

**Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study**

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## ***Abstract***

**Background:** Pulmonary arteriovenous malformations (PAVMs) are associated with severe neurological complications in patients with hereditary hemorrhagic telangiectasias (HHT). The objective of our study was to prospectively establish the diagnostic value of TTCE as a screening technique for PAVM using chest HRCT as the gold standard for PAVMs.

**Methods:** All consecutive adult persons referred for HHT screening underwent a chest HRCT (n=299), TTCE (n=281), arterial blood gas analysis (n=291), shunt fraction measurement (n=111) and chest radiography (n=296).

**Results:** TTCE was positive in 87 (58.8%), 12 (16.7%) and 4 (6.7%), and chest HRCT was positive in 54 (36.5%), 3(4.2%) and 0 patients with respectively a definite, possible and negative clinical diagnosis HHT. Two patients with a negative TTCE were diagnosed with PAVMs on CT; in both cases the PAVMs were too small for embolotherapy. Sensitivity of TTCE was 97% (95% CI 93.6-98.3) and NPV 99% (95% CI 96.9-99.8). The other diagnostic tests showed a considerable lower diagnostic value.

**Conclusion:** This prospective study shows that TTCE has an excellent diagnostic value and can be used as an initial screening procedure for PAVM. The high falsely positive rate of TTCE possibly represents microscopic PAVMs.

**Key words:**

pulmonary arteriovenous malformations; hereditary hemorrhagic telangiectasia; contrast echocardiography

## ***Introduction***

### *Background*

A pulmonary arteriovenous malformation (PAVM) is a direct communication between a pulmonary artery and pulmonary vein. This results in a right-to-left shunt (RLS) causing hypoxemia and risk for paradoxal embolism through bypassing the filtering capillary network. Complications occurring in patients with PAVM and hereditary hemorrhagic telangiectasia (HHT) are stroke (10-19%), transient ischemic attacks (6-37%), cerebral abscess (5-9%), migraine headaches, seizures, massive hemoptysis and (spontaneous) hemothorax.(1-3) Antibiotic prophylaxis prior to procedures carrying risk for bacteremia is recommended.(3-5) At least 80% of PAVMs are associated with HHT.(3) HHT is an autosomal dominant disorder characterised by vascular abnormalities varying from small telangiectases to large arteriovenous malformations. The clinical diagnosis is based on the Curaçao Criteria.(6) Based on genetic analysis HHT is divided in type 1 and 2, corresponding with mutations in the genes ENG and ACVRL1 coding for endoglin and ALK1 (activin A receptor type-like kinase) respectively.(7;8) The prevalence of PAVM, as documented by chest HRCT, in all HHT patients is 20 to 45%.(4;9) The PAVM prevalence differs between these two subtypes, in HHT type 1 the prevalence is 48%, whereas the prevalence in HHT type 2 is 5%.(10) PAVMs can be effectively treated with transcatheter embolotherapy which has been proven safe and effective in long-term studies.(11-18) Recently it has been proven that embolisation of PAVMs is effective in the prevention of brain abscess and ischaemic stroke if complete occlusion of all PAVMs is achieved.(5) Because of the high incidence of severe complications early diagnosis of PAVMs, and treatment if possible, is warranted.(3;5) Therefore, patients with HHT are routinely screened for PAVMs, even if they are asymptomatic.

### *Screening for PAVMs*

Screening tests used for detecting PAVMs are chest radiography, arterial oxygen measurement using the 100% oxygen technique, radionuclide lung scanning, magnetic resonance imaging, pulmonary angiography, chest computed tomography (CT) and contrast transthoracic echocardiography (TTCE). Chest radiography, arterial blood gas analysis including shunt measurement using the 100% oxygen technique and radionuclide scanning lack sensitivity and are not recommended as a single procedure for excluding PAVMs and/or RLS.(1;3;4) Chest CT is presently referred to as the gold standard and has shown to be even more accurate than angiography.(19) Pulmonary angiography is indicated only for endovascular treatment of PAVMs.(1) The main disadvantage of CT is radiation exposure. TTCE is a simple, widely available and easy technique which can detect RLS and differentiate between intra-cardiac and pulmonary shunting. Although there might be concern about complications resulting from paradoxical cerebral air embolism, side effects of TTCE appear to be rare.(20) Its sensitivity for detecting PAVMs has been proven excellent in mainly retrospective studies.(4;21-24) The aim of our prospective study is to establish the role of TTCE in screening for PAVM as compared to chest CT as 'gold standard'. We hypothesized that TTCE can be used as a single first screening method in which further analysis with chest CT only is recommended in case TTCE suggests a pulmonary RLS. To our knowledge, this is the first prospective study for screening PAVM by TTCE compared to chest CT, systematically.

## ***Methods***

### *Patients*

We prospectively studied 317 consecutive persons (> 16 years of age) who were referred for possible HHT or were family members of index cases. Screening was performed in the period between May 2004 till June 2007. Almost all patients underwent a chest radiography, arterial blood gas analysis, chest CT and TTCE in a one-day-protocol. In addition, on the same day all patients visited a pulmonologist and an otorhinolaryngist, both experienced in HHT patients. The clinical diagnosis HHT was established according to the Curaçao criteria.(6) At least three of the following four criteria were required for a clinical diagnosis: spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral malformations (PAVM, CAVM (Cerebral AVM), HAVM (Hepatic AVM), or GI telangiectases) and a first degree relative with HHT. In the presence of two criteria the diagnosis was considered 'possible', and the clinical diagnosis was rejected in the presence of one criterium.

All patients were informed by letter about the screening protocol and procedures before visiting our clinic. TTCE is part of our routine screening protocol for possible HHT patients.

### *Study objective*

The main objective of our study was to prospectively establish the diagnostic value of TTCE as a screening technique for PAVM using chest HRCT as the gold standard.

### *Diagnostic tests*

The PaO<sub>2</sub> was measured at rest breathing room air and an additional shunt measurement breathing 100% oxygen for at least 15 minutes was performed if PaO<sub>2</sub> was below 13 kPa or 12kPa for patients younger or older than 30 years respectively. Shunt was estimated using the formula:  $Q_s/Q_t = (C_{cO_2} - C_{aO_2}) / (C_{cO_2} - C_{vO_2})$  in which  $Q_s/Q_t$  = shunt as a fraction of cardiac

output,  $C_{cO_2}$  = oxygen content at the end of the pulmonary capillary,  $C_{aO_2}$  = oxygen content of arterial blood, and  $C_{vO_2}$  = oxygen content of mixed venous blood.(25)  $P_{cO_2}$  is assumed to equal  $pO_2$  ( $P_B - P_{aCO_2} - P_{AH_2O}$ ).  $P_B$  is barometric pressure (101.3 kPa) and  $P_{AH_2O}$  is saturated water vapour pressure in the allveoli, which is 6.3 kPa at a body temperature of 37°C.  $SO_2$  at the end of the pulmonary capillary is assumed to be 100%. Oxygen content (C) was calculated as follows:  $C = (0,0225 \times PO_2) + (2,24 \times Hb \times SO_2/100)$  ml  $O_2$  / 100 ml blood.  $C_{vO_2}$  was assumed as  $C_{aO_2} - 4.4$  ml  $O_2$  / 100 ml blood. Using the 100% oxygen method a shunt measurement of more than 5% was considered pathological.(3;26)

High resolution CT scanning (Philips, The Netherlands) of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1 mm. Both sagittal and coronal reformats were used. Identification of PAVM was based on the presence of a nodular opacity with both an afferent and efferent vessel. We did not employ a lower limit for the size of PAVMs. CTs were scored as positive, negative and indeterminate by two independent observers (a radiologist, and a pulmonologist experienced in interpreting chest HRCT for the presence of PAVMs),, both blinded to the other results of the protocol. In case of disagreement between both observers, the study was considered positive for PAVM. TTCE was performed by three experienced echocardiographers. An intravenous line (18-gauge) was preferentially placed in the right antecubital vein. Two 10-ml syringes were connected, one filled with 8 ml saline solution and 1 ml of air. One ml blood was drawn in the other syringe and mixed with the saline-filled syringe by reverse flushing, creating agitated saline (microbubbles). The patient was positioned in the left lateral decubitus position and 10 ml agitated saline was injected while projecting the four-chamber apical view without a Valsalva manoeuvre.(21) TTCE was considered positive for a pulmonary right-to-left shunt if ( $\geq 1$ ) microbubbles appeared in the left atrium after four cardiac cycles.(3) The results were interpreted by a cardiologist without knowledge of the other test results and scored as

positive, negative or indeterminate (no discrimination possible between patent foramen ovale and pulmonary RLS) or inappropriate for interpretation because of poor quality. Patients in whom the difference between an intracardiac and pulmonary shunt could not be made were considered positive for purpose of the analysis. A physician was present at all TTCE studies and watched out for possible complications resulting from paradoxical air embolism. Chest CT was referred to as the gold standard for detecting PAVMs in this study.

### *Statistical analysis*

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution were presented as mean  $\pm$  standard deviation. Median with range was used when normal distribution was absent. The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) with their 95% confidence intervals (CI) were calculated for each screening test or a combination of two different tests, using the chest CT as the gold standard.

Statistics were performed using SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA).

## **Results**

### *Study population*

Three hundred and seventeen persons were screened for possible HHT. From this group 299 persons (94%) underwent chest CT scanning which was regarded as the gold standard for detecting PAVMs. Eighteen patients refused a chest CT or had a contraindication (e.g. pregnancy). Of all patients who underwent chest CT, chest radiography was performed in 296 (99%), arterial blood gas analysis in 291 (97%), and shunt measurement using the 100% oxygen method in 111 patients (37%), respectively. TTCE was performed in 283 patients (95%), in 16 patients placement of an intravenous line failed or was refused. In 2 patients

TTCE images could not be interpreted because of poor quality. A clinical diagnosis of HHT was definite, possible and rejected in 155 (51.8%), 80 (26.8%) and 64 (21.4%) patients, respectively. These data are summarized in table 1. So, the study population available for analysis (both CT and TTCE) consisted of 281 patients, with a mean age of  $44 \pm 15$  years and 61% female.

### *Diagnostic value of screening methods*

Chest CT was positive for PAVM in 60 (20,1%), negative in 238 (79,6%) and indeterminate in 1 patient (0,3%). The kappa coefficient for interobserver agreement concerning chest CT was 0.83. TTCE was positive for a pulmonary RLS in 107 patients (38,1%). The sensitivity (calculations are based on 281 patients, see previous section) of TTCE for detecting PAVM was 96.5% (95% CI 93.6-98.3) and NPV 98.9% (95% CI 96.9-99.8). In contrast, specificity for TTCE was only 76.8% (95% CI 71.5–81.7). In two patients out of 174 with a negative TTCE there was evidence for PAVMs on chest CT. This is shown in table 2. In these 2 patients with a falsely negative result, chest CT showed PAVMs much too small for embolization therapy (in both patients afferent and efferent vessels were  $\leq 1$ mm with a venous sac of respectively 3mm and 4mm in diameter).. In 1 of these 2 patients image quality of the echocardiogram was relatively poor but interpreted as sufficient for correct interpretation. In both of these falsely negative patients PaO<sub>2</sub> measurement was below our prespecified threshold but in neither of them the additional 100% oxygen method showed a shunt larger than 5% (0,6% and 1,6%). Chest radiography was negative in both falsely negative patients. Twenty one (7,5%) of all patients who underwent echocardiography had signs of a cardiac RLS, of whom 2 patients met criteria for both a pulmonary and cardiac shunt. In 4 patients there was doubt whether the RLS was based on a pulmonary or cardiac shunt (detection of contrast material in left atrium at 4 cardiac cycles).



When combining the TTCE and arterial oxygen pressure measurement the sensitivity increased to 100% (95% CI 98.7-100) and the NPV increased to 100% (95% CI 98.7-100). However, the specificity and PPV decreased to 40.6% (95% CI 34.8-46.6) and 30% (95% CI 24.6-35.6), respectively. The sensitivity, specificity, NPV, and PPV for each test and the combination of different tests is summarized in table 3.

TTCE was positive in 87 of 148 (58.8%) patients with a definite clinical diagnosis HHT. In 4 (6.7%) patients without a clinical diagnosis HHT, TTCE showed a pulmonary shunt. Twelve (16.7%) patients with possible HHT also showed positive TTCE studies. Chest HRCT was positive in 54 (36.5%) patients with clinically confirmed HHT and was negative in all patients without HHT. In 7 patients the presence of PAVMs on chest HRCT was required as a criterium for the (definite) clinical diagnosis HHT. These data are shown in table 4.

## ***Discussion***

This study shows that TTCE has an excellent negative predictive value for the detection of PAVM. No PAVMs treatable by embolisation were missed using contrast echocardiography. Therefore TTCE can be used as an initial screening technique for PAVM. The high falsely positive rate of TTCE possibly in part represents microscopic PAVMs below the detection limit of chest HRCT. In addition, TTCE appears also to be positive in a minority of patients without HHT suggesting this might partially reflect normal variation in the general population.

Screening for PAVMs in all possible patients with HHT is warranted because of the high incidence of neurological complications in this population. Consensus exists to treat all PAVMs applicable for intervention(1). This strategy is supported by a recent study that

demonstrated that no strokes or brain abscesses occurred if obliteration of all angiographically visible PAVMs was achieved.(5) Furthermore, it appeared that the risk for stroke and brain abscess was independent of the severity of PAVMs.(5) TTCE has been studied as a screening technique for PAVMs in retrospective studies.(4;21-24) Several studies compared TTCE with pulmonary angiography as a gold standard but the numbers of patients were limited and angiography was only performed when TTCE or other screening methods were positive.(23;24;27) Therefore, true sensitivity and specificity values remain unknown. Cottin and colleagues made an important contribution to the literature on screening for PAVMs in HHT patients. They retrospectively studied 105 HHT patients with TTCE using chest CT and/or pulmonary angiography as a reference. TTCE proved to have a sensitivity and predictive value for a negative test result of both 93%.(4) TTCE has been proposed as an initial screening test in HHT patients.(4;24;27;28) Chest CT is regarded as the current gold standard for detecting (treatable) PAVMs.

In our prospective study, we evaluated the diagnostic value of TTCE as compared with chest CT as a gold standard in a one-day protocol in almost 300 subjects. For TTCE we found a sensitivity of 97% and a predictive value for a negative test result of 99%. In 2 patients TTCE was falsely negative. In both these patients chest CT showed PAVMs too small for embolization therapy. Hence, of importance, no treatable PAVMs were missed by TTCE. In our clinic, we advise antibiotic prophylaxis prior to non-sterile procedures in HHT patients, unless a right to left shunt is excluded by TTCE. Consequently, when using TTCE as an initial screening method in our population only 2 patients (<1%) would have been incorrectly denied antibiotic prophylaxis to prevent cerebral abscess. These 2 patients met all 4 Curaçao criteria..

As expected, the combination of TTCE with chest radiography did not improve negative predictive value or sensitivity.

The combination of TTCE with PaO<sub>2</sub> measurement increased the sensitivity and NPV to both 100%. Patients screened for PAVMs in our study underwent a PaO<sub>2</sub> measurement and shunt measurement was performed if PaO<sub>2</sub> was below our pre-specified cut off value. Both patients with falsely negative TTCE appeared to have a low PaO<sub>2</sub> (explaining the 100% sensitivity and NPV when combining TTCE and PaO<sub>2</sub> measurement) but subsequent shunt measurement was within normal limits. Therefore it seems unlikely that pulmonary shunting caused the low PaO<sub>2</sub> in these patients. As a consequence we do not think it is justified to conclude that addition of PaO<sub>2</sub> measurement to TTCE improves diagnostic accuracy. We found a sensitivity for shunt measurement of 77% and a predictive value for a negative test result of 89%. However, it should be taken into account that shunt measurement was only performed in case of low PaO<sub>2</sub> so a lower falsely negative rate might be expected and these results must not be considered as representative for our study population overall. The diagnostic value of this screening test compares negatively to other studies of which a pooled analysis showed a sensitivity of 97,5%.(3) An explanation for this difference probably is the fact that those data were based only on PAVMs large enough for embolization therapy. Cottin and colleagues found a considerably lower sensitivity and negative predictive value (68% and 76% respectively) but performed shunt measurement in all patients.(4)

In our opinion chest radiography, arterial blood gas analysis and shunt fraction measurement lack diagnostic value as screening methods for PAVM or RLS. However, shunt fraction measurement on 100% oxygen can be of value in the assessment of severity of RLS, and follow-up after embolotherapy.

When a screening algorithm with TTCE as an initial screening technique (only followed by chest CT if positive) would be followed it is of particular importance none of the treatable PAVMs are overlooked. No PAVMs suitable for embolotherapy were present in our 2 patients with falsely negative TTCE. In 52 patients (23,2%) TTCE was positive in the absence

of PAVMs on chest CT. On the contrary, 172 patients (76,8%) did not have signs of pulmonary RLS and would not undergo chest CT in such a screening algorithm. In our hospital, this reduces charges on hospital resources and logistics given the fact that TTCE is a simple, little time-consuming procedure at low expenses, but this depends on local facilities and logistics. In only 2 patients the acoustic window was inadequate for interpretation. However, the inability to interpret and correctly judge TTCE outside specialized centers will probably be higher. The latter may reduce the sensitivity of TTCE. We did not experience any adverse events as a result of contrast echocardiography. However, there may be concern about the risk for paradoxical air embolism. Data about cerebral air embolism are scarce. A survey of 363 physicians performing contrast echocardiography revealed neurologic and respiratory side effects in 0.062% of all procedures, and no residual complications were observed.(20) Other literature regarding this subject is predominantly based on case reports.(29-31) We used 1ml added air in our protocol but lower volumes of air have become custom in some centers to minimize risk for air embolism. Current guidelines for contrast echocardiography still recommend the use of 1ml of air.(29-32)

Concerns have been made about the high false positive rate, and therefore high costs, of TTCE as a screening technique.(28) Falsely positive might not be an accurate term because a pulmonary RLS which is seen on TTCE in the absence of PAVMs on chest CT, might still represent microscopic PAVMs or telangiectases below the detection limit of CT scanning. This was also suggested by a study which showed that TTCE frequently remains positive after embolotherapy of PAVMs, even if no residual PAVMs were seen on angiography.(23) Furthermore, microscopic PAVMs were histologically proven in a child with HHT and a pulmonary shunt on echocardiography but without visible PAVMs on chest CT, and in a report of two patients in whom this diagnosis was proven by autopsy.(29-34) However, we also show that TTCE is positive in 6.7% of patients without a clinical diagnosis HHT,

suggesting that positive TTCE studies in part reflect normal variation in the general population.

The influence of postural changes on pulmonary RLS in patients with PAVM (orthodeoxia) has been described in several studies.(17;35-37) However, Cottin and coworkers did not find a different diagnostic value of TTCE in patients in whom echocardiography was performed in both the supine and upright position.(4) We hypothesize that postural changes only influence the degree of shunting and not the diagnosis of a pulmonary RLS per se

When there is evidence for a PAVM or a pulmonary RLS, antibiotic prophylaxis is recommended prior to procedures carrying risk for bacteremia.(3;4) The importance of antibiotic prophylaxis in HHT patients was suggested by Shovlin et al. who could indentify preceding events known to be associated with bacteremia in a high proportion of patients with brain abscess.(5) However, it is not known what impact antibiotic prophylaxis in patients with microscopic PAVMs or telangiectasia might have on neurological sequelae. Data about the follow-up of patients with positive contrast echocardiography are lacking. There might be concern for possible microscopic PAVMs to evolve to treatable PAVMs and therefore follow-up to detect an opportunity for treatment seems justified in our opinion. In addition to interpreting contrast echocardiography for the presence / absence of a pulmonary shunt, grading of TTCE has been shown to be able to predict the presence of PAVM on chest CT.(38) This modality might possibly further improve the diagnostic value of TTCE.

Given the results of our prospective study of almost 300 patients we conclude that a screening algorithm for PAVMs in HHT patients can be based on an initial TTCE, because of its excellent sensitivity and predictive value for a negative test result. If there is evidence for a pulmonary RLS on echocardiography, a chest CT is performed, to detect PAVMs that can be

treated by embolisation. Obviously, the preferred screening strategy also depends on local institutional logistics and experience

***Table 1 Baseline characteristics***

	n	%
Total	299	
Female	183	61,2
Age (mean±SD)	44±15	
Screening method for PAVM		
HRCT	299	100
TTCE	281	94,0
Chest radiograph	296	99,0
PaO <sub>2</sub>	291	97,3
RLS*	111	37,1

### *Legend*

\* A right-to-left shunt measured with the 100% oxygen method was only performed if PaO<sub>2</sub> was below 13 kPa or 12kPa for patients younger or older than 30 years respectively

Definition of abbreviations: n = Number of patients; SD = Standard Deviation; PAVM = Pulmonary ArterioVenous Malformation; HRCT = High Resolution Computed Tomography; TTCE = TransThoracic Contrast Echocardiography; PaO<sub>2</sub> = Partial arterial oxygen pressure; RLS = Right-to-Left Shunt

***Table 2. Contrast echocardiography versus chest CT***

No. of patients	HRCT (n)				
Contrast	Positive	Negative	Indeterminate*	Total	
echocardiography (n)	Positive	54	49	0	103
	Negative	2	171	1	174
	Indeterminate†	1	3	0	4
	Total	57	223	1	281

### *Legend*

\* Chest CT showed small nodules or opacities of uncertain origin, possibly PAVMs

† Contrast echocardiography was indeterminate for discrimination between an intracardiac and pulmonary shunt

Definition of abbreviations: HRCT = High Resolution Computed Tomography; n = number of patients



**Table 3 Diagnostic value of the different screening methods for PAVM**

	n	Positive (n,%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TTCE	281	107* (38,1)	96,5 (93.6-98.3)	76,8 (71.5–81.7)	98,9 (96.9 - 99.8)	51,4 (45.2-57.2)
Chest radiography	296	17 (5,7)	28,3 (23.0-33.5)	100 (99.0-100)	84,9 (80.2-88.7)	100 (99.0-100)
PaO2	291	156 (53,6)	74,6 (69.2-79.5)	51,7 (45.6-57.4)	88,9 (84.8-92.4)	28,2 (23.1-33.7)
Shunt using 100% O2	111	36 (32,4)	77,1 (68.6-84.9)	88,2 (80.8-93.6)	89,3 (81.9-94.3)	75,0 (65.7-82.5)
TTCE and chest radiography	298	107(38,1)	96,5 (93.9-98.4)	61,2 (55.3-66.6)	97,9 (95.7-99.3)	51,4 (45.5-57.2)
TTCE and PaO2	281	190 (67,6)	100 (98.7-100)	40,6 (34.8-46.6)	100 (98.7-100)	30 (24.6-35.6)
TTCE and shunt using 100% O2	281	115(40,9)	96,5 (93.6-98.3)	73,2 (67.7-78.4)	98,8 (96.9-99.8)	47,8 (41.7-53.7)
Chest radiography and PaO2	298	157 (52,7)	75,0 (69.9-80.0)	52,9 (47.2-58.6)	89,4 (85.2-92.5)	28,7 (23.8-34.4)

*Legend*

Definition of abbreviations: n = Number of patients; NPV = Negative Predictive Value; PPV = Positive Predictive Value; CI = Confidence Interval; PAVM = Pulmonary ArterioVenous Malformation; TTCE = TransThoracic Contrast Echocardiography; PaO2 = Partial arterial oxygen pressure

\* Includes 4 patients with an indeterminate shunt (no clear differentiation possible between intracardiac and pulmonary shunt, see also methods section)

Table 4 Contrast echocardiography and chest HRCT versus clinical diagnosis HHT\*

		Clinical diagnosis HHT (n,%)			
		Yes	No	Possible	Total
TTCE	Positive	87 (58.8)	4 (6.7)	12 (16.7)	103
	Negative	59 (39.9)	55 (90)	60 (83.3)	174
	Indeterminate	2 (1.3)	2 (3.3)	0	4
	Total	148	61	72	281
HRCT	Positive	54 (36.5) <sup>†</sup>	0	3 (4.2)	57
	Negative	94 (63.5)	61 (100)	68 (94.4)	223
	Indeterminate	0	0	1 (1.4)	1
	Total	148	61	72	281

*Legend*

Definition of abbreviations: HHT = Hereditary Hemorrhagic Telangiectasia; TTCE = Transthoracic Contrast Echocardiography; HRCT = High Resolution Computed Tomography; n = number of patients

\* This table is based on the population screened with both a TTCE and chest HRCT

† In 7/54 patients a definite diagnosis of HHT was based on three Curacao criteria, requiring a PAVM on chest CT as a diagnostic criterium

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