (80–144)
Time between TTCE and thoracic CT days	15.7 (0–180)
Time between thoracic CT and angiography days	104.0 (29–152)

Data are presented as mean (range) or n/N (%). N=95. #: missing data in five patients. HHT: hereditary haemorrhagic telangiectasia; CT: computed tomography; TTCE: transthoracic contrast echocardiography.

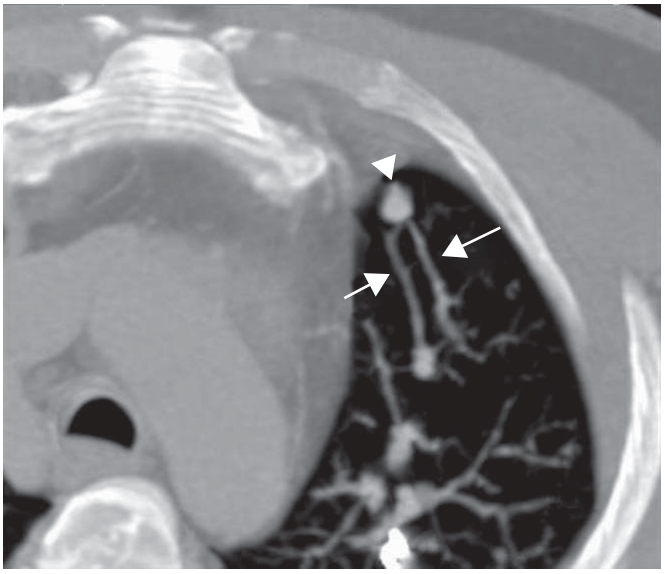

FIGURE 2. A 36-yr-old male with type I hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations in the left upper lobe with a nodule (arrowhead), an afferent artery and efferent vein (arrows).

(25%) of the 20 patients with grade 2, eight (80%) with grade 3, and all (100%) the patients with grade 4 showed PAVMs on thoracic CT. We found a significant association between TTCE grades and detection of PAVM on thoracic CT ($p<0.0001$). PPV was 0% (95% CI 0–10.2%) for grade 1; 25% (95% CI 8.7–49.1%) for grade 2; 80% (95% CI 44.7–97.5%) for grade 3; and 100% (95% CI 59–100%) for grade 4. The sensitivity and negative predictive values of TTCE in our study were 100%.

Conversely, we found a significant relationship ($p<0.0001$) between the cardiac cycle in which the contrast flow was first detected in the left atrium and TTCE grade, so that patients with higher TTCE grade showed an earlier left atrium opacification (table 5). In grades 2 and 3 the cardiac cycle was not useful to differentiate whether PAVMs were present or not on thoracic CT.

In the 10 patients with thoracic CT and angiography, we did not find differences in the number and location of the lesions between both techniques.

No significant adverse effects were observed in the patients related to the administration of the contrast agent, except for an 11-yr-old male with a PAVM who reported dizziness after the administration of the agitated fluid gelatine (grade 4 TTCE).

DISCUSSION

Early diagnosis of PAVMs in HHT patients is recommended, in order to prevent local or, more often, neurological complications [14]. Among the different screening techniques, TTCE (followed by CT in positive cases), is the most accepted screening method, given its low cost, accessibility, sensitivity and high negative predictive value of 90–100% [16, 26]. In according to these data, none of our patients with negative TTCE for extracardiac RLS showed PAVMs on thoracic CT.

However, TTCE shows problems derived from its high false positive rate when compared with CT, probably related to its capability to detect unimportant PAVMs at a microscopic level [16, 17], a finding that may lead to further unnecessary CT investigation. In our study, only 20 (28%) out of 71 patients with positive TTCE and a subsequent CT scan demonstrated PAVMs on thoracic CT. Similar results have been found by other investigators [22, 23]. Owing to these findings, several recent articles [22–24] have analysed the usefulness of adding a graded system to TTCE to improve the selection of patients for whom a further CT is necessary, in order to avoid unnecessary radiation exposure. Two grading systems have been used in these studies: one based on the classification model described by BARZILAI *et al.* [25] and followed by ZUKOTYNSKI *et al.* [22] and ourselves with a 4 grade scale, and another employed by GAZZANIGA *et al.* [23] and VAN GENT *et al.* [24] with a 3 grade scale, where grade 3 is equivalent to grades 3 and 4 in the scale of BARZILAI *et al.* [25]. Regardless of the grading scale used, all the studies have found a statistically significant correlation between the presence of detectable PAVMs on thoracic CT and TTCE grades, so that the probability of detecting PAVMs on thoracic CT is increased in higher TTCE grades.

If we compare our results in each TTCE grade with those obtained by other authors [22–24], we find that none of the patients with TTCE grade 1 in our series and in the GAZZANIGA *et al.* [23] series showed PAVMs on thoracic CT (using a similar cut-off to differentiate between TTCE grade 1 and 2). However, they were present in 2% of the patients in the study of ZUKOTYNSKI *et al.* [22] and in 22.9 % in the VAN GENT *et al.* [24] study, the latter with a cut-off of 30 microbubbles. In TTCE grade 2, 3 and 4, 25%, 80% and 100%, respectively, of our patients had PAVMs. These results are in the range of these other studies, in which the incidence of PAVMs in grade 2 varies between 25% and 56% and in grade 3 or grade 3 and 4, according to the classification scale used, between 56% and 100% [22–24].

TABLE 2 Characteristics of 20 patients with pulmonary arteriovenous malformations (PAVMs) on thoracic computed tomography (CT)

Patient	Curaçao criteria	HHT genetic type	TTCE grade	Cardiac cycle#	PAVMs on thoracic CT n	PAVM: lung location	PAVM: lung lobe location	Afferent artery size mm	Angiography/PAVM lung lobe location
1	4	II	2	8	1 embolised	Peripheral	RLL		
2	3	I	2	6	1	Peripheral	RLL	2.4	
3	4	I	2	5	1	Peripheral	RLL	3	1 PAVM/RLL
4	4	I	2	4	1 and 2 embolised	Peripheral	Lingule (RLL; LUL embolised)	3.3	
5	4	II	2	5	1 and 1 embolised	Peripheral	Lingule (LLL embolised)	4.3	
6	4	II	3	3	1	Peripheral	RLL	2.8	
7	4	II	3	3	1	Peripheral	LLL	3	
8	4	I	3	3	1	Peripheral	LLL	3.1	1 PAVM/LLL
9	4	I	3		1	Central	LUL	3.3	1 PAVM/LUL
10	4	I	3	3	1	Peripheral	RLL	4	
11	3	I	3	4	1	Peripheral	RUL	4	1 PAVM/RUL
12	4	II	3	4	1	Peripheral	RML	4.3	1 PAVM/RML
13	4	II	3	4	1	Peripheral	RLL	5.3	1 PAVM/RLL
14	3	II	4	3	1	Peripheral	RUL	3.6	
15	4	I	4		1 and 1 embolised	Peripheral	RLL (LLL embolised)	4	1 PAVM/RLL
16	4	I	4	3	1	Peripheral	RLL	6.6	
17	4	I	4	4	Multiple				Multiple PAVMs
18	4	I	4	3	Multiple (3 embolised)				Multiple PAVMs
19	4	I	4	3	Multiple (2 embolised)				Multiple PAVMs
20	4	I	4	3	Multiple				

HHT: hereditary haemorrhagic telangiectasia; TTCE: transthoracic contrast echocardiography; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RML: right median lobe; Embolised: PAVM previously treated with embolotherapy. #: number of cardiac cycles when the contrast is first visualised in the left atrium.

These findings justify the need of a thoracic CT after positive TTCE in all patients with grade 3 or grade 3 and 4 where almost all of the patients will have a PAVM on CT and almost of them will be suitable for embolisation [24]. In patients with TTCE grade 2, only a reduced proportion will have a PAVM detected on CT and most of them will have a feeding artery too small to perform embolotherapy [24]. However, it still appears justified to perform a CT after TTCE because, as shown in our study, it is possible to find patients with a feeding artery of $\geqslant$2 mm. Although we did not find PAVMs on CT in patients with TTCE grade 1, it is feasible that they may be seen, as

TABLE 3 Relationships between transthoracic contrast echocardiography (TTCE) grades and afferent artery size on thoracic computed tomography in 12 patients with a single pulmonary arteriovenous malformation

TTCE grades	Afferent artery size mm
Grade 2 TTCE	2.7±0.4
Grade 3 TTCE	3.7±0.8
Grade 4 TTCE	5.1±2.1

Data are presented as mean±SD.

TABLE 4 Relationship between graded transthoracic contrast echocardiography (TTCE) and thoracic computed tomography (CT) findings

Graded TTCE	Patients n	Patients with PAVMs on thoracic CT
Negative TTCE	24	0
Grade 1	34	0
Grade 2	20	5 (25%) 3 single (1 embolised) and 2 multiple
Grade 3	10	8 (80%) 8 single
Grade 4	7	7 (100%) 2 single and 5 multiple
Total	95	20

PAVM: pulmonary arteriovenous malformation; single: only one PAVM detected on thoracic CT; multiple: more than one PAVM detected on thoracic CT; embolised: PAVM previously treated with embolotherapy.

TABLE 5 Relationship between transthoracic contrast echocardiography (TTCE) grades and the cardiac cycle when the contrast was first visualised in the left atrium

TTCE grade	Patients n/n	Cardiac cycle (mean)
Grade 1 TTCE	33/34	7 (6.9)
Grade 2 TTCE	20/20	5 (5.2)
Grade 3 TTCE	8/10	4 (3.6)
Grade 4 TTCE	6/7	3 (3.2)
Patients with PAVMs on thoracic CT	18/20	4 (3.94)
Patients without PAVMs on thoracic CT	48/51	6 (6.26)

PAVM: pulmonary arteriovenous malformation; CT: computed tomography.

discussed previously [22, 24]. An important finding in our study, partially confirmed by the results of VAN GENT *et al.* [24] (where none of the patients with PAVMs on thoracic CT and a TTCE grade 1 were candidates for embolotherapy), is that there is an apparent relationship between the size of the feeding artery and TTCE grade. Although this was detected only in a small group of patients, we would expect that the few patients with grade 1 TTCE and a PAVM on thoracic CT will not have a feeding artery large enough to permit embolotherapy. Therefore, it could avoid in this group, the performance of a CT following TTCE or, the control studies with CT. However, more data are probably necessary before discontinuing thoracic CT after a positive TTCE for RLS.

According to the international guidelines for the diagnosis and management of HHT [14], all patients with a positive TTCE, including those with PAVMs not detectable on thoracic CT, should receive prophylactic antibiotics, especially before high-risk surgery and oral or dental manipulations [27].

In addition to the TTCE grade we investigated if the timing of contrast arrival in the left atrium could be helpful, to differentiate patients with or without detectable PAVMs on thoracic CT. In accordance with ZUKOTYNSKI *et al.* [22], we have not found a significant difference within TTCE grades 2 and 3, to allow us to distinguish between patients with or without PAVMs on CT. Nevertheless, there was a statistically significant relationship between the cardiac cycle in which the contrast flow was localised in the left atrium and the TTCE grade, so that patients with higher grade had an earlier appearance of flow in the left atrium. These findings suggest that the moment of the visualisation of the contrast flow in the left atrium is dependent on the shunt intensity. The delay in the bubble detection in the left atrium after complete opacity of the right atrium is the parameter used to differentiate intracardiac from intrapulmonary shunts in TTCE. Traditionally, three or fewer cardiac cycles for intracardiac and four or more cardiac cycles for intrapulmonary RLS are used [28, 29]. In our study, in agreement with ZUKOTYNSKI *et al.* [22], several patients with PAVMs on CT and TTCE grade 3 or 4 showed presence of flow in the left atrium in the third and fourth cardiac cycles. Although the presence of a PFO cannot be completely ruled out in these patients, as a transoesophageal echocardiogram was not carried out, the absence of flow through the interauricular septum by colour Doppler, and the absence of modification in the pattern of the appearance of bubbles with Valsalva, renders the existence of a right to left intracardiac shunt unlikely. The timing in which bubbles appear in the left atrium might be conditioned by the intensity of the shunt and sometimes could not be, as has been suggested, an accurate indicator of the localisation of RLS [22].

The safety of TTCE has been well documented elsewhere [30]. This procedure is generally well tolerated, with a low incidence of side-effects, all of them minimal and self-resolving [23]. We had only one patient with grade 4 TTCE and PAVM confirmed on thoracic CT that suffered a short-lived episode of dizziness.

Our results have some limitations, *e.g.* the small number of patients in whom PAVMs were detected and the fact that graded TTCE is a semi-quantitative technique. We considered, however, that a better definition of grade 1 and 2 should be achieved with a clear cut-off between these two grades. Differentiation between TTCE grades 3 and 4 appears less important because most of the patients will have a PAVM, and thoracic CT seems to be mandatory after TTCE. Another potential problem includes the inter-observer variability in the measurements of the feeding artery diameter when callipers are used on CT, since it can over or underestimate the size of the measured vessel compared to angiography, although these differences do not appear significant [18].

Conclusions

Graded TTCE appears a useful technique for the reduction of CT studies, especially in grade 1 TTCE patients, although at present more studies are needed before generalising this indication. It also appears that, in patients with large PAVMs, there is a tendency for an earlier contrast flow appearance in the left atrium and an association between the size of the afferent artery and the TTCE grade.

STATEMENT OF INTEREST

None declared.

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