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Graded contrast echocardiography in pulmonary arteriovenous malformations.

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

Methods: Ninety five 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.

Results: Of the 95 patients (50.5% female; mean age 46 years), none with normal or grade 1 TTCE had detectable PAVMs on thoracic CT. Shunts 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.

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

Key words

Hereditary haemorrhagic telangiectasia

Osler- Weber- Rendu syndrome

Pulmonary angiography

Pulmonary arteriovenous malformations.

Thoracic computed tomography

Transthoracic contrast echocardiography

Abbreviations

CI: Confidence interval

CT: Computed tomography

HHT: Hereditary haemorrhagic telangiectasia.

PAVMs: Pulmonary arteriovenous malformations

PFO: Patent foramen ovale

PPV: Positive predictive value

RLS: Right to left shunt.

SD: Standard deviation

TTCE: Transthoracic contrast echocardiography.

Introduction

Hereditary haemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu syndrome is a rare disorder (1 in 5000/8000) (1,2) transmitted in an autosomal dominant pattern and characterized 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 (4), 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. 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 hemothórax or massive hemopthysis especially in pregnancy) (11), dyspnoea, and neurological complications such as transient ischemic 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).

Several screening tests have been proposed alone or in combination (chest radiography, arterial oxygen measurements, radionuclide studies or 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 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 localization of the PAVMs, making it necessary to perform complementary tests.

For many years, pulmonary arteriography has been the gold standard to study 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 pixel or 3D reconstructions has converted CT to a powerful, sensitive and specific technique with a performance similar to 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 emphasized 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 rationalize the utilization of both techniques.

Material and Methods

A total of 125 HHT patients and their relatives were evaluated in the Sierrallana Hospital 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). 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 3 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 within less than 4 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 (less than 20 bubbles), grade 2 indicates moderate opacity, grade 3 extensive opacity without

outlining the endocardium and grade 4 extensive opacity with endocardial definition (Figure 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 non ionic contrast agent (300mg of iodine per millilitre with a rate of 3 ml/sec and a maximum dose of 2 ml/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 workstation in axial, multiplanar, maximum intensity pixel 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, embolization of the PAVM was performed when possible, by positioning a microcatheter (Rebar-18 microcatheter, eV3, Microtherapeutics Inc, Irvine, California, USA) in the feeding artery. Embolization was performed with electrodetachable coils (GDC 360, 3D and Vortex microcoils, Boston Scientific Corporation, Natick, Massachusetts, 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 X^2 test for association was performed for variables not following a normal distribution, and Student's t test was used to evaluate the association between the amount of contrast visualized in the left ventricle, the cardiac cycle where the contrast was first visualized 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).

Results

Out of the 125 patients evaluated for suspected HHT, only those patients with 3 or 4 Curaçao criteria, and a TTCE, thoracic CT and angiography performed within less than 180 days of difference were included in the study. Three patients with HHT (2 type I HHT and 1 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. Ninety five patients met all the criteria (table 1)

Table 1. Characteristic of the study population

	Study Population (n = 95)
Mean age, years (range)	46.4 (6-78)
Sex (%) Female Male	 48/95 (50.5) 47/ 95 (49.5)
Curacao criteria (%) 3 4	 54/95 (56.8) 41/95 (43.2)
Genetic test (%)* Type I HHT Type II HHT No type I or type II HHT	 33/90 (36.7) 55/90 (61,1) 2/90 (2.2)
Mean time between intravenous contrast injection and thoracic CT image acquisition; seconds (range)	103.0 (80-144)
Mean time between TTCE and thoracic CT; days (range)	15.7 (0 – 180)
Mean time between thoracic CT and angiography, days (range)	104.0 (29-152)

* Missing data in 5 patients

According to the thoracic CT findings 20 (21%) of the 95 patients studied had PAVMs (Figure 2); 10 females, mean age 41.1 years, standard deviation (SD) 14.4; range 11-67 years. All 20 patients underwent a genetic study and 13 (65%) were type I (Table 2).

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

Patient nº	Number of Curaçao criteria	Genetic Type: Type I; II HHT	TTCE grade	Cardiac cycle (*)	Number of PAVMs on thoracic CT	PAVM: lung location	PAVM: lung lobe location (***)	Afferent artery size (mm)	Angiography/ PAVM lung lobe location
1	4	II	2	8	1 embolized (**)	Peripheral	RLL		
2	3	I	2	6	1	Peripheral	RLL	2.4	
3	4	I	2	5	1	Peripheral	RLL	3	1 PAMV/RLL
4	4	I	2	4	1+2 embolized	Peripheral	Lingule (RLL; LUL embolized)	3.3	
5	4	II	2	5	1+1 embolized	Peripheral	Lingule (LLL embolized)	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 PAMV/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+1 embolized	Peripheral	RLL (LLL embolized)	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 embolized)				Multiple PAVMs
19	4	I	4	3	Multiple (2 embolized)				Multiple PAVMs
20	4	I	4	3	Multiple				

(*) Cardiac cycle: number of cardiac cycles when the contrast is first visualized in the left atrium. (**) Embolized: PAVM previously treated with embolotheraphy. (***) Lung lobe location: RUL: right upper lobe, RML: right median lobe, RLL: Right lower lobe; LUL: left upper lobe, LLL: left lower lobe.

In 15 patients we measured the size of the feeding artery in the thoracic CT (Table 2). The mean size of the feeding artery was of 3.78 mm, SD 1.08, 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 the Pearson correlation 0.6 (p=0.035) (Table 3).

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

TTCE grades	**Mean afferent artery size (SD)**
Grade 2 TTCE	2.7 mm (0.4)
Grade 3 TTCE	3.7 mm (0.8)
Grade 4 TTCE	5.1 mm (2.1)

SD: standard deviation

TTCE was considered positive for extracardiac RLS in 71 of the 95 patients (74.7%). Of these 71 patients, 34 patients were considered grade 1, 20 grade 2, 10 grade 3 and 7 grade 4 (Table 4).

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

Graded TTCE	**nº patients**	**Nº patients with PAVMs on thoracic CT**

		(%)
Negative TTCE	24	0 (0)
Grade 1	34	0 (0)
Grade 2	20	5 (25) Single (*) 3 (1 embolized)*** Multiple (**) 2
Grade 3	10	8 (80) Single 8 Multiple 0
Grade 4	7	7 (100) Single 2 Multiple. 5
Total	95	20

** Single: only one PAVM detected on thoracic CT; **Multiple: more than one PAVM detected on thoracic CT; *** Embolized: PAVM previously treated with embolotheraphy*

None of the patients with negative TTCE or grade 1 TTCE, showed images compatible with PAVMs on thoracic CT. Five (25%) of the 20 patients with grade 2, eight (80%) with grade 3, and all the patients with grade 4 (100%) 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% confidence interval (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%.

On the other hand, 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 difference whether PAVMs were present or not on thoracic CT.

Table 5: Relationship between transthoracic contrast echocardiography (TTCE) grades and the cardiac cycle when the contrast was first visualized in the left atrium.

TTCE grade (nº patients)	**Cardiac cycle (mean)**
Grade 1 TTCE (33/34 patients)	7 (6.9)
Grade 2 TTCE (20/20 patients)	5 (5.2)
Grade 3 TTCE (8/10 patients)	4 (3.6)
Grade 4 TTCE (6/7 patients)	3 (3.2)
Patients with PAVMs on thoracic CT (18/20 patients)	4 (3.94)
Patients without PAVMs on thoracic CT (48/51 patients)	6 (6.26)

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 year old boy 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 highly predictive negative value of 90 to 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 is compared to 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 others investigators (22, 23). Due to these findings, several recent articles (22-24) have analyzed the usefulness of adding a graded system to TTCE to improve the selection of patients where 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 four 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 of these authors (22-24) we find that none of the patients with TTCE grade 1 in our series and in the

Gazzaniga´s 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. study (24), this last 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 where the incidence of PAVMs in grade 2 varies between 25 to 56% and in grade 3 or 3 and 4, according to the classification scale used, between 56 to 100% (22-24).

These findings justify the need of a thoracic CT after positive TTCE in all patients with grade 3 or 3 and 4 where almost all of the patients will have a PAVMs on CT and most of them will be suitable for embolization (24). In patients with TTCE grade 2, only a reduced percentage will have a PAVMs detected on CT and most of them will have a feeding artery too small to perform embolotheraphy (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 2 mm or more. In patients with TTCE grade 1, as discuss previously, although we did not find PAVMs on CT it is feasible to see them (22, 24). An important finding in our study and, 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, probably more data are necessary, before to discontinuing thoracic CT after a positive TTCE for RLS.

According to the international guidelines for the diagnosis and management of HHT (14), all the patients with a positive TTCE, including those with PAVMs no detectable on thoracic CT, should receive prophylactic antibiotic, 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 localized 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 visualization of the contrast flow in the left atrium is dependant 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, 3 or fewer cardiac cycles for intracardiac and 4 or more cardiac cycles for intrapulmonary RLS (28, 29) are used. 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 3rd and 4rd cardiac cycles. Although, the presence of a PFO cannot be completely ruled out in these patients, as a transesophageal 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 localization 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. The small number of patients in who were detected PAVMs 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 achieve 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 usefulness technique in order to reduce CT studies, especially in grade 1 TTCE patients, although at present more studies are needed before generalizing 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.

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Figures:

Figure. 1 A-D: TTCE grades 1 to 4 with minimal, moderate, extensive and extensive with endocardial definition amount of contrast in left heart cavities.

Fig. 1 A-

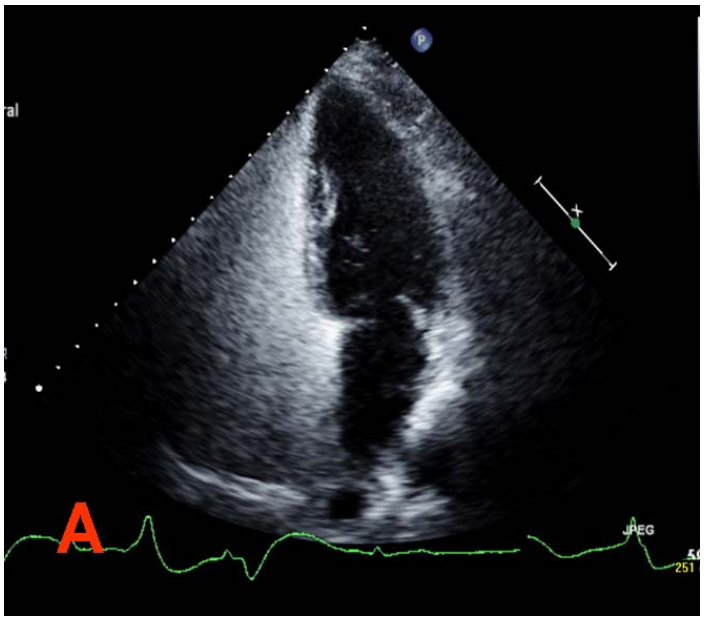

Fig 1 B

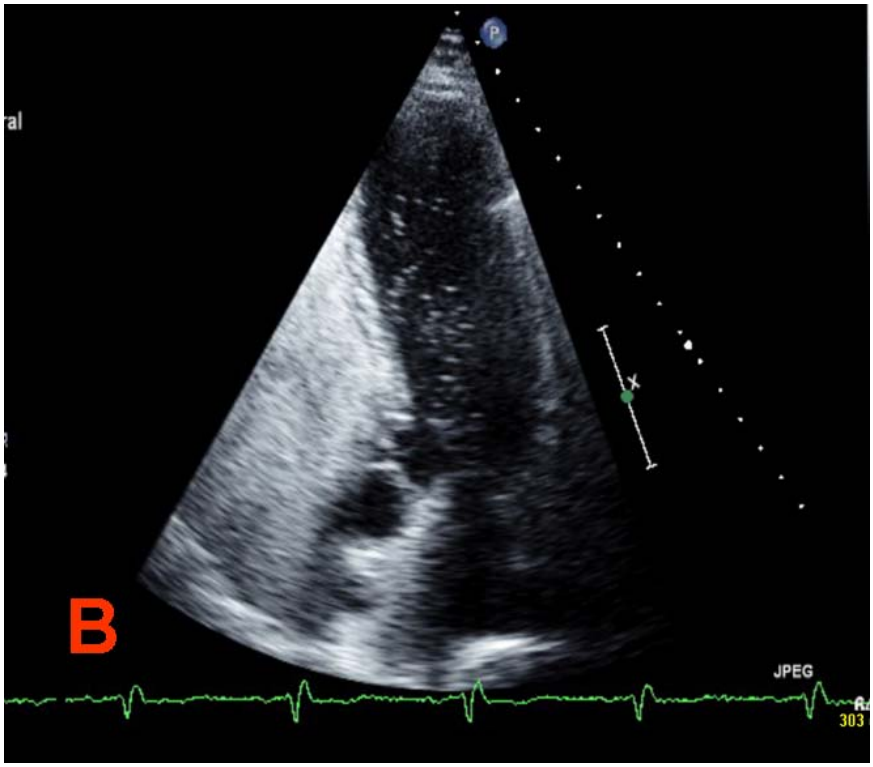

Fig 1 C

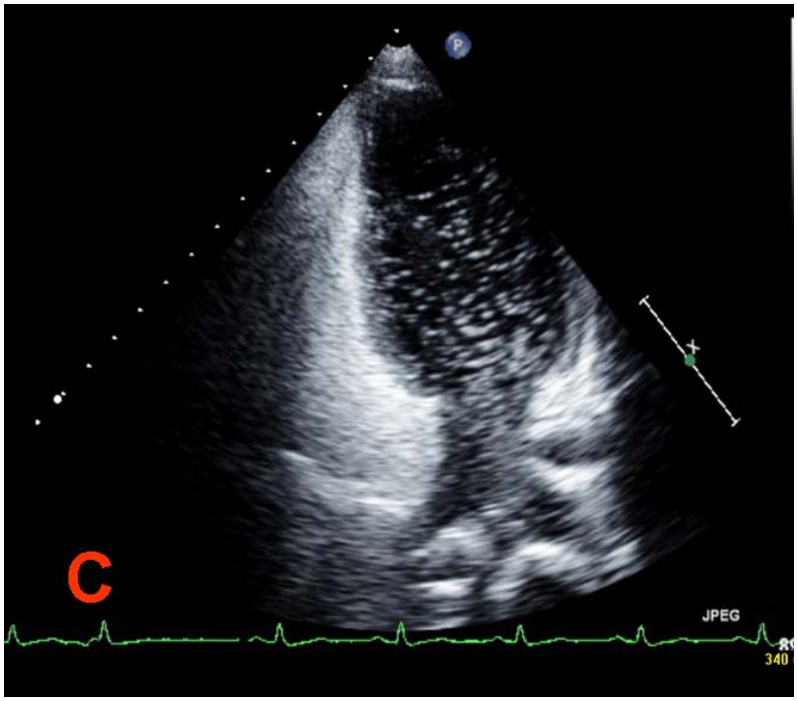

Fig 1 D

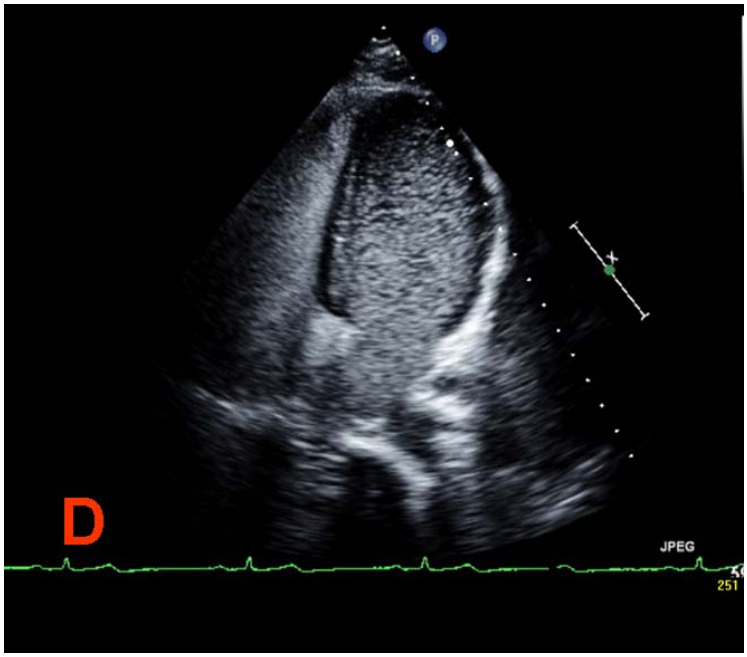

Figure. 2: A 36 year old man with type I HHT and a PAVM in the left upper lobe with a nodule (arrowhead), an afferent artery and efferent vein (arrows).