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# Grade of pulmonary right-to-left shunt on contrast echocardiography and cerebral complications; a striking association.

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*Background:* A pulmonary right-to-left shunt (RLS) carries the risk of cerebral paradoxical embolization and severe neurological complications. Recognising patients at risk is important to facilitate appropriate management strategies, but a direct relation between pulmonary shunt size and risk of complications remains controversial.

*Objective*: This study evaluated the potential relation between pulmonary shunt size on transthoracic contrast echocardiography (TTCE) and prevalence of cerebral manifestations in persons screened for hereditary haemorrhagic telangiectasia (HHT).

*Methods:* We conducted a two-center, cross-sectional study of all consecutive persons screened for HHT between 2004 and 2011. Pulmonary shunt grading was performed according to contrast opacification of the left ventricle on TTCE (grade 0, no microbubbles; 1, <30 microbubbles; 2, 30-100 microbubbles; 3, >100 microbubbles). Cerebral manifestations were defined as ischemic stroke, transient ischemic attack or brain abscess, diagnosed by a neurologist and confirmed by appropriate imaging techniques.

*Results:* A pulmonary RLS was present in 530 out of 1038 patients (51.1%, mean age 44.3±15.6 years, 58.6% women). The presence of a cerebral manifestation (n=51) differed significantly between pulmonary shunt grades on TTCE; 1.4%, 0.4%, 6.5% and 20.9% for grade 0, 1, 2 and 3 respectively. Pulmonary shunt grade 1 was not associated with an increased prevalence of cerebral manifestations (OR 0.44, 95%CI 0.05-4.13, p=0.47), while pulmonary shunt grade 2 (OR 4.78, 95%CI 1.14-20.0, p=0.03) and grade 3 (OR 10.4, 95%CI 2.4-45.3, p=0.002) were both independent predictors for the prevalence of a cerebral ischemic event or brain abscess.

*Conclusion:* Pulmonary RLS grade on TTCE is strongly associated with the prevalence of cerebral complications in patients screened for HHT.

## *Abbreviation list:*

RLS = Right-to-Left Shunt

HHT = Hereditary Haemorrhagic Telangiectasia

TTCE = Transthoracic Contrast Echocardiography

HRCT = High Resolution Computed Tomography

PAVM = Pulmonary Arteriovenous Malformation

PFO = Patent Foramen Ovale

TIA = Transient Ischemic Attack

mL = milliliter

SD = Standard Deviation

OR = Odds Ratio

CI = Confidence Interval

## Introduction.

A pulmonary arteriovenous malformation (PAVM) is a thin walled abnormal vessel that replaces normal capillaries between the pulmonary arterial and venous circulation. A PAVM causes a permanent right-to-left shunt (RLS) that bypasses the pulmonary capillary filter, which carries the risk of cerebral paradoxical embolization of both thrombotic and septic origin [1]. A paradoxical embolization is considered the likely predominant mechanism of cerebral ischemia or brain abscesses in patients with PAVMs [2, 3]. According to literature, 70-90% of PAVMs is associated with hereditary haemorrhagic telangiectasia (HHT) [2, 4]. HHT is an autosomal dominant inherited disorder, characterized by vascular abnormalities varying from small telangiectases in skin and mucosal membranes, to large arteriovenous malformations, predominantly in the brain, liver and lungs. The diagnosis is based on the clinical Curaçao criteria [5], or the presence of responsible gene mutations. There are mainly two types of HHT, corresponding with gene mutations coding for Endoglin (HHT1) and ALK1 (HHT2) [6, 7]. A third disease-causing mutation has been shown in the SMAD4 gene, which causes a combined syndrome of juvenile polyposis and HHT [8]. In addition, two more loci causing HHT have been mapped to chromosome 5 and 7, although the causative genes have not been identified yet [9, 10]. Transthoracic contrast echocardiography (TTCE) is recommended in all (suspected) HHT patients as initial screening for the presence of PAVMs [2, 11-13]. Based on TTCE, a pulmonary RLS is present in 85% of patients with HHT1, and in 35% of patients with a HHT2 genotype [13]. TTCE is used to guide further decisions in the screening algorithm for PAVMs, in which a grading system is used to characterize the pulmonary shunt size [14]. An additional chest high-resolution computed tomography (HRCT) scan is deferred in the absence of a pulmonary RLS on TTCE [15]. Several authors questioned whether we should also defer chest HRCT scanning in patients with a small RLS on TTCE [14-16], but a direct relation between pulmonary shunt size and risk of cerebral complications remains a matter of debate. According to the present guideline for the diagnosis and management of HHT, all patients with any pulmonary RLS on TTCE currently receive a chest HRCT scan and are recommended to use antibiotic prophylaxis for procedures with risk of bacteraemia to prevent cerebral abscesses [11]. Understanding which patients with PAVMs are indeed at risk of cerebral paradoxical embolizations is important to improve PAVM management strategies. We present the first, large cross-sectional study investigating the potential relation between (functional) pulmonary shunt size on TTCE and the prevalence of cerebral complications in patients screened for HHT.

## Methods.

### *Study population.*

From May 2004 till March 2011, 1129 persons were screened for HHT at two specialised clinics: the St. Antonius Hospital in Nieuwegein, the Netherlands and the Maggiore Hospital in Crema, Italy. Persons above fifteen years of age were screened as family members of index patients with HHT, or in case of clinical symptoms suggesting HHT. All persons underwent complete history and physical examination by a physician with dedicated expertise in HHT. The clinical diagnosis of HHT was established according to the Curaçao criteria [5]. These criteria consist of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral arteriovenous malformations, and a first-degree relative with HHT. Genetic testing for the HHT-causing gene mutation was offered to all screened subjects and performed as published previously [17]. A definite diagnosis of HHT was established in case of three or more Curaçao criteria, or when genetic testing identified the HHT-causing gene mutation. HHT was held possible in patients with two clinical Curaçao criteria, in which no genetic testing was performed or no gene mutation was found after genetic testing. Patients with 0-1 clinical Curaçao criteria in which no genetic testing was performed or no gene mutation was found after genetic testing were defined as "HHT unlikely". HHT was rejected when genetic testing excluded the HHT-causing family mutation. Patients with previously treated PAVMs were not included in the analysis. All patients provided informed consent and the study was approved by the institutional review board of both hospitals (17/2004 and LTME/Z-12.41).

### *Pulmonary RLS on TTCE.*

TTCE was performed by placing an intravenous line in the right hand to which two 10mL syringes were connected, one filled with an 8mL physiologic saline solution and the other with 1mL air. Subsequently, 1mL blood was drawn in the air-filled syringe and mixed with the saline-filled syringe by reverse flushing between both syringes, creating agitated saline (microbubbles). The patient was positioned in the left lateral position and 5mL of agitated saline was injected within three seconds, while projecting the 4-chamber apical view, with and without a Valsalva manoeuvre. The TTCEs were performed by a constant group of three trained echocardiographists. Shunt interpretation was performed by two experienced cardiologists with dedicated expertise in HHT, who were unaware of the patients medical history. In case of RLS, visualization of shunt origin was pursued in every TTCE. All shunts that were visualized through a pulmonary vein were classified as pulmonary shunts. On the occasion of poor visualization of shunt origin, we used a delay of four cardiac cycles to distinguish a pulmonary from a cardiac RLS, in which TTCE was considered positive for a pulmonary RLS if microbubbles appeared in the left atrium after four cardiac cycles, as published before [13, 14, 18]. The delay in appearance of microbubbles in the left atrium was measured in number of cardiac cycles after the first appearance of microbubbles in the right atrium. Opacification of the left ventricle was graded as 1 (maximum of 29 microbubbles in left ventricle), 2 (30-100 microbubbles, or 3 (>100 microbubbles). This division was based on the maximum number of microbubbles in the left ventricle counted in one still-frame. Local institutional logistics and experience in the TTCE procedure are important requirements for an optimal and accurate RLS grading system. A good κ coefficient of 0.85 was found for inter-observer agreement concerning pulmonary shunt grade in previous studies [13-15]. Shunts within four cardiac cycles and poor visualization of shunt origin were classified as "indeterminate" shunts. A patent foramen ovale (PFO) was diagnosed only after a positive

Valsalva maneuver, without spontaneous RLS. The presence of an atrial septum defect (ASD) was routinely excluded in all shunts using colour Doppler and potential negative contrast in the right atrium.

### *Prevalence of cerebral manifestations.*

All available medical records were analyzed for the prevalence of potential cerebral manifestations. Presence of cerebral ischemic stroke, transient ischemic attack (TIA), or brain abscess was diagnosed by a neurologist based on clinical evaluation and appropriate brain imaging. Cerebral ischemic stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours. An event matching this definition but lasting less than 24 hours was considered to be a TIA. A brain abscess was diagnosed in case of a focal intracranial infection of parenchyma that evolves into collections of pus enclosed by a well-vascularized capsule.

### *Statistical analysis.*

Descriptive statistics were used to describe patient characteristics. Differences between groups were analyzed by the unpaired Student's *t* test for continues variables and Chi-squared test for nominal variables. Data are given as mean ± SD or number (%). Level of significance was set at $p<0.05$. Univariate and multivariate statistical analyses with logistic regression were used to identify and estimate risk factors for the presence of cerebral manifestations. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. Statistics were performed using a statistical software package (SPSS, version 17.0; SPSS Inc., Chicago).

## Results.

### *Study population.*

A diagnostic TTCE was available in 1088 out of 1129 screened patients (96.4%). An indeterminate RLS was found in 50 out of 1088 patients (4.6%), who were excluded in order to aspire purely pulmonary shunts for our analysis. In these 50 patients only one TIA was documented (2%) and their exclusion will probably not have influenced our results. The remaining 1038 patients were included for further analysis. Genetic testing was performed in 853 out of 1038 screened persons (82.2%). HHT was definite in 689 (66.4%), possible in 84 (8.1%), unlikely in 99 (9.5%) and excluded in 166 (16.0%) patients. HHT1 was found in 218 patients (21.0%) and 294 patients had HHT2 (28.3%). The baseline characteristics of our study population are listed in Table 1.

### *Pulmonary RLS on TTCE.*

A pulmonary RLS on TTCE was present in 530 out of 1038 patients (51.1%) (Table 2). Out of 530 patients with a pulmonary RLS, definite HHT was diagnosed in 460 (86.8%), possible HHT in 25 (4.7%), HHT remained unlikely in 24 patients (4.5%) and HHT was excluded in 21 persons (4.0%). A pulmonary shunt grade 1, 2 or 3 was present in 228 (22.0%), 139 (13.4%) and 163 (15.7%) patients. There were only six patients (1.1%) with a pulmonary shunt grade 2 or 3 in which HHT was unlikely or excluded. None of these patients had comorbidities that could explain the shunt. They were diagnosed with an idiopathic, solitary PAVM, which may be caused by referral bias in our HHT screening program. In 58 patients (5.6%) there was evidence of a clear Valsalva-induced PFO. There were no ASD detected in our screenings population.

### *Prevalence of cerebral manifestations.*

The overall prevalence of a cerebral manifestation (ischemic stroke, TIA or brain abscess) in patients with a pulmonary RLS on TTCE was 8.3% compared to 1.4% in patients without a pulmonary RLS ($p<0.001$). The prevalence of a cerebral manifestation differed significantly between the pulmonary shunt grades; 1.4%, 0.4%, 6.5% and 20.9% for pulmonary shunt grade 0, 1, 2 and 3 on TTCE respectively (Table 2). The time course between the neurological event and TTCE was 4.8±5.7 years. Pulmonary shunt grade 2 and 3 on TTCE were strong significant predictors for the prevalence of a cerebral manifestation using multivariate analysis ($p=0.03$ and $p=0.002$ respectively, table 3). Interestingly, there was no significant difference in the prevalence of cerebral manifestations between patients with a pulmonary shunt grade 1 on TTCE and patients without a pulmonary RLS ($p=0.47$).

A chest HRCT was available in all 44 patients (100%) with a pulmonary RLS on TTCE and a cerebral manifestation, and identified a PAVM in 40 of these patients (90.9%). There were two grade 2 and two grade 3 pulmonary shunts on TTCE in the four patients (9.1%) without a PAVM on chest HRCT and a prior cerebral manifestation. These probably represent diffuse, microscopic shunts not detectable on chest HRCT. As expected, the presence of a PAVM on chest HRCT was also a significant predictor for the prevalence of a cerebral manifestation using multivariate analysis ($p=0.02$, table 3). There were no cerebral manifestations documented in the 58 patients with a Valsalva-induced PFO.

## Discussion.

This is the first, large cross-sectional study evaluating the potential relation between pulmonary shunt size on TTCE and prevalence of cerebral complications. Our study demonstrates that the occurrence of a cerebral ischemic event or brain abscess is strongly associated with the pulmonary shunt grade on TTCE, which has not been established before.

A pulmonary RLS carries the risk of cerebral paradoxical embolization by bypassing the pulmonary capillary filtering system, resulting in cerebral ischemic stroke, TIA or brain abscess [13]. In our study, the overall prevalence of a cerebral manifestation was 8.3% in patients with a pulmonary shunt on TTCE. Previous studies showed higher prevalence of neurological complications (9-47%), using pulmonary angiography or chest HRCT for the detection of PAVMs [19-22]. TTCE is a more sensitive screening method and detects microscopic PAVMs as well, which are not visualized by pulmonary angiography or chest HRCT. Therefore, our study population is different and also includes PAVMs that would not have been included in prior studies solely based on angiography and chest HRCT.

Contrasting with the potentially high rate of cerebral complications from paradoxical embolization, PAVMs may also cause pulmonary hemorrhagic complications [23]. These occur due to intrabronchial or intrapleural rupture of PAVMs ensuing hemoptysis or hemothorax. In our study population we encountered only 12 patients with hemoptysis (1.2%) and one patient with a hemothorax (0.1%, table 2).

It is hypothesized that the risk of cerebral paradoxical embolization depends on the relative perfusion of PAVM. This concept is also suggested in patients with a PFO, in which a larger diameter and a more extensive, or permanent, right-to-left interatrial shunt on TTCE is associated with a significantly higher prevalence of cerebral ischemic stroke [24-26]. The existence of a relation between pulmonary shunt size and risk of cerebral complications remains controversial. Moussouttas et al. previously evaluated the presence of cerebral paradoxical embolizations in patients with PAVMs on pulmonary angiography [21]. They included 75 patients with a PAVM feeding artery diameter of ≥3mm on pulmonary angiography. The prevalence of ischemic stroke increased from 14% in patients with a single PAVM to 27% in those with multiple PAVMs on pulmonary angiography. Similar to their findings for ischemic stroke, the prevalence of brain abscess also increased two-fold in patients with multiple PAVMs, suggesting an increased predisposition for cerebral complications in patients with a greater number of PAVMs. This correlation was also shown by Gazzaniga et al., who described a potential relation between echocardiographic pulmonary shunt grading and a history of neurological complications related to paradoxical embolization [12]. However, since their analysis dealt with only 9 complications in 36 patients with PAVMs, they emphasized that this correlation could have been biased by the low number of events.

In a well-performed study by Shovlin et al., no association was found between PAVM feeding artery diameter on chest HRCT and risk of cerebral ischemic stroke or brain abscess in a cohort of 219 patients with PAVMs [22]. Possible explanations for the different findings in our study might be the use of TTCE instead of chest HRCT. Echocardiographic shunt grading represents a more functional measurement of pulmonary RLS, instead of the anatomic shunt measurements with chest HRCT. Previous studies demonstrate high false negative results from HRCT in up to 50% compared to TTCE in detecting PAVMs [14]. Diffuse small PAVMs can be missed on HRCT, while there may be a large functional shunt on TTCE, which carries a risk of cerebral paradoxical embolization as well [16]. In the study of Shovlin et al. functional pulmonary shunt size was measured with technetium and oximetry. Pulmonary shunt grade 1 and 2 on TTCE are still small shunts, usually associated with normal oximetry, and were probably not detected with the methods used in the study by Shovlin et al.

### *Clinical relevance.*

Previously, van Gent et al. demonstrated that patients with a pulmonary shunt grade 1 on TTCE do not have PAVMs on chest HRCT that are large enough for embolotherapy [14], which implies that a chest HRCT may be withheld in these patients. The results from our present study suggest that a pulmonary shunt grade 1 on TTCE is not associated with an increased prevalence of cerebral ischemic events, brain abscesses, or pulmonary hemorrhagic complications. We believe a conservative management strategy (without HRCT and antibiotic prophylaxis) is probably justified in patients with a pulmonary shunt grade 1 on TTCE considering the absence of treatable PAVMs and the negligible risk of cerebral paradoxical embolizations in this subset of patients. Deferring chest HRCT in these patients could result in a tremendous cost saving and reduction of radiation exposure in mainly young adults [16]. Additional chest HRCT may than be reserved for patients with a pulmonary shunt grade 2 or 3 on initial TTCE to evaluate the opportunity for embolotherapy.

Although we do not have sufficient long-term data on potential growth of PAVMs, it seems conceivable that follow-up of patients without a pulmonary RLS on TTCE, or those with a pulmonary shunt and absence of a treatable PAVM on chest HRCT, is performed by TTCE every five years. Additional chest HRCT would than only be indicated if the echocardiographic pulmonary shunt grade increases. Of course, follow-up should still be performed with chest HRCT scanning in patients with a pulmonary shunt grade 3 on TTCE without visible PAVMs on chest HRCT. Given the impact of a missed treatable PAVM and subsequent risk for cerebral complications, our data and hypotheses need to be confirmed in future prospective studies.

### *Study limitations.*

This study presents some limitations. First of all, we are well aware of its cross-sectional nature, which makes a real causal inference difficult. The study was not primary designed to analyse the diagnostic value of TTCE in predicting the risk of neurological complications. Cross-sectional studies can be used for hypothesis generation and show associations rather than causalities. Cross-sectional studies cannot exactly describe the temporal relationship between risk factors and disease development; in this case pulmonary shunt grade and cerebral manifestation. Furthermore, cross-sectional studies carry the risk of selection bias, which may have contributed to a less precise prevalence of both PAVMs and complications in our study population, compared to a prospective study design. Despite the cross-sectional design, we do think our study presents a firm observation and contributes important elements to the challenging discussion about the optimal approach to the patient with a pulmonary shunt grade 1 on initial TTCE screening.

A second limitation to our study is the fact that we did not record the classical vascular risk factors, such as smoking status, arterial hypertension, known diabetes mellitus, hypercholesterolemia, atrial fibrillation, or cardiac and carotid artery disease. Although our study population is relatively young, we cannot exclude atherosclerotic disease in both patients with and without a pulmonary RLS and a cerebral ischemic event.

A third limitation can be the absence of detailed echocardiographic data on left ventricular function, valvular heart disease, right ventricular systolic pressure, heart rate, cardiac output and anemia, which may influence the pulmonary grading system.

A fourth limitation is that patients with a pulmonary shunt on TTCE were not routinely screened for the prevalence of cerebral ischemic events, since this seems to have little clinical consequences. Asymptomatic cerebral ischemic events were missed and this may have influenced the prevalence of cerebral manifestations in our study population, which may be higher than reported.

## Conclusions.

Pulmonary RLS grade on TTCE is strongly associated with the prevalence of a cerebral ischemic event or brain abscess in patients screened for HHT. Patients with a pulmonary shunt grade 1 on TTCE do not appear to have an increased risk for cerebral complications.

### Author Contributions

Conception and design: SV, EB, MG, PG, GM, CD, WS, CW, RS, JM, MP.
Acquisition of data: SV, EB, MG, PG, GM, CD, WS, CW, RS, JM, MP.
Analysis and interpretation of data: SV, EB, MG, WS, CW, RS, JM, MP.
Drafted the manuscript: SV, JM, MP.
Revision of the manuscript for important intellectual content: EB, MG, PG, GM, CD, WS, CW, RS.

Both Sebastiaan Velthuis and Martijn C Post can be noted as guarantors of the manuscript.

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**Table 1:** Baseline characteristics. *n*: number. *y*: years. *RLS:* right-to-left shunt. *TTCE:* transthoracic contrast echocardiography. *HHT:* hereditary haemorrhagic telangiectasia. *PFO:* patent foramen ovale. * Only Valsalva induced.

| | |
|---|---|
| **Patients, n** | 1038 |
| | |
| **Age (y)** | 44.3 ± 15.6 |
| | |
| **Sex, n (%)** | |
| *Male* | 430 (41.4) |
| *Female* | 608 (58.6) |
| | |
| **Pulmonary RLS on TTCE, n (%)** | |
| *Yes* | 530 (51.1) |
| *No* | 508 (48.9) |
| | |
| **HHT, n (%)** | |
| *Definite* | 689 (66.4) |
| *Possible* | 84 (8.1) |
| *Unlikely* | 99 (9.5) |
| *Excluded* | 166 (16.0) |
| | |
| **Genetic testing, n (%)** | 853 (82.2) |
| *HHT1* | 218 (21.0) |
| *HHT2* | 294 (28.3) |
| *SMAD4 mutation* | 6 (0.6) |
| *HHT excluded* | 166 (16.0) |
| *Gene mutation not found* | 169 (16.3) |
| *Not performed* | 185 (17.8) |
| | |
| **PFO*, n (%)** | 58 (5.6) |

**Table 2:** Characteristics of patients with different pulmonary shunt grades on transthoracic contrast echocardiography. *RLS:* right-to-left shunt. *n:* number. *y:* years. *HHT:* hereditary haemorrhagic telangiectasia. *TIA:* transient ischemic attack.

* *One patient with both an ischemic stroke and TIA, one patient with both an ischemic stroke and brain abscess.*

| | No RLS | Grade 1 RLS | Grade 2 RLS | Grade 3 RLS |
|---|---|---|---|---|
| **Patients, n (%)** | 508 (48.9) | 228 (22.0) | 139 (13.4) | 163 (15.7) |
| | | | | |
| **Age (y)** | 45.5±15.4 | 42.7±16.1 | 42.6±15.7 | 44.6±14.8 |
| | | | | |
| **Sex, n (%)** | | | | |
| *Male* | 225 (44.3) | 91 (39.9) | 62 (44.6) | 52 (31.9) |
| *Female* | 283(55.7) | 137 (60.1) | 77 (55.4) | 111 (68.1) |
| | | | | |
| **HHT, n (%)** | | | | |
| *Definite* | 229 (45.1) | 176 (77.2) | 132 (95.0) | 152 (93.3) |
| *Possible* | 59 (11.6) | 13 ( 5.7) | 4 (2.9) | 8 (4.9) |
| *Unlikely* | 75 (14.8) | 19 (8.3) | 2 (1.4) | 3 (1.8) |
| *Excluded* | 145 (28.5) | 20 (8.8) | 1 (0.7) | 0 |
| | | | | |
| **Cerebral manifestation, n (%)** | 7 (1.4) | 1 (0.4) | 9 (6.5) | 34 (20.9)* |
| *Ischemic stroke* | 2 (0.4) | 1 (0.4) | 3 (2.2) | 22 (13.5) |
| *TIA* | 4 (0.8) | 0 | 3 (2.2) | 5 (3.1) |
| *Brain abscess* | 1 (0.2) | 0 | 3 (2.2) | 9 (5.5) |
| | | | | |
| **Hemorrhagic complication, n (%)** | 2 (0.4) | 0 | 2 (1.4) | 9 (5.5) |
| *Hemoptysis* | 2 (0.4) | 0 | 1 (0.7) | 9 (5.5) |
| *Hemothorax* | 0 | 0 | 1 (0.7) | 0 |

**Table 3:** Predictors of cerebral manifestations in patients screened for HHT.

*n:* number. *y:* years. *ref:* reference. *RLS:* right-to-left shunt. *PAVM:* pulmonary arteriovenous malformation. *HRCT:* High-resolution computed tomography. *CI:* confidence interval.

| | *Univariate* | | *Multivariate* | |
|---|---|---|---|---|
| **Cerebral manifestation (n=51)** | **Odds ratio (95% CI)** | **P value** | **Odds ratio (95% CI)** | **P value** |
| **Age (y)** | 1.02 (1.00-1.04) | 0.08 | 1.02 (1.00-1.04) | 0.11 |
| | | | | |
| **Sex (female)** | 1.20 (0.67-2.15) | 0.54 | | |
| | | | | |
| **HHT, n (%)** | | | | |
| *Definite* | 11.5 (1.6-84.3) | 0.02 | 1.06 (0.11-10.3) | 0.96 |
| *Possible* | 4.02 (0.36-45.0) | 0.26 | 1.13 (0.08-15.4) | 0.93 |
| *Unlikely* | 5.16 (0.53-50.3) | 0.16 | 3.23 (0.31-33.9) | 0.33 |
| *Excluded (ref)* | *ref* | *ref* | *ref* | *ref* |
| | | | | |
| **Pulmonary RLS on TTCE** | 6.51 (2.90-14.6) | *<0.001* | | |
| *Grade 1 RLS* | 0.32 (0.04-2.58) | *0.28* | 0.44 (0.05-4.13) | 0.47 |
| *Grade 2 RLS* | 4.96 (1.81-13.6) | *0.002* | 4.78 (1.14-20.0) | 0.03 |
| *Grade 3 RLS* | 18.9 (8.18-43.5) | <0.001 | 10.4 (2.4-45.3) | 0.002 |
| *No RLS (ref)* | *ref* | *ref* | *ref* | *ref* |
| | | | | |
| **PAVM on chest HRCT** | 16.3 (7.74-34.0) | <0.001 | 3.73 (1.29-10.8) | 0.02 |

**Figure 1:** Prevalence of cerebral manifestations within different pulmonary shunt grades on transthoracic contrast echocardiography. *RLS:* right-to-left shunt. *TIA:* transient ischemic attack.