Pulmonary Shunt Fraction Measurement Compared to Contrast Echocardiography in Hereditary Haemorrhagic Telangiectasia Patients: Time to Abandon the 100% Oxygen Method?

Sebastiaan Velthuis^a Veronique M.M. Vorselaars^a Cornelis J.J. Westermann^b
Repke J. Snijder^b Johannes J. Mager^b Martijn C. Post^a

Departments of ^aCardiology and ^bPulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands

Key Words

Pulmonary right-to-left shunting · Transthoracic contrast echocardiography · 100% oxygen method · Hereditary haemorrhagic telangiectasia · Shunt fraction measurement

Abstract

Background: The presence of pulmonary right-to-left shunting (RLS) is associated with severe neurological complications from paradoxical embolisation in patients with hereditary haemorrhagic telangiectasia (HHT) and screening is warranted. Pulmonary shunt fraction measurement with the 100% oxygen method can be used for the detection and quantification of functional pulmonary RLS, although transthoracic contrast echocardiography (TTCE) has emerged as the gold standard over the last few years. **Objective:** The aim of this study was to determine the true diagnostic accuracy of the established 100% oxygen method in detecting pulmonary RLS, as compared to TTCE. **Methods:** We analysed 628 persons screened for HHT between 2004 and 2010, all of whom underwent TTCE. A quantitative 3-point grading scale was used to differentiate between minimal, moderate or extensive pulmonary RLS on TTCE (grade 1–3, respectively). Additional shunt fraction measurement with the 100% oxy-

gen method was pursued in cases of $pO_2 < 13$ or < 12 kPa in patients younger or older than 30 years, respectively. A shunt fraction $> 5\%$ was considered pathological. **Results:** Both TTCE and the 100% oxygen method were performed in 210 subjects. Although the presence of a pathological shunt fraction correlated with an increased pulmonary shunt grade on TTCE, the 100% oxygen method confirmed a $> 5\%$ shunt fraction in only 51% of patients with pulmonary RLS on TTCE (14, 20 and 72% for grade 1, 2 and 3, respectively). **Conclusion:** Pulmonary shunt fraction measurement with the 100% oxygen method is not a useful screening technique for the detection of pulmonary RLS in HHT as its sensitivity is too low and large pulmonary shunts on TTCE may remain undetected using this method.

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Introduction

Pulmonary arteriovenous malformations (PAVMs) are thin-walled abnormal vessels replacing normal capillaries between the pulmonary arterial and venous circulation [1]. A PAVM causes permanent pulmonary right-to-left shunting (RLS), thereby bypassing the pulmonary

capillary filter. Consequently, both emboli of thrombotic and septic origin may directly reach the systemic circulation, causing potential severe neurological complications, such as ischemic strokes or brain abscesses [2]. Gas exchange may also be compromised in the presence of pulmonary RLS, resulting in hypoxaemia and dyspnoea. The majority of PAVMs (70–90%) are associated with hereditary haemorrhagic telangiectasia (HHT) [3, 4]. HHT is an autosomal dominant inherited disorder, characterised by vascular abnormalities varying from small telangiectasias in skin and mucosal membranes to large arteriovenous malformations, predominantly in the brain, liver and lungs. There are mainly two types of HHT, corresponding with gene mutations coding for endoglin (HHT1) and ALK1 (HHT2) [5, 6]. Pulmonary RLS has been reported in 91% of HHT1 and in 53% of HHT2 patients [7]. Due to this high prevalence coupled with its potential severe complications and the existence of effective treatment options with transcatheter embolotherapy, screening for pulmonary RLS is recommended in all patients with possible or confirmed HHT [8–10]. Pulmonary shunt fraction measurement with the 100% oxygen method has long been performed as the initial screening technique, based on alveolar-arterial oxygen differences after breathing 100% oxygen [3], but during the last few years transthoracic contrast echocardiography (TTCE) has evolved as the recommended first-line screening technique for the detection of pulmonary RLS [9, 11]. However, the 100% oxygen method has never been directly compared to TTCE and is still in use for the detection and quantification of pulmonary RLS and analysis of unexplained hypoxaemia. Therefore, the present large observational study determined the true diagnostic accuracy of pulmonary shunt fraction measurement with the established 100% oxygen method in detecting functional pulmonary RLS compared to TTCE as the modern gold standard.

Methods

Study Population

Between May 2004 and December 2010, 669 subjects above 15 years of age were screened for HHT in the St. Antonius Hospital, Nieuwegein, The Netherlands. Subjects were screened in a 1-day protocol, as family members of index patients or in case of clinical symptoms suggesting HHT. A complete history and physical examination were performed by a pulmonologist with dedicated expertise in HHT. The clinical diagnosis of HHT was established according to the Curaçao criteria [12]. These criteria consist of spontaneous and recurrent epistaxis, telangiectasias 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 [13]. A definite diagnosis of HHT was established in the case of three or more clinical Curaçao criteria, or when genetic testing identified the HHT-causing mutation. The diagnosis of HHT was 'possible' in patients with two clinical Curaçao criteria without genetic testing or if no mutation had been found in the family. The diagnosis of HHT was 'unlikely' in the presence of less than two clinical Curaçao criteria without genetic testing or if no mutation had been found in the family. HHT was rejected when genetic testing excluded the known HHT-causing family mutation. The study was approved by the institutional review board (LTME/Z-12.41).

Pulmonary Shunt Fraction Measurement with the Established 100% Oxygen Method

The arterial partial oxygen pressure (pO_2 , kPa) was measured at rest, breathing room air in a semi-recumbent position. An additional shunt fraction measurement with the 100% oxygen method was pursued in cases with a $pO_2 < 13$ or < 12 kPa in patients younger or older than 30 years, respectively. Patients breathed 100% oxygen from a Douglas bag, via a closely fitting mouthpiece and two-way valve, while wearing a nose clip and taking a deep inspiration every minute. An arterial blood sample was obtained after breathing 100% oxygen for 30 min and the samples were cooled on ice and analysed immediately for oxygen and carbon dioxide tensions. The pulmonary shunt fraction was calculated using the established classical equation: $Q_s/Q_t = (C_{c,O_2} - C_{a,O_2}) / (C_{c,O_2} - C_{v,O_2})$, in which Q_s/Q_t is the RLS as a fraction of the cardiac output, C_{c,O_2} is the oxygen content at the end of the pulmonary capillary, C_{a,O_2} is the oxygen content of arterial blood and C_{v,O_2} is the oxygen content of mixed venous blood [14]. The C_{v,O_2} was defined as the $C_{a,O_2} - 4.4$ ml O_2 /100 ml blood [15]. Since the total blood oxygen content is composed of dissolved O_2 plus HbO_2 and the solubility of oxygen in blood is 0.0225 ml/100 ml/kPa, the oxygen content was calculated as follows: oxygen content (ml O_2 /100 ml blood) = $(0.0225 \times pO_2) + (2.24 \times \text{haemoglobin} \times SaO_2/100)$, where pO_2 is the partial oxygen pressure (kPa), haemoglobin is expressed in mmol/l and SaO_2 is the arterial oxygen saturation (%). The haemoglobin oxygen saturation at the end of the pulmonary capillary is assumed to be 100%. The partial pressure of carbon dioxide (pCO_2) is assumed to equal the alveolar partial pressure of oxygen (pO_2) and can be calculated as follows: $pO_2 = \text{barometric pressure (101.3 kPa)} - pCO_2 - \text{alveolar saturated water vapour pressure (} P_{A,H_2O})$. P_{A,H_2O} is 6.3 kPa at a body temperature of 37°C. Using the 100% oxygen method, a pulmonary shunt fraction of >5% was considered pathological [3, 15]. Patients with previously treated PAVMs were not included in our analysis.

Transthoracic Contrast Echocardiography

TTCE was performed by placing an intravenous line in the right ante-cubital vein to which two 10-ml syringes were connected, one filled with an 8-ml physiologic saline solution and the other with 1 ml of air. Subsequently, 1 ml 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 5 ml of fresh agitated saline was injected within 3 s while projecting the 4-chamber apical view, with and without a Valsalva manoeuvre. TTCE was performed by a constant group of three trained echocardiographers. Interpretation of RLS was performed by two cardiologists with dedicated expertise in both TTCE and HHT,

Fig. 1. Flow chart of the selected study population.

who were unaware of the patients' medical history or prior shunt fraction measurement. In the case of RLS, visualisation of shunt origin was pursued in every TTCE. All RLS visualised through a pulmonary vein was classified as pulmonary RLS. On the occasion of poor visualisation of shunt origin, we used a delay of 4 cardiac cycles to distinguish pulmonary from cardiac RLS, in which TTCE was considered positive for pulmonary RLS if microbubbles appeared in the left atrium after 4 cardiac cycles, as published previously [11, 16, 17]. This delay in the appearance of microbubbles in the left atrium was measured in the number of cardiac cycles after the first appearance of microbubbles in the right atrium. Opacification of the left ventricle was quantitatively graded as 1 (a maximum of 29 microbubbles in the 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. A good κ coefficient of 0.85 up to 0.94 was found for interobserver agreement concerning this pulmonary shunt grade on TTCE in previous studies [17, 18]. RLS within 4 cardiac cycles with poor visualisation of shunt origin was classified as indeterminate shunting and excluded from further analysis. A patent foramen ovale was diagnosed only after a positive Valsalva manoeuvre, without spontaneous RLS. The presence of an atrial septum defect was routinely excluded in all RLS using colour Doppler or potential negative contrast in the right atrium [19].

Chest CT

Chest CT images were routinely obtained on a 16+ multi-detector CT scanner (Philips Medical Systems), with a dedicated high-resolution algorithm and maximum slice thickness of 1 mm. Identification of PAVMs on chest CT was based on the presence of a nodular opacity with both an afferent and efferent vessel. Chest CT scans were evaluated by two independent observers highly experienced in evaluating PAVMs (a radiologist and a pulmonologist), both blinded to the results from TTCE and shunt fraction measurement.

When the observers disagreed, chest CT was considered positive for a PAVM and additional angiography of the pulmonary artery was performed given the impact of potential complications from a missed treatable PAVM.

Statistics

Descriptive statistics were used to describe patient characteristics. Continuous variables with a normal distribution were presented as the mean $\pm$ standard deviation. A median range was used when normal distribution was absent. Sensitivity, specificity, positive predictive value and negative predictive value with their 95% confidence intervals (CI), and the area under the receiver operating characteristic (ROC) curve were determined for shunt fraction measurement with the 100% oxygen method compared to TTCE as the gold standard. Statistical analyses were performed using the statistical software application SPSS (version 17.0; SPSS Inc., Chicago, Ill., USA).

Results

Study Population

Out of the 669 individuals screened for HHT, a diagnostic TTCE was available in 628 (93.9%). Arterial blood gas analysis was performed in 614 out of these 628 subjects (97.8%). Based on the previous described pO_2 values, 210 persons (34.2%) underwent additional pulmonary shunt fraction measurement with the 100% oxygen method and were included for further analysis (fig. 1). Out of

Fig. 2. Pulmonary shunt fraction measurement with the 100% oxygen method compared to different pulmonary shunt grades on TTCE (n = 210).

Fig. 3. Dot plot demonstrating the shunt fractions measured with the 100% oxygen method compared to graded TTCE as the gold standard (n = 210).

these 210 persons, the presence of HHT was definite in 135 patients (64.3%), possible in 17 (8.1%), unlikely in 19 (9.0%) and excluded in 39 (18.6%). Genetic testing was performed in 188 out of the 210 patients (89.5%), which identified 62 (29.5%) with HHT1 and 62 (29.5%) with HHT2. The baseline characteristics of our final study population are described in table 1.

Table 1. Baseline characteristics of the study population analysed with both TTCE and the 100% oxygen method

Patients	210
Female	128 (61.0)
Age, years	46.8 ± 15.1
HHT	
Definite	135 (64.3)
HHT 1	62 (29.5)
HHT 2	62 (29.5)
Possible	17 (8.1)
Unlikely	19 (9.0)
Excluded	39 (18.6)
Pulmonary shunt on TTCE	
Grade 1	22 (10.5)
Grade 2	15 (7.1)
Grade 3	61 (29.0)
No pulmonary shunt on TTCE	112 (53.3)
PFO	10 (4.8)
Shunt fraction ≤5%	144 (68.6)
Shunt fraction >5%	66 (31.4)
PAVM on chest CT	
Yes	66 (31.4)
No	141 (67.1)

Data are presented as n with percentages in parentheses, or the mean ± standard deviation. PFO = Patent foramen ovale.

Pulmonary Shunt Fraction Measurement with the 100% Oxygen Method Compared to TTCE

Pulmonary RLS on TTCE was present in 98 out of the 210 patients (46.7%). A pulmonary shunt grade 1 was diagnosed in 22 patients (22.4%), grade 2 in 15 (15.3%) and grade 3 in 61 (62.2%). The 100% oxygen method documented a pathological shunt fraction of >5% in 13.6, 20.0 and 72.1% of the patients with a pulmonary shunt grade 1, 2 or 3 on TTCE, respectively (fig. 2). The mean pulmonary shunt fraction in patients with pulmonary shunt grades 1, 2 and 3 on TTCE was 2.2, 3.8 and 10.1%, respectively (fig. 3). Using TTCE as the gold standard for the detection of functional pulmonary RLS, the 100% oxygen method had a sensitivity of 51% (95% CI 0.41–0.61) and a specificity of 86% (95% CI 0.78–0.91; table 2a), with an area under the ROC curve of 0.74 (95% CI 0.67–0.81). The diagnostic accuracy of the 100% oxygen method in detecting only moderate to large pulmonary shunts on TTCE (grades 2 and 3) slightly increased to a sensitivity of 62% (95% CI 0.51–0.72) and a specificity of 86% (95% CI 0.79–0.9; table 2b), with an area under the ROC curve of 0.82 (95% CI 0.75–0.88).

Table 2. Pulmonary shunt fraction measurement using the 100% oxygen method compared to TTCE
a Diagnostic accuracy of the 100% oxygen method in detecting any pulmonary RLS on TTCE

	Shunt fraction $\leq 5\%$	Shunt fraction $> 5\%$	Total
No pulmonary shunt on TTCE	96	16	112
Any pulmonary shunt on TTCE	48	50	98
Total	144	66	210

Sensitivity 51% (0.41–0.61), specificity 86% (95% CI 0.78–0.91), positive predictive value 76% (95% CI 0.64–0.84), negative predictive value 67% (95% CI 0.58–0.74).

b Diagnostic accuracy of the 100% oxygen method in detecting only pulmonary shunt grades 2 and 3 on TTCE

	Shunt fraction $\leq 5\%$	Shunt fraction $> 5\%$	Total
No or grade 1 pulmonary shunt on TTCE	115	19	134
Only pulmonary shunt grade 2 or 3 on TTCE	29	47	76
Total	144	66	210

Sensitivity 62% (95% CI 0.51–0.72), specificity 86% (95% CI 0.79–0.9), positive predictive value 71% (95% CI 0.59–0.81), negative predictive value 80% (95% CI 0.73–0.86).

The 100% oxygen method revealed a pathological shunt fraction of $> 5\%$ in 14.3% of subjects without any RLS on TTCE. A mean shunt fraction of 9.1% was found in these false-positive cases. Chest CT demonstrated regions with atelectasis and/or pulmonary fibrosis in 53.3% of these persons, but no alternative explanation was found in the other 46.7% of false-positive cases.

TTCE showed a patent foramen ovale in 10 out of the 210 patients (4.8%), where the 100% oxygen method revealed a pathological shunt fraction of $> 5\%$ in only 3 of these patients. No atrial septum defect was documented.

Chest CT was performed in 207 out of the 210 patients (98.6%) with both TTCE and shunt fraction measurement. Although already selected by a lower pO_2 , chest CT confirmed the presence of PAVMs in 66 out of 98 patients (67.3%) with pulmonary RLS on TTCE. Pulmonary shunt fraction measurement with the 100% oxygen method identified a pathological shunt fraction in 46 out of 66 patients with a PAVM on chest CT (69.7%). The 100% oxygen method did not reveal an abnormal shunt fraction in the other 41.7% of patients with visible PAVMs on chest CT.

Discussion

To our knowledge, this is the first large study evaluating the true diagnostic accuracy of pulmonary shunt fraction measurement with the 100% oxygen method in detecting functional pulmonary RLS compared to TTCE as

the modern gold standard. Our results firmly indicate that pulmonary shunt fraction measurement with the 100% oxygen method is not a reliable test to screen for PAVMs in patients with HHT.

Screening for PAVMs is warranted in all patients with possible or confirmed HHT, given the high risk of neurological complications that may be prevented by transcatheter embolotherapy. Arterial blood gas analysis and additional pulmonary shunt fraction measurement with the 100% oxygen method have been used as non-invasive screening tests for the detection of functional pulmonary RLS in these subjects. Under normal conditions, the fraction of cardiac output that shunts from right-to-left (i.e. the shunt fraction) is $\leq 5\%$. A pathological shunt fraction of $> 5\%$ has been reported in up to 97.5% of patients with PAVMs prior to transcatheter embolotherapy [20–25] and the 100% oxygen method has long been assumed to be accurate enough for the detection of clinically important pulmonary RLS. However, a retrospective study of 105 individuals screened for HHT by Cottin et al. [26] previously suggested a markedly lower sensitivity (up to 68%) of the 100% oxygen method in detecting pulmonary RLS compared to anatomical-based tests like chest CT and pulmonary angiography. Over the last few years, TTCE has evolved as the first-line screening technique for the detection of functional pulmonary RLS based on its excellent sensitivity, high negative predictive value and wide availability with low risks and costs [9, 11, 17, 27–29]. However, studies directly comparing the 100% oxygen method

to TTCE are lacking. The current analysis was warranted to reveal the true diagnostic accuracy of pulmonary shunt fraction measurement with the 100% oxygen method as we know that chest CT confirms the presence of PAVMs in only 45% of patients with pulmonary RLS on TTCE [7]. The present study demonstrates that the 100% oxygen method detects a pathological shunt fraction of >5% in only 51% of patients with any pulmonary RLS on TTCE. The majority of patients with a pulmonary shunt grade 1 or 2 on TTCE remain undetected using the 100% oxygen method (86.4 and 80.0%, respectively). Even in patients with a large, pulmonary shunt grade 3 on TTCE, the 100% oxygen method fails to detect an abnormal shunt fraction in 27.9% of cases. Our group recently described that only pulmonary shunt grades 2 and 3 on TTCE have clinical implications [2, 7, 30], as neurological complications due to paradoxical embolisations are encountered in up to 14.2% of these shunts [2] and transcatheter embolotherapy of PAVMs is indicated in 52.5% of these patients [7]. However, the present study reveals that the 100% oxygen method fails to detect a pathological shunt fraction of >5% in 38.2% of patients with a pulmonary shunt grade 2 or 3 on TTCE. Furthermore, the current international guideline on the diagnosis and management of HHT recommends the use of antibiotic prophylaxis before procedures with risk of bacteraemia in patients with any documented pulmonary RLS in order to prevent the occurrence of brain abscesses [9]. The current study illustrates that up to 49% of these patients will not be identified using shunt fraction measurements with the 100% oxygen method.

On the other hand, we documented a pathological shunt fraction of >5% in 14.3% of individuals without any RLS on TTCE. Additional chest CT imaging showed regions with atelectasis and/or pulmonary fibrosis in 53.3% of these persons, but no alternative explanation for the increased shunt fraction was found in the remaining 46.7% (true false positives). Besides the fact that a small degree of physiologic RLS normally takes place via the bronchiolar system of the lung perfusion and Thebesian veins, there may be several sources of error resulting in false-positive or negative findings with the 100% oxygen method. The detection of pulmonary RLS using TTCE is based on the true anatomical and functional shunt, while the 100% oxygen method measures the alveolar-arterial oxygen difference, which is then converted into a shunt magnitude. The 100% oxygen method will be influenced by the presence of multiple small PAVMs, where oxygen uptake may still take place and the actual RLS is underestimated. Furthermore, the arteriovenous difference in oxygen content is not routinely measured in the established 100% oxygen method and devia-

tions from the assumed value could therefore result in deviations from the calculated shunt fraction. Measurement of the actual individual arteriovenous difference would improve the accuracy of the 100% oxygen method, but is not feasible in daily practice because of its invasive character. In addition, an accurate test can only be obtained when the patient truly receives 100% oxygen. A small leak in the oxygen delivery system will overestimate the degree of shunt fraction by lowering the true alveolar partial oxygen pressure. Similarly, breathing 100% oxygen for an inadequate period of time may result in an overestimation of the shunt fraction, owing to inadequate denitrogenation of poorly ventilated alveoli (which was not the case in the present study). It has also been reported that breathing 100% oxygen can occasionally cause a small amount of pulmonary RLS (up to 11%) in healthy subjects, due to complete denitrogenation and micro-atelectasis [31]. Taking a deep inspiration every minute helps to prevent this 100% oxygen-related micro-atelectasis [20]. Further study limitations are the fact that additional shunt fraction measurement was not routinely performed in all 669 screened persons and that the 100% oxygen method was tested in a population at high pre-test risk for PAVMs (HHT). Therefore, our results do not automatically support generalisation to all other aetiologies of pulmonary shunting.

Conclusion

Pulmonary shunt fraction measurement with the 100% oxygen method is not a useful screening technique for the detection of pulmonary RLS in HHT. The reasons for this are that its sensitivity is too low and a large proportion of clinically important pulmonary RLS remains undetected.

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