Sensitivity and Specificity of Radioisotope Right-Left Shunt Measurements and Pulse Oximetry for the Early Detection of Pulmonary Arteriovenous Malformations*

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Study objectives: To assess the effectiveness of pulse oximetry and radioisotope measurement of right-to-left (R-L) shunt for the early detection of pulmonary arteriovenous malformations (PAVMs) in patients with hereditary hemorrhagic telangiectasia (HHT).

Design: Patients with HHT had serial measurements of the following: (1) arterial oxygen saturation (SaO_2) by pulse oximetry in erect and supine positions, and on maximal exercise using cycle ergometry; (2) quantitative radioisotope measurements of R-L shunt using IV ^{99m}Tc-labeled macroaggregates of albumin; and (3) routine pulmonary function. After percutaneous transcatheter embolization of all PAVMs with feeding vessel diameters > 3 mm, residual PAVMs were assessed with selective digital subtraction pulmonary angiography. Using postembolization angiography as the "gold standard," SaO_2 and radioisotope shunt measurements after embolization were analyzed retrospectively using logistic regression to assess the ability of each test to predict for the presence of residual PAVMs.

Results: Of the 66 patients included, 40 had small PAVMs remaining postembolization. Using univariate logistic regression, radioisotope shunt and erect saturation showed a significant relationship with the presence of residual PAVMs (p = 0.001, 0.005, respectively). Erect SaO_2 ≤ 96% had 73% sensitivity and 35% specificity for detecting PAVMs. Radioisotope shunt >3.5% of cardiac output had 87% sensitivity and 61% specificity for detecting PAVMs.

Conclusions: These results confirm that noninvasive measurements are useful in the screening of patients with HHT for the presence of PAVMs without need for angiography and its associated risks, and that radionuclide scanning is better than pulse oximetry.

(CHEST 1999; 115:109–113)

Key words: angiography; arteriovenous malformations; embolization, therapeutic; oximetry; radionuclide imaging; telangiectasia, hereditary hemorrhagic

Abbreviations: CE = contrast echocardiography; HHT = hereditary hemorrhagic telangiectasia; PAVM = pulmonary arteriovenous malformation; SaO_2 = arterial oxygen saturation; R-L shunt = right to left shunt; ^{99m}Tc-MAA = ^{99m}technetium-labeled macroaggregates of albumin

Hemorrhagic hereditary telangiectasia (HHT) is a rare familial condition with an autosomal dominant mode of inheritance. While the most common clinical features are those of recurrent epistaxis and mucocutaneous telangiectasia, large arteriovenous malformations can develop, most commonly in pulmonary, cerebral, or hepatic vascular beds. While affecting only one third of HHT patients, pulmonary arteriovenous malformations (PAVMs) are a significant cause of morbidity and mortality,[1] and this is particularly so during pregnancy.[2,3] Cerebral ischemic events and cerebral abscesses, secondary to paradoxical embolism, are the most common problems,[4] but massive hemoptysis and hemothorax can occur and may prove fatal.[2,3] In recent years, percutaneous transcatheter embolization has become the treatment of choice.

Only a minority of HHT patients with PAVMs will

admit to respiratory symptoms or present because of them.[4,5] Given the high frequency of complications and the availability of safe and effective treatment, it is desirable to screen HHT patients for PAVMs early, before such complications occur. There are numerous tests available and much debate as to the most effective way of employing them.[1,5–7]

We report our experience of two relatively noninvasive tests: pulse oximetry and a radioisotope measurement of right-to-left (R-L) shunt using ^{99m}Tc-labeled macroaggregates of albumin (MAA). The aim of this study was to assess the usefulness of these two tests in screening for minimal disease, using pulmonary angiography as the "gold standard." A retrospective analysis was undertaken, reviewing the results of investigations taken at routine follow-up once all treatable lesions had been embolized, in all patients who had undergone angiography in our department. By assessing the usefulness of these two investigations in a group of patients with, by definition, minimal disease, it was our intention to simulate a group of patients being screened for PAVMs, where small/early lesions would be expected to predominate.

MATERIALS AND METHODS

Patient records, radiology reports, and pulmonary function results were reviewed to identify all patients with HHT who had undergone pulmonary angiography in our department between 1987 and 1997. As part of our normal practice, serial measurements of a number of physiologic parameters were measured before and after percutaneous transcatheter embolization: (1) routine pulmonary function tests; (2) arterial oxygen saturation (SaO$_2$) breathing room air using a pulse oximeter and ear probe, measured after 10 min in both supine and erect positions, and at maximal exercise on a cycle ergometer; and (3) R-L shunt measured by IV injection of ^{99m}Tc-labeled MAA, followed by gamma camera imaging as described previously.[8]

All patients had undergone selective digital-subtraction pulmonary angiography at the hands of an experienced radiologist to determine the site and size of any PAVMs. Where possible, all lesions with feeding vessels > 3 mm in diameter were embolized using metallic coils. In some cases, more than one procedure was required. Once all treatable lesions had been occluded, the presence or absence of any residual PAVMs was noted. Following radiological intervention, patients were reviewed in clinic 3 months later (range, 2 to 6 months) and the tests outlined above were performed. Patients were excluded from subsequent analysis if patients attended later than 6 months after angiography or if results from this visit were not available.

Statistics

Data from all suitable patients were collected and tabulated. Differences between groups were analyzed by Student t tests not assuming equal variances, or Fisher's Exact Test where appropriate. Using univariate and multivariate logistic regression with robust standard errors, the ability of follow-up investigations to predict the presence or absence of disease was determined. Statistical analysis was performed using software (Stata Release 5; Stata Corporation; College Station, TX).

RESULTS

Between 1987 and 1997, 81 patients with HHT underwent pulmonary angiography as part assessment and treatment of PAVMs. Of these 81 patients with HHT and PAVMs, 15 were excluded from the final analysis because of either large PAVMs still to be treated (n = 5) or because of unsuitable follow-up data (not seen within 6 months, n = 4; no record of test results at follow-up, n = 6). In the remaining 66 patients, 40 (61%) had residual PAVMs whose feeding vessels were too small for further coil embolization therapy. The results from these 66 patients are

Table 1—*Results From HHT Patients Following Embolization of All Treatable PAVMs**

| | | Residual PAVMs | | |
	All Patients (n = 66)	Patients With (n = 40)	Patients Without (n = 26)	p Values†
Age, yr	42.7 (15.1)	41.4 (14.5)	42.7 (15.1)	0.6
No. of procedures	1.6 (1.1)	1.9 (1.2)	1.2 (0.5)	0.002
Sex ratio, M:F	1:2.5	1:3	1:1.9	0.4‡
FEV$_1$/VC, %	77 (14)	79 (11)	75 (17)	0.4
VC, % predicted	94 (18)	92 (21)	97 (12)	0.2
DLCO, % predicted	87 (22)	85 (24)	90 (20)	0.4
Erect SaO$_2$, %	94 (5)	93 (6)	96 (2)	0.002
Supine SaO$_2$, %	95 (5)	94 (4)	96 (2)	0.007
Supine-erect SaO$_2$, %	1.2 (2.4)	1.7 (2.7)	0.3 (1.5)	0.01
SaO$_2$ at maximum exercise, %	92 (7)	91 (9)	95 (3)	0.01
R-L shunt, % cardiac output	7.0 (6.8)	9.3 (7.6)	3.6 (3.1)	<0.001

*Data in parentheses = SD. VC = vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide.
†p Values shown relate to comparisons between the "with" and "without" residual PAVMs groups, using Student t test.
‡Fisher's Exact Test.

summarized in Table 1. There were no significant differences in age or routine pulmonary function between the group with residual PAVMs and the group without. Taking the two groups together (n = 66), there was a significant sex bias (male: female 1:2.5, p = 0.0003: Fisher's Exact Test), but there was no significant difference in the male: female ratio between the two subgroups. In total, the 66 patients underwent 108 procedures (median, 1; range, 1 to 7), with the group with residual PAVMs requiring the greater number (p = 0.005: Table 1).

There were significant differences between the groups for SaO_2 however it was measured: erect, supine, supine minus erect, at peak exercise (Table 1). Univariate logistic regression demonstrated that R-L shunt and erect SaO_2 were the best predictors of the presence or absence of disease (p = 0.001 and p = 0.005, respectively). Stepwise logistic regression was used to determine whether a combination of variables might be more sensitive than a single test. Neither the addition of erect SaO_2 to R-L shunt nor, if R-L shunt was excluded, the addition of other tests

to erect SaO_2 could improve the ability of the model to predict the presence or absence of residual PAVMs.

The sensitivities and specificities of both R-L shunt and erect SaO_2 for predicting the presence or absence of residual PAVMs were calculated as the cutoff between "normal" and "abnormal" was varied (Fig 1). When an erect $SaO_2 \leq 96\%$ was considered abnormal, sensitivity and specificity were 73% and 35%, respectively (Table 2). At this level, all moderate-sized shunts ($\geq 7\%$ cardiac output) were detected, and overall 60% of patients were correctly classified. The predictive value of a positive result was 65%, and that of a negative result, 44%. As expected, the sensitivity and specificity varied inversely as the cutoff changed. For example, if $\leq 97\%$ was considered abnormal, all residual shunts were detected (sensitivity 100%), but specificity fell to 10%, representing an unacceptably high false-positive rate. Correspondingly, if the cutoff for SaO_2 was lowered to $\leq 95\%$, sensitivity fell to 61%, but specificity rose to 75% (Table 2). While this improved the number of patients correctly classified to 66%, it was believed that the consequent rise in the number in false negatives would render the test less useful for screening purposes. The values for radioisotope shunt at cutoffs of $> 3.5\%$ and $> 5\%$ are also set out in Table 2.

Overall $SaO_2 \leq 96\%$ and R-L shunt $> 3.5\%$ were considered to give the most appropriate balance between sensitivity and specificity for screening purposes. At these limits ($SaO_2 \leq 96\%$, R-L $> 3.5\%$), the radioisotope shunt method had a higher sensitivity and specificity, and correctly classified more patients (Table 2).
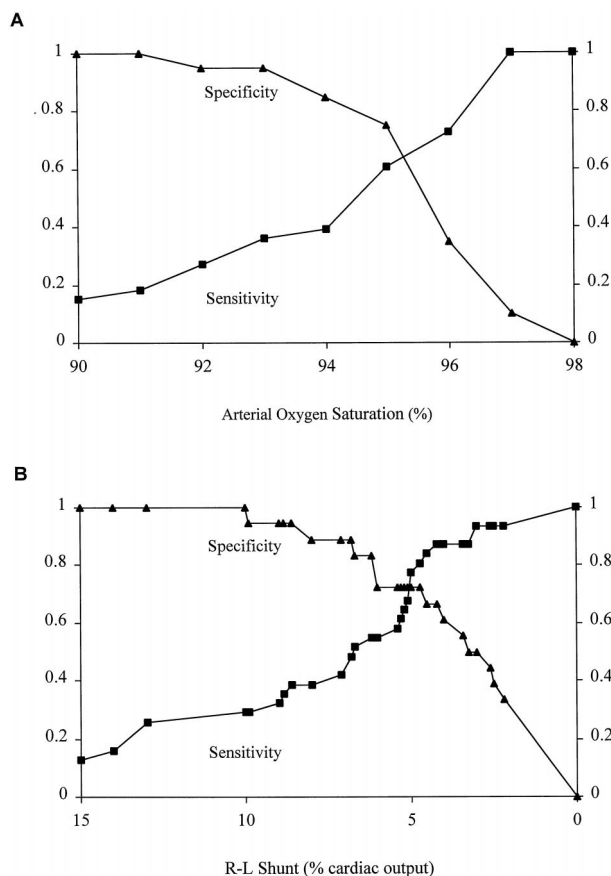

FIGURE 1. The relationship between the sensitivity and the specificity of (*top, A*) pulse oximetry in the erect position and (*bottom, B*) radioisotope R-L shunt for the detection of PAVMs.

DISCUSSION

This study sought to examine the usefulness of pulse oximetry and radioisotope measurements of R-L shunt for the detection of PAVMs in patients with HHT, using pulmonary angiography as the gold standard. Radionuclide scanning using ^{99m}Tc-MAA proved superior to pulse oximetry for the detection of residual PAVMs.

Our study was retrospective. The timing of the investigations was dictated by usual clinical practice over the last 10 years. The choice of a 2- to 6-month interval between angiography and subsequent testing was arbitrary. Testing in the 24 h postprocedure, before patients left hospital, was considered to be too early to be reliable. Residual PAVMs seen at angiography might have increased in size during the 2- to 6-month interval, but this would not affect the comparison between the two detection methods.

Table 2—Sensitivity, Specificity, and Predictive Values of Pulse Oximetry and Radioisotope R-L Shunt for the Detection of PAVMs in Patients With HHT*

	Pulse Oximetry			Radioisotope Shunt	
Cutoff	≤ 95%	≤ 96%†	≤ 97%	> 5%	> 3.5%†
Sensitivity	61	73	100	68	87
Specificity	75	35	10	72	61
Predictive value of positive result	79	65	63	79	79
Predictive value of negative result	56	44	100	59	73
% of all patients correctly classified	66	59	65	70	78

*All values are quoted as percentages.
†Recommended cutoffs for screening.

PAVMs not detected at angiography might also have enlarged and this would undermine the validity of the gold standard. To our knowledge, there are no data on the rate of growth of PAVMs, except in pregnancy,[2] and none of our patients became pregnant in this interval. Rapid growth from "undetectable by angiography" to "detectable by angiography" in 2 to 6 months seems unlikely in view of the natural history of telangiectasias in HHT.

Screening for PAVMs is necessary if complications are to be avoided. Ideally the test employed should be simple, safe, inexpensive, accurate, and possibly portable. Above all, it must be acceptable to the subject. None of the currently available modalities fulfils all these criteria.

Screening Methods Other Than Pulse Oximetry and ^{99m}Tc-MAA Shunt

Of the variety of different investigations available for identifying PAVMs, the two most accurate are pulmonary angiography[9] and helical CT.[10] Both, however, involve a significant exposure to ionizing radiation, are relatively costly, and in the case of pulmonary angiography, invasive. The chest radiograph is frequently abnormal if examined carefully, and one study suggests a sensitivity and specificity of 83% and 92%, respectively, but these may be overestimates since only a proportion of subjects examined underwent either angiography or CT to confirm the exclusion of PAVMs.[5]

The presence of anatomic R-L shunts can also be detected by the 100% O_2 breathing method. In our hands, there is no difference between this and the ^{99m}Tc-MAA method,[11] but there are limited data on its sensitivity vs angiography or CT. Haitjema et al[5] went some way to addressing this point. In their study, the 100% O_2 shunt method gave a sensitivity of 88% and a specificity of 71% for the detection of PAVMs, and proved superior to PaO_2 measured by arterial blood sampling (sensitivity 67% and specificity 61%). These results, however, may be an overestimate. In their study, all patients were initially

screened using arterial blood sampling, and only hypoxic patients (PaO_2 < 78 to 98 mm Hg dependent on age) underwent shunt measurement by the 100% O_2 breathing method, and subsequently only if this proved abnormal was pulmonary angiography undertaken. Thus, only a minority of patients underwent a gold standard investigation, and the calculated sensitivity and specificity for each of the two tests are likely to be overestimates due to the presence of misclassified patients.

In recent years, contrast echocardiography (CE) has become available for the detection of PAVMs. It has advantages in that it is minimally invasive, involves no radiation, and suitable equipment is widely available. However, it is qualitative rather than quantitative,[12] and there are little data regarding its sensitivity and specificity. In one recent study,[13] 55 HHT patients underwent CE, and of these, 35 (64%) had findings suggestive of PAVMs. However subsequent angiography in 24 of those with a positive result demonstrated PAVMs in only 12, suggesting either a high false-positive rate for CE, or the ability of CE to detect PAVMs not seen at angiography. Further evaluation is awaited.

Pulse Oximetry

It is relatively easy to detect large PAVMs, but the exclusion of very limited disease is much more problematic. Pulse oximetry has the advantage that it is noninvasive, inexpensive, and highly portable. The results of this study have confirmed that pulse oximetry can play a role in screening, but its relatively low specificity means that is not suitable for use in isolation. It is interesting to note that SaO_2 measured in the erect position alone proved superior to the difference in SaO_2 between supine and erect positions.

Radioisotope ^{99m}Tc-MAA R-L Shunt

As might be expected, the radioisotope measurement of R-L shunt using ^{99m}Tc-labeled MAA proved

a more robust test than pulse oximetry in detecting PAVMs in patients with very limited disease. It involves a lower radiation exposure than either angiography or CT, and it is only minimally invasive, requiring a single venous puncture. The sensitivity of 87% gives it an acceptably low false-negative rate, but with a specificity of 61%, 11 of the 26 patients without PAVMs would have undergone "unnecessary" further investigation. It must be emphasized that most patients positive for PAVMs had mild disease at the time of study, since the presence of treatable lesions was a criterion for exclusion. Of course, it could be argued that in the absence of treatable disease, little is to be gained by detecting them. We would disagree. Patients with even small PAVMs need antimicrobial prophylaxis at the time of dental or surgical procedures to reduce the risk of cerebral abscess, and will continue to require careful surveillance to detect enlargement later in life, such as may occur during pregnancy.

PAVMs: Genetic and Environmental Influences

In the future, advances in the understanding of the genetic basis of HHT should prove valuable. Since those patients with a defect linked to endoglin appear more likely to develop PAVMs,[14] genotyping may help identify those most at risk, and conversely spare some the inconvenience, risk, and expense of unnecessary investigations. For the moment, a positive family history of PAVMs should lead to earlier screening and lower the threshold for more detailed investigations. Given that the incidence of HHT itself has no gender bias,[15] the female preponderance in our study suggests that sex hormones play a role in the development of PAVMs, although the nature of this effect awaits complete explanation. Our confirmation of a gender bias and the knowledge that pregnancy confers extra risks confirm the need for preconception screening.[16]

Conclusion

This study shows that both pulse oximetry and radioisotope measurements of R-L shunt are useful in screening for pulmonary involvement in HHT. The assessment of the diagnostic accuracy of CE and CT scanning are awaited. Until more is known, there will continue to be debate as to the most appropriate algorithm for screening such patients.

References

1 Hughes JM. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia. Semin Respir Crit Care Med 1998; 19:79–89

2 Shovlin CL, Winstock AR, Peters AM, et al. Medical complications of pregnancy in hereditary haemorrhagic telangiectasia. QJM 1995; 88:879–887

3 Laroche CM, Wells F, Shneerson J. Massive hemothorax due to enlarging arteriovenous fistula in pregnancy. Chest 1992; 101:1452–1454

4 Dutton JA, Jackson JE, Hughes JM, et al. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. AJR Am J Roentgenol 1995; 165:1119–1125

5 Haitjema T, Disch F, Overtoom TT, et al. Screening family members of patients with hereditary hemorrhagic telangiectasia. Am J Med 1995; 99:519–524

6 White RI. Pulmonary arteriovenous malformations: how do we diagnose them and why is it important to do so? Radiology 1992; 182:633–635

7 Kjeldsen AD, Vase P, Oxhoj H. Hereditary hemorrhagic telangiectasia. N Engl J Med 1996; 334:331–332

8 Chilvers ER, Peters AM, George P, et al. Quantification of right to left shunt through pulmonary arteriovenous malformations using 99Tcm albumin microspheres. Clin Radiol 1988; 39:611–614

9 White RI Jr, Mitchell SE, Barth KH, et al. Angioarchitecture of pulmonary arteriovenous malformations: an important consideration before embolotherapy. AJR Am J Roentgenol 1983; 140:681–686

10 Remy J, Remy-Jardin M, Giraud F, et al. Angioarchitecture of pulmonary arteriovenous malformations: clinical utility of three-dimensional helical CT. Radiology 1994; 191:657–664

11 Whyte MK, Peters AM, Hughes JM, et al. Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. Thorax 1992; 47:790–796

12 Barzilai B, Waggoner AD, Spessert C, et al. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991; 68:1507–1510

13 Kjeldsen AD. Epidemiological and clinical aspects of hereditary haemorrhagic telangiectasia. Faculty of Health Sciences, Odense University, Denmark; 1997

14 Berg JN, Guttmacher AE, Marchuk DA, et al. Clinical heterogeneity in hereditary haemorrhagic telangiectasia: are pulmonary arteriovenous malformations more common in families linked to endoglin? J Med Genet 1996; 33:256–257

15 Plauchu H, de Chadarevian JP, Bideau A, et al. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 1989; 32:291–297

16 Guttmacher AE, Marchuk DA, White RI. Hereditary hemorrhagic telangiectasia. N Engl J Med 1995; 333:918–924