



Contrast echocardiography for pulmonary arteriovenous malformations screening: does any bubble matter?

P. Gazzaniga¹, E. Buscarini^{2*}, G. Leandro³, L. Reduzzi⁴, M. Grosso⁵, G. Pongiglione⁶, C. Pedrinazzi¹, L. Lanzarini⁷, V. Portugalli⁴, P. Blotta⁸, P. Forner⁸, E. Boccardi⁹, F. Pagella¹⁰, G. Manfredi², C. Olivieri¹¹, A. Zambelli², C. Danesino¹¹, and G. Inama¹

¹Cardiology Department, Maggiore Hospital, Crema, Italy; ²Gastroenterology Department, Maggiore Hospital, Largo Dossena 2, 26013 Crema, Italy; ³Gastroenterology Dept 1, IRCCS, Castellana Grotte, Italy; ⁴Radiology Department, Maggiore Hospital, Crema, Italy; ⁵Radiology Department, Santa Croce Hospital, Cuneo, Italy; ⁶Pediatric Cardiology Department, Hospital Gaslini, Genova, Italy; ⁷Cardiology Department, Policlinico S Matteo, Pavia, Italy; ⁸ENT Department, Maggiore Hospital, Crema, Italy; ⁹Interventional Neuroradiology, Niguarda Hospital, Milan, Italy; ¹⁰ENT Department, Policlinico S Matteo, Pavia, Italy; and ¹¹Genetic Institute, University of Pavia, Pavia, Italy

Received 19 July 2008; accepted after revision 22 November 2008

KEYWORDS

Arteriovenous malformations;
Echocardiography;
Hereditary haemorrhagic
telangiectasia

Aims To evaluate diagnostic accuracy of contrast echocardiography (CE) as compared with CT, for the screening of pulmonary arteriovenous malformations (PAVMs) in hereditary haemorrhagic telangiectasia (HHT); to evaluate the clinical significance of semi-quantitative analysis of a shunt on CE.

Methods and results A blinded prospective study was conducted in 190 consecutive subjects at risk of HHT who underwent screening for PAVMs, including clinical evaluation, pulse oximetry, standard and CE, and chest multirow CT without contrast medium. A semi-quantitative analysis of the shunt size was performed according to the contrast echo opacification of the left-sided chambers: Grade 0, no bubbles; 1, occasional filling with <20 bubbles; 2, moderate filling; 3, complete opacification. The first 100 patients were compared with 100 controls. A total of 119 (63%) patients had positive CE (32.2% Grade 1, 13.1% Grade 2, 11% Grade 3, 6.3% with patent foramen ovale). The overall diagnostic performance of CE was sensitivity 1.00, specificity 0.49, positive predictive value (PPV) 0.32, negative predictive value (NPV) 1.00. The PPV for the different grades was 0.00 for Grade 1, 0.56 for Grade 2, 1.00 for Grade 3; the NPV of Grade 0 was 1.00. A significant correlation was found between the CE grading and the number of PAVM, and complications ($P < 0.0001$).

Conclusion CE is an extremely sensitive procedure for the detection of PAVMs with substantial clinical impact.

Introduction

Hereditary haemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is a genetic disease characterized by widespread cutaneous, mucosal, and visceral telangiectases with a frequency of ~1–2 cases out of 10 000 subjects.^{1–3} Telangiectasia are the underlying lesion of HHT, and bypass the capillary system by direct fusion of the arteriole to the venule. Clinical presentation varies greatly, depending on the number, type and location of telangiectases or larger vascular malformations (VMs) with potential morbidity and mortality. Clinical criteria for the diagnosis were established by a panel of experts (Curaçao criteria).⁴ Genetic testing has

recently become available, although its operating characteristics are not yet well defined.

The evaluation of visceral involvement in HHT can help to determine severity of the disease in terms of the Curaçao criteria, and this is especially important for visceral VMs, such as those in the lung, brain, and liver, which can cause life-threatening complications.^{4–6}

Pulmonary arteriovenous malformations (PAVMs) are direct communications between pulmonary arteries and veins, resulting in a right-to-left shunt that reduces the arterial oxygen saturation (SaO₂). As the lung loses its filtering function, paradoxical emboli may occur resulting in severe neurological complications such as stroke or cerebral abscess; these complications can often be the first manifestations of the disease.⁶ Large PAVMs may induce severe hypoxaemia with secondary dyspnoea and polycythaemia.

* Corresponding author. Tel: +39 0373 280278; fax: +39 0373 280654.
E-mail address: ebuscarini@rim.it

Haemoptysis is another potential complication and it can be life-threatening.⁷

Treatment of PAVMs by transcatheter embolization has been shown to be safe^{8,9} and effective to reduce or prevent PAVMs complications,¹⁰ and the screening of patients with HHT for asymptomatic PAVMs has therefore been recommended. Contrast echocardiography (CE) has been shown to be very effective for the detection of PAVMs in HHT,^{11–14} with a sensitivity of up to 93%,¹⁴ and for the monitoring during follow-up after treatment.¹⁵ Recent technical advances with second harmonic imaging have substantially enhanced diagnostic effectiveness of echocardiography equipments. Pulmonary angiography (PA) has so far been considered the standard of reference to compare the utility of CE in screening; however, as PA is an invasive test, it has been performed in only a small minority of those patients who were negative on the screening tests. Therefore, the diagnostic accuracy of CE cannot be correctly evaluated on the basis of studies using PA as the gold standard.^{11–13} A grading system for estimating the severity of a shunt during CE has been proposed,¹¹ with lower grades associated with shunts of smaller size and of less clinical significance; however, the scant number of validated diagnoses is a limitation of previous studies.

CT scanning, particularly with new technology using helical multirow detectors, is considered to be as sensitive and specific as PA for the diagnosis of PAVMs, and to be a highly effective, non-invasive alternative diagnostic tool to PA.¹⁶

Therefore, a prospective controlled study was conducted with the following aims: (i) to evaluate the diagnostic accuracy of CE for the diagnosis of PAVMs in comparison with multislice chest CT and (ii) to evaluate the clinical significance of semi-quantitative analysis of shunts as assessed by CE.

Methods

This study was prospectively performed at the Crema HHT Clinic, a specialized HHT Clinic, at Maggiore Hospital; this hospital is a secondary care, university-affiliated, teaching hospital belonging to the Italian national network for rare diseases. Patients at risk of HHT across Italy were referred to this clinic and underwent a multidisciplinary HHT family screening protocol approved by the Institutional Review Board of the Crema Hospital, and aimed to establish the HHT affection status (definite, possible, and unlikely) according to the Curaçao criteria.⁴ All patients or parents of patients younger than 18 years gave informed consent for the tests.

From May 2003 to December 2006, 190 consecutive subjects (87 males, mean age 41, range 5–73) underwent screening for PAVMs, including the following evaluations, all conducted in the same day:

- (1) clinical evaluation including collection of information on history of complications possibly related to PAVMs (and in particular: a transient ischemic attack was defined as a focal cerebral deficit of rapid onset, lasting <24 h, and with no apparent cause other than a vascular one); an ischaemic stroke was defined by review of either imaging or medical files; cerebral abscess);
- (2) pulse oximetry with the patient breathing room air, in both supine and upright positions, after 2 min of quiet breathing (an $\text{SaO}_2 < 96\%$ and/or a gradient of 2 or more percentage points on changing posture was considered abnormal);
- (3) standard echocardiography with second harmonic imaging was performed with a 2.0–3.5 MHz transducer (Acuson Sequoia C256, Siemens USA, Mountain View, CA, USA) and a 1.5–4.3 MHz

transducer (Vivid 7, GE Vingmed, Horten, Norway); CE was performed with subjects in supine position with manual injection of 10 mL of agitated saline, while images were obtained in the apical four-chamber view. A CE finding was defined positive for PAVMs if any bubble appeared in the left atrium after more than three cardiac cycles after initial opacification of the right chambers, while an earlier bubble appearance was attributed to a patent foramen ovale.^{14,17} A semi-quantitative analysis of the shunt size was performed according to the contrast echo opacification of the left ventricle: Grade 0, no bubbles; 1, occasional filling with <20 bubbles; 2, moderate filling; 3, complete opacification (Figure 1).¹⁸ Digital records were taken of all CE exams and afterwards reviewed and scored by a second echocardiographer (one out of the three echocardiographers); the interobserver agreement between the scores assigned at the time of CE and during revision was calculated. Patients were observed during and for 2 h after CE for detection of complications resulting from paradoxical air embolism.

- (4) chest multirow CT without contrast medium was performed with the single breath-holding technique with a slice thickness of 1 mm (Philips Brilliance 16 row CT scanner); both sagittal and coronal reformats were used. A nodular opacity with both afferent and efferent vessel was identified as PAVM; a lower limit for the size of PAVMs was not used; number, site, size of feeding vessels and of aneurysmal sac of PAVMs were specified. CT findings were classified as positive or negative for PAVM on the basis of evaluation of CTs specifically for the study by three observers (radiologists specifically trained for PAVMs diagnosis, and the HHT Centre medical coordinator experienced in interpreting chest CT for the presence of PAVMs) with a consensus.

All tests were performed by independent operators blinded to the results of other tests.

PA was indicated on the basis of CT, CE, and clinical findings results: PA was recommended if (i) CT was positive or (ii) CT was negative and CE was positive with a history of complications possibly related to PAVMs. To date, 34 patients with CE+/CT+ have been referred for PA; one patient with CE+/CT– and previous cerebral abscess has been referred to PA. Antibiotic prophylaxis before interventional procedures (as defined by American Heart Association¹⁹) was recommended to all subjects who were CE+ regardless of their grading.

PA was done with a preliminary study of main, right, and left pulmonary arteries; embolization of feeding arteries of PAVMs was obtained by positioning a six French introducer in the relevant pulmonary artery and a five French catheter (wire-guided) was inserted up to the feeding arteries of the PAVM. Embolization was done with detachable coils (Nester Embolization coils, Cook Medical Inc, Bloomington, IN, USA; Vortex, Boston Scientific, Natick, MA, USA; MDS, Balt Extrusion, Montmorency, France) of different sizes according to the diameter of feeding artery; larger fistulas were embolized by Amplatzer vascular plug (AGA Medical Corporation, Plymouth, MN, USA). An angiographic check was done at the completion of the procedure to evaluate the complete exclusion of PAVM.

The first 100 patients were compared with a group of 100 subjects not belonging to HHT families, matched for age and sex (48 males, mean age 42, range 6–70); the controls included healthy volunteers and patients undergoing echocardiography because of chest pain, who were studied with CE for a search of pulmonary right-to-left shunt and its semi-quantitative analysis.

The diagnostic performance of CE was evaluated by calculation of specificity, sensitivity, positive (PPV), and negative predictive values (NPV) using the chest CT as the gold standard; patients with a CE diagnosis of patent foramen ovale were not included in this analysis. Descriptive statistics, percentage distribution, association tests, correlation tests, non-parametric tests, Pearson's χ^2 , and standardized deviates were also applied as appropriate. Differences were considered statistically significant at $P < 0.05$. Statistical analyses

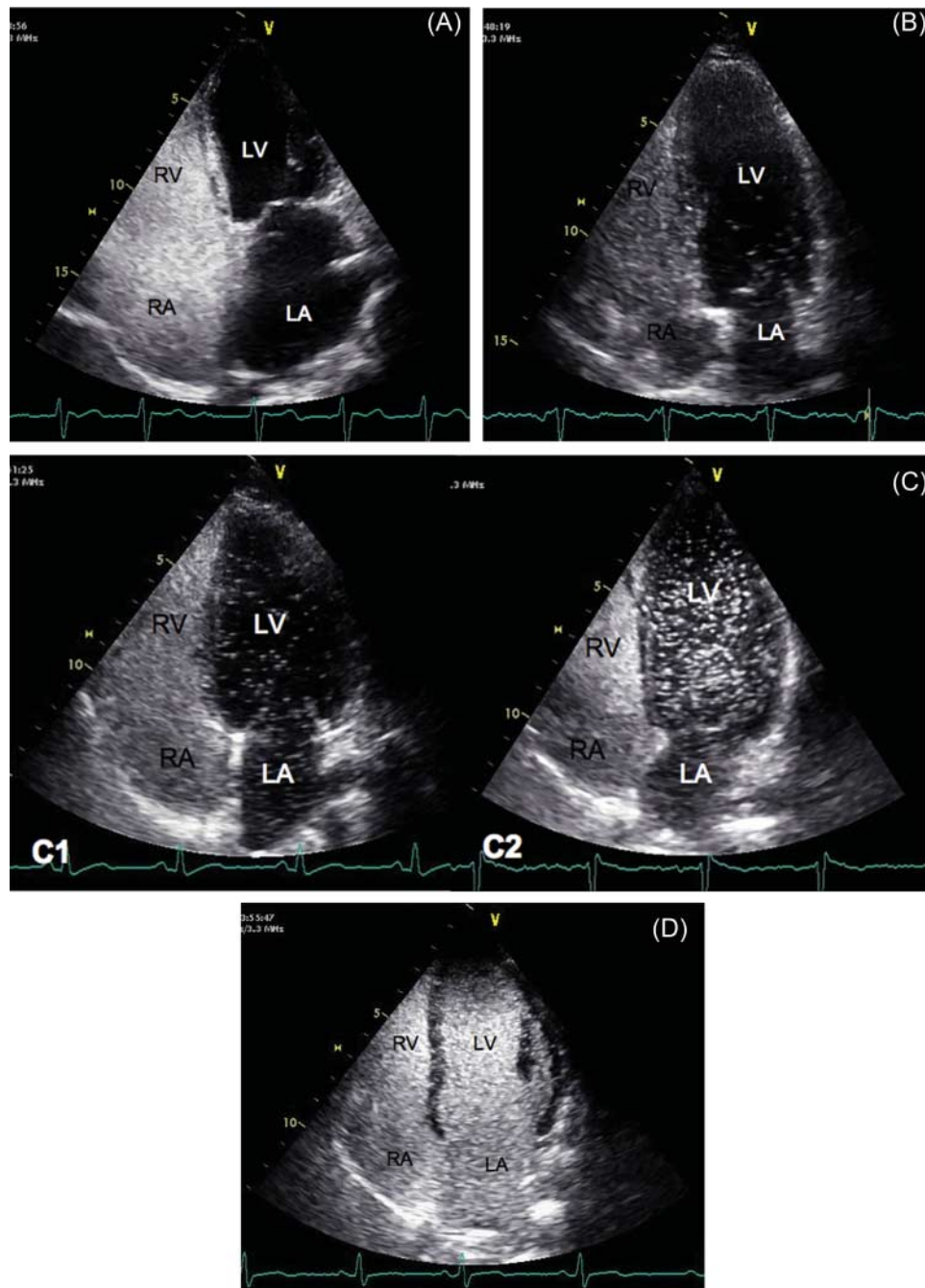


Figure 1 With contrast echocardiography, after iv injection of agitated saline solution, left ventricular opacification was graded as: (A) Grade 0, no bubbles; (B) 1, occasional filling with <20 bubbles; (C) 2, moderate filling, with discrete bubbles, either they are less or more numerous (C1, C2); (D) 3, complete opacification. RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.

were done with the SPSS software (version 11.5; SPSS, Inc., Chicago, IL, USA).

Results

A clinical diagnosis of HHT was definite, possible, and unlikely in 132 (69.5%), 19 (10%), and 39 (20.5%) patients, respectively; genetic testing in 151 affected has so far established that 31 have a mutation in *ENG* (HHT1) and 81 in *ACVRL1* (HHT2).

One hundred and nineteen patients had positive CE scans: 61 with Grade 1, 25 with Grade 2, 21 with Grade 3, 12 with

patent foramen ovale (in 11 cases CE findings were considered sufficient for diagnosis of patent foramen ovale, in one case transesophageal echocardiography was done to confirm the diagnosis).

CT was done in 189 patients (one patient with a Grade 2 shunt refused it); no PAVMs were detected in 61 patients with positive CE Grade 1, and none in 11 patients with Grade 2; all patients with Grade 3 were CT positive. Altogether CT identified PAVMs (Figure 2) in 36 out of 151 affected subjects (23.8%), and in particular, in 34 patients with positive CE grades 2–3, and in two patients with patent foramen ovale; PAVMs were judged not amenable to



Figure 2 Three-dimensional reconstruction of pulmonary multi-slice CT, a centrally located pulmonary arteriovenous malformation is shown (arrow).

Table 1 Results of contrast echocardiography and chest multirow CT vs. clinical definition of HHT affection status

		Clinical diagnosis of HHT			
		Definite	Possible	Unlikely	Total
CE	Negative	29	7	35	71
	Grade 1	51	8	2	61
	Grade 2	22	3	0	25
	Grade 3	21	0	0	21
	PFO	9	1	2	12
	Total	132	19	39	190
mCT	Positive	34	2	0	36
	Negative	98	17	39	154
	Total	132	19	39	190

PFO, patent foramen ovale.

treatment in two cases (on the basis of a feeding vessel diameter); in remaining 34 PAVMs as shown by CT were diffuse in one case, <5 in 30 cases, 6–11 in three cases.

Results of CE and CT vs. the clinical diagnosis of HHT are shown in *Table 1*.

Overall diagnostic performance of CE, as compared with the gold standard, was therefore 1.00 for sensitivity, 0.49 for specificity, 0.32 for PPV, and 1.00 for NPV. PPV of different grades was 0.00 for Grade 1, 0.56 for Grade 2, 1.00 for Grade 3; NPV of Grade 0 was 1.00. Interobserver agreement regarding CE grading was 94%.

A χ^2 test for linear trend showed a significant association between CE grading and number of PAVMs (counted as single or multiple for statistical analysis purpose), $P < 0.0001$. The PAVM location was peripheral in 28 cases, central in three, and both peripheral and central in five; the average diameter of afferent vessel to the PAVMs was 5.6 mm

(range 2–13); average size of the aneurysmal sac was 14.8 mm (3–60). Mean SaO₂ was 97 (± 2.5). Spearman's correlation test showed a poor correlation between CE grading and either the diameter of the afferent vessel or the diameter of the aneurysmal sac or the SaO₂, with r coefficients of 0.293, 0.124, and -0.541 , respectively.

Complications possibly related to PAVM occurred in 9 of the 36 patients (25%): 1 haemoptysis, four cerebral abscesses, and four strokes. Of the patients with Grade 0 or 1, none had complications, whereas 16% and 23.8% of patients with CE grades 2 and 3, respectively, suffered complications. A χ^2 test for linear trend showed a highly significant association between CE grading and complications, $P < 0.0001$.

To date, 32 patients with CE+/CT+ received the PA (one patient with diffuse PAVMs died before a scheduled PA, and another could not undergo PA because of a generally poor health condition) which has confirmed PAVMs in all cases; in the patient with CE+/CT– and previous cerebral abscess PA has not yet been performed due to the patient's condition.

In 100 control subjects, CE demonstrated a Grade 1 right-to-left shunt in seven cases, and a patent foramen ovale in six. Standardized deviates showed a significantly less frequency of patients in Grade 0, and a significantly less frequency of non-affected people in Grade 1, 2, and 3 with a Pearson's χ^2 : $P < 0.0001$ (*Table 2*); prevalence of patent foramen ovale was not significantly different in the two groups ($P = 1.000$).

Complications possibly related to paradoxical air embolism due to CE occurred in three patients (2%) with Grade 3 shunt, in none of control group, and they were migraine (2) and distal paresthesias (1) occurring within few minutes after saline injection, with rapid and spontaneous recovery in all cases.

Discussion

Previous studies,^{11–14–20} either prospective or retrospective, have shown the efficacy of CE for screening PAVMs in HHT. However, these studies can entail potential biases in data interpretation due to either the retrospective design or the absence of a gold standard applied to patients with negative CE. This is the first prospective controlled blinded study to evaluate the role of CE in screening PAVMs in HHT, along with the potential clinical implications of CE grading.

The present study shows an excellent sensitivity of CE to detect PAVMs, confirming that CE has operative characteristics best suited for PAVMs screening: considering the 1.00 NPV of CE, CT should be omitted in CE negative cases. Should any bubble found in CE lead to CT, regardless of the scoring? The 0.00 PPV of CE in Grade 1 cases would support the suggestion of Zukotynski *et al.*²⁰ (who found a PPV of 0.02 for Grade 1) of omitting CT in these cases as, considering altogether the results of present and Zukotynski *et al.*²⁰ series, one PAVM was found out of the 112 patients (0.9%) with CE Grade 1. Therefore a screening policy for PAVMs based on CE would realize a decrease of biological risk due to ionizing radiations. CE is theoretically not risk free for patients with right-to-left shunts due to the potential paradoxical air embolism; actually in our series, we had only minimal and self-resolving side-effects; in a multicentre survey, a 0.062% of neurological and respiratory

Table 2 Results of contrast echocardiography in patients and controls

	Grade 0	Grade 1	Grade 2	Grade 3	PFO
Patients <i>n</i> (%)	71 (37.4)	61 (32.2)	25 (13.1)	21 (11)	12 (6.3)
Controls <i>n</i> (%)	87 (87)	7 (7)	0	0	6 (6)
<i>P</i> -value	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> = 1.000

PFO, patent foramen ovale.

side effects, with no residual complications;²¹ a recent series including 281 CE done in the context of HHT screening reported no adverse events.²² Safety profile of CE could therefore be considered good.

An economic benefit can also be considered for the use of CE as first line examination for PAVM screening wherever CE is cheaper than CT (as it is for Italian health-care system).

Does any bubble reflect the presence of PAVMs? It is possible that CT negativity in all patients with CE positivity Grade 1 and in 11 with CE positivity Grade 2 found in our study reflects a high number of false positives. One limitation of present study is that patients with CE positive/CT negative were not subject to angiography unless they had complications. Although this is clinically understandable, it reduces the conclusions that can be drawn about the value of CT. However, the inclusion of a control arm in present study provides convincing data regarding the meaning of CE positivity, even if Grade 1, in HHT patients: in fact the significantly different percentages of CE positivity in HHT subjects and control arm seem to confirm that in HHT patients the phenomenon could be related to the presence of minimal PAVMs undetectable either by CT or by PA, where this has already been hypothesized in other studies.²⁰ This possibility is also supported by the persistence of positive CE in a great percentage of HHT patients who had no residual PAVMs at angiographic check after transcatheter embolotherapy, indicating the presence of additional minimal/microscopic PAVMs.¹⁵

Therefore, our controlled study provides the theoretical background for some modifications of clinical management of HHT patients: (i) it suggests that CE could be more sensitive than standards of reference (CT, PA) for the detection of PAVMs; (ii) it introduces the concept of a bias in the currently available data about prevalence of PAVMs in HHT related to the use of a less sensitive standard of reference (e.g. the prevalence of 69.5% of PAVMs found with CE in our 151 affected subjects appears to be substantially greater than the 23.8% found with CT, or the 67% vs. 27% in the series by Zukotynski *et al.*²⁰); (iii) it suggests that CE positivity in HHT population, even if Grade 1, means the presence of PAVMs and thus one Curaçao criterium for judging affection status; (iv) PAVMs are usually silent and can be difficult to diagnose; on this basis it has been recently suggested to propose antibiotic prophylaxis before interventional procedures in all individuals with HHT;¹⁰ but, if this recommendation has to be given to patients with the diagnosis of PAVMs,¹⁷ then antibiotic prophylaxis should be advised to patients with CE (even if Grade 1) positivity even if pulmonary CT is negative. (v) appropriate follow-up schedule to detect potential growth of PAVM should be advised,²⁰ possibly according also to the age of patient; the appropriate follow-up timing will be clarified

in the future when the outcome data of HHT subjects with CE positivity Grade 1 will become available.

Our study has shown a highly significant correlation between CE grading with a history of complications related to PAVMs such as cerebral abscess or stroke, as well as a correlation between CE grading and number of PAVMs. These correlations would suggest a prognostic significance of CE grading and this would further enhance the clinical value of CE for PAVM screening. However, it has to be also underscored that the correlations with PAVM number and complications could reflect purely the low proportion of positive cases in Grades 0 and 1, and low number of complications (9 overall) which could preclude assessment of differences between grades 2 and 3. This cautious data interpretation is also suggested by the recent study of Shovlin *et al.*¹⁰ which failed to find any correlation between six parameters of PAVM severity (given by clinical and instrumental findings) and 57 PAVM complications.

The lack of any correlation between CE grading and diameter of the afferent vessel in PAVMs found in our study does not allow prediction of the amenability of PAVMs to transarterial embolization.

The role of CE as first-line imaging for screening PAVMs in the general HHT population certainly calls for interobserver reproducibility of results reported to date with this technique. Recently an interobserver agreement of 87% has been reported in a retrospective evaluation of CE grading.²⁰ In comparison with latter study, we have chosen a simplified CE grading¹⁸ to maximize reproducibility and actually a greater interobserver agreement has been obtained in the present study; this excellent reproducibility makes this grading very suitable for routine classification of CE findings in the screening of extracardiac right-to-left shunts.

In conclusion, our study confirms that CE is an extremely sensitive, non-invasive procedure for the detection of PAVMs, with substantial impact on clinical management of HHT patients.

Acknowledgements

Authors would gratefully acknowledge Mrs Donata Bombelli, Nurse Chief and staff coordinator of Crema HHT Clinic, for her invaluable commitment and untiring work.

Conflict of interest: none declared.

Funding

This work has been supported by a grant of Italian HHT Foundation for Hereditary Haemorrhagic Telangiectasia 'Onilde Carini'.

References

- Bideau A, Plauchu H, Brunet G, Robert JM. Etude épidémiologique de la maladie de Rendu Osler en France: répartition géographique et prévalence. *Population* 1989;1:9–28.
- Dakeishi M, Shioya T, Wada Y, Shindo T, Otaka K, Manabe M et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat* 2002;19:140–8.
- Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet* 1989;32:291–7.
- Shovlin CL, Guttmacher AE, Buscarini E, Faughnan M, Hyland RH, Westermann CJJ et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber Syndrome). *Am J Med Genet* 2000;91:66–678.
- Buscarini E, Plauchu H, Garcia Tsao G, White RI Jr, Sabbà C, Miller F et al. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. *Liver Internat* 2006;26:1040–6.
- Cottin V, Chinet T, Lavalé A, Corre R, Marchand E, Reynaud-Gaubert M et al. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. *Medicine (Baltimore)* 2007;86:1–17.
- Ference BA, Shannon TM, White RI, Zawin M, Burdge CM. Life-threatening pulmonary hemorrhage with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia. *Chest* 1994;106:1387–90.
- White RI, Pollak JS, Wirth JA. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. *J Vasc Interv Radiol* 1996;7:787–804.
- Gupta P, Mordin C, Curtis J, Hughes JM, Shovlin CL, Jackson JE. Pulmonary arteriovenous malformations: effect of embolization on right to left shunt, hypoxemia, and exercise tolerance in 66 patients. *AJR Am J Roentgenol* 2002;179:347–55.
- Shovlin C, Jackson JE, Bamford KB, Jenkins ICH, Benjamin AR, Ramadan H et al. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. *Thorax* 2008;63:259–66.
- Barzilai B, Waggoner AD, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. *Am J Cardiol* 1991;68:1507–10.
- Kjeldsen AD, Oxhøj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. *Chest* 1999;116:432–9.
- Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA et al. Contrast echocardiography for detection of pulmonary arteriovenous malformations. *Am Heart J* 2001;141:243–6.
- Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with HHT. *Am J Respir Crit Care Med* 2004;169:994–1000.
- Lee WL, Graham AF, Pugash RA, Hutchinson SJ, Grande P, Hyland RH et al. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. *Chest* 2003;123:351–8.
- Remy J, Remy-Jardin M, Giraud F, Wattinne L. Angioarchitecture of pulmonary arteriovenous malformations: clinical utility of three-dimensional helical CT. *Radiology* 1994;191:657–64.
- Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med* 1998;158:643–61.
- Feinstein JA, Moore P, Rosenthal DN, Puchalski M, Brook M. Comparison of contrast echocardiography versus cardiac catheterization for detection of pulmonary arteriovenous malformations. *Am J Cardiol* 2002;89:281–5.
- American Heart Association. Prevention of infective endocarditis. Guidelines from the American Heart Association. *Circulation* 2007;116:1736–54.
- Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast Echocardiography Grading Predicts Pulmonary Arteriovenous Malformations on CT. *Chest* 2007;132:18–23.
- Bommer WJ, Shah PM, Allen H, Meltzer R, Kisslo J. The safety of contrast echocardiography: report of the Committee on Contrast Echocardiography for the American Society of Echocardiography. *J Am Coll Cardiol* 1984;3:6–13.
- van Gent MWF, Post M, Luermans JGLM, Snijder RJ, Westermann CJJ, Plokker T et al. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. *Eur Resp J* 2008; Sep 17. (Epub ahead of print).