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Reproducibility Of Exercise Testing In Patients With Pulmonary Arteriovenous Malformations

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Reproducibility of Exercise Testing in Patients with Pulmonary Arteriovenous Malformations

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Patients with pulmonary arteriovenous malformations (PAVMs) are at risk for complications, hemorrhagic and neurological, and therefore require close follow-up.

The primary hypothesis of this project poses that the exercise stress test (EST) and 6-minute walk test (6MWT) are reproducible and reliable in patients with PAVMs. Secondarily, if these tests are shown to be reproducible, they may become a surrogate follow-up tool for patients with PAVMs after quantification with non-contrast CT and may replace contrast echocardiography in asymptomatic children under age 12.

Twenty-two patients with PAVMs, most of whom had hereditary hemorrhagic telangiectasia (HHT), participated in a Human Investigations Committee-approved protocol. Patients ranged from 9 to 74 years of age (mean 28) and had a broad spectrum of anatomic subtypes of PAVMs, including focal and diffuse. Standard 6MWT and cycle ergometry EST were both performed twice with adequate rest between tests. Heart rate (HR) and oxygen saturation were measured at the beginning and end of each test. Distance walked and maximum resistance were also recorded. The intraclass correlation coefficients (r_i) at the end of 6MWT were as follows: HR (r_i = 0.940; 95% CI = 0.863-0.975), post test oxygen saturations (r_i = 0.973; 95% CI = 0.933-0.989), distance walked (r_i = 0.942; 95% CI = 0.867-0.975). The r_is at the end of EST were as follows: HR (ri = 0.941; 95% CI 0.865–0.975), oxygen saturation (ri = 0.993; 95% CI 0.982–0.997), and maximum resis- tance (r_i = 0.941; 95% CI 0.864–0.975). 6MWT and EST were reproducible measures of exercise capacity and oxygen saturation and are potential adjunct tests in the follow-up assessment for patients with PAVMs.

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Introduction

Background on pulmonary arteriovenous malformations

Pulmonary arteriovenous malformations (PAVMs) were first described by Churton in 1897 (1). PAVMs are abnormal thin-walled vascular communications between pulmonary veins and arteries. As thin-walled vascular dilations, PAVMs may rupture and cause pulmonary hemorrhage (2,3). PAVMs are extracardiac right-to-left shunts, allowing blood to bypass the capillary filtration system in the lungs. PAVMs are a route that allows the passage of paradoxical emboli into the systemic circulation. Neurologic consequences such as transient ischemic attack, cerebrovascular accident, and cerebral abscess occur as a result of PAVMs (4).

Historical evidence and experience at the Yale Hereditary Hemorrhagic Telangiectasia (HHT) Center shows greater than 70% of patients with PAVMs have underlying HHT (2,5,6). An autosomal dominant genetic disease with mutations in the protein endoglin (type 1) and activin receptor-like kinase (type 2), HHT involves many organ systems through arteriovenous malformations in the lungs (7), brain (8), liver (9), GI tract (10), and uncommonly in the retina (11). The phenotypic manifestations of HHT may prompt the clinician to investigate the possibility of PAVMs and vice versa. In fact, PAVMs are the leading cause of morbidity and mortality among patients with HHT (12).

Current guidelines on treatment of pulmonary arteriovenous malformations

Treatment of PAVMs has three main goals: 1) prevention of paradoxical embolization, 2) prevention of consequences of pulmonary hemorrhage such as hemothorax or hemoptysis, and 3) improving symptomatic dyspnea or exercise

intolerance.

The "International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia" published in 2011 recommends transcatheter embolization as primary treatment for PAVMs as it has been shown to be efficacious and safe with rare complications (2,13–17). The selection of PAVMs for embolization is based on feeding artery diameter, generally 3mm or greater due to neurologic complications associated with paradoxical emboli (14,18). The HHT center at Yale reported on a series of 415 PAVMs occluded in a period of three years (14). Clinical and imaging follow-up were available in all patients. Radiographic imaging showed pulmonary AVM involution in 97% of embolized lesions (14).

Albeit rare at 2%, the procedure of transcatheter embolotherapy comes with some complications as well, including angina, transient ischemic attack, and pleurisy (14,19,20). In addition, reperfusion of PAVMs may recur after transcatheter embolization (14).

Current guidelines on screening and follow-up of pulmonary arteriovenous malformations

The current guidelines recommends using transthoracic contrast echocardiography as initial screening test for PAVMs (17). Contrast echocardiography has been demonstrated to be reliable as a predictor of PAVMs, and a correlation has been shown to exist between contrast echocardiography grade and probability of PAVMs (19). Positive screening with contrast echocardiography is followed by unenhanced multidetector thoracic CT with thin-cut reconstructions (17). However, the choice of

screening tests is unclear in children. Current recommendations leave the decision to the clinician on a case by case basis. From parent reports at our institution, children with HHT often receive chest CTs in place of detailed history and physicals at outside hospitals and emergency departments especially.

The guidelines also recommends long-term follow-up for patients with PAVMs to detect growth of untreated PAVMs and any reperfusion of treated ones (17). There is no recommendation for methods of follow-up for children with untreated PAVMs. For adults, the follow-up schedule after transcatheter embolization includes an unenhanced CT at 6 months and then every 3 years after embolization (17). Transthoracic contrast echocardiography has been shown to not be useful after embolization, as it remains positive in 90% of patients post-repair (20).

Exercise testing for patients with diffuse pulmonary arteriovenous malformations

Pulmonary arteriovenous malformations can be grouped into similar categories depending on distribution in the lungs. The anatomy of PAVMs is crucial in its involution because successful elimination of the PAVM requires embolization of all feeding arteries.

A simple PAVM involves one or branches from the same pulmonary segmental artery, whereas a complex PAVM involves contributing branches from more than one segmental artery. Diffuse disease is signified by an entire segmental artery having small PAVMs diffusely (21). Approximately 55% of patients have simple PAVMs, 40% have complex and simple, and 5% have diffuse disease involvement (22). Diffuse disease may have unilateral or bilateral involvement of the lung (21,23). Patients with a diffuse

pattern of involvement have a higher incidence of complications including brain abscess compared to patients with focal disease (21).

Initially, non-contrast CT was used as the main method to identify large focal PAVMs that occurred in some diffuse patients. Diffuse patients with large focal PAVMs need to be treated with transcatheter embolization to prevent complications from paradoxical emboli and hemoptysis. These patients with a high-risk natural history need yearly follow up (23). Unenhanced CT was not as useful in follow-up imaging to detect changes of diffuse PAVMs (21,23).

Six years ago, frustrated by the inability of unenhanced CT to define progression or predict deterioration, the Yale center examined exercise testing data from 40 diffuse patients. Serendipitously, the results showed stability of exercise tolerance from year to year in patients who were evaluated with exercise stress test with increasing interval resistance cycle ergometer (23,24). Patients exhibited a change in their exercise test results only when symptoms deteriorated with enlargement of PAVMs; they showed an increased fall in oxygen saturation during exercise (24).

Therefore, our institution began evaluating both those with diffuse and focal PAVMs with cardiorespiratory exercise using a cycle ergometer. We have established exercise stress testing (EST) as a safe and non-invasive method to monitor patients with diffuse PAVMs (24). Serial EST showing increasing oxygen desaturation during exercise correlates with decreased functionality (24).

Previous literature on exercise stress test (EST) and 6-minute walk test (6MWT)

Intrapulmonary shunts allow cyanotic blood to return to systemic circulation

deoxygenated. PAVMs are a form of intrapulmonary shunts due to abnormal vessel formations between the pulmonary arteries and veins that bypass the pulmonary capillary bed and allow right to left shunting of blood. The degree of cyanosis varies with the amount of right-to-left shunt through intrapulmonary shunts. When the flow of blood through intrapulmonary shunts is a small fraction of the total cardiac output, the cyanosis may not be significant at rest.

However, strenuous exercise will result in lowering the systemic venous oxygen content further and, thus, the systemic oxygen saturation. When the returning systemic mixed venous oxygen content is decreased further in exercise, the cyanosis will be worsened. As opposed to patients with chronic lung disease, exercise tolerance is relatively well-maintained (70% of predicted maximum heart rate) in PAVM patients, and no complications have previously been reported in adult PAVM patients undergoing EST (25).

6MWT has been shown to be a reliable and valid functional test for assessing exercise tolerance and endurance in a study of 78 Chinese secondary school students (26). While studies of reliability and validity of exercise testing have been shown in healthy children and adults (26,27), there has not been a demonstration of the reproducibility of 6MWT in patients with PAVMs.

Another study assessed exercise tolerance and oxygen saturation in severely ill children awaiting heart-lung or lung transplantation by comparing the 6MWT and EST results (28). The results showed close correlation of the minimum oxygen saturations during the 6MWT and EST (28). Furthermore, reduced muscle mass in patients who are chronically ill may lead to early thigh muscle fatigue, which limits their ability to

overcome pedal resistance (28). Whereas, walking uses overall muscle mass and shows less localized muscle fatigue (28). The study concluded that the 6-minute walk test provides an alternative method for measuring functional capacity in chronically ill children with limited exercise tolerance (28). In short, the 6MWT has the added advantage of simplicity to administer, less expense, and avoidance of patient fatigue, all of which are of great benefit for our elderly and more ill patients with PAVMs.

Various case studies have observed the increase in oxygen saturation during exercise of patients after repair of pulmonary arteriovenous fistulas (29,30). One such study of a 16-year-old girl, who had a 2cm long fistulous connection between the right intermediate pulmonary artery and the right upper pulmonary vein that varied with a diameter of 6-13mm, was treated with transcatheter embolization of the fistula and exercise testing thereafter (30). At EST before the procedure, her oxygen saturation was 92% and decreased to 79% with exercise (30). At follow-up six months after embolization, her oxygen saturation was 99% and decreased to 97% with exercise (30).

In a 2002 study, EST was used before and after transcatheter embolization in patients with PAVMs. Patients reported an improvement after embolization in exercise capacity in daily living (31). The study reported a median increase of 3.5% in the oxygen saturation at maximal exercise after PAVM repair compared to before (31). This study shows the growing interest in using exercise testing to monitor patients with PAVM, and it mimics our observations that elimination of right-to-left shunting results in higher oxygen saturations and more efficient gas exchange during exercise.

Nevertheless, EST and the standard 6MWT have not been shown to be reproducible in patients with PAVMs.

Statement of Purpose and Hypothesis

PAVMs are the leading cause of morbidity and mortality among patients with hereditary hemorrhagic telangiectasia (12,32). The overall degree of shunting from PAVMs depends on hemoglobin level, vascular resistance of the PAVM and pulmonary arterioles, and systemic mixed venous oxygen saturation. Therefore, patients may or may not show signs of cyanosis or clubbing despite having PAVMs; nevertheless, they remain at risk for morbid conditions such as stroke, brain abscesses, hemothorax, and hemoptysis.

Previous reports from the Yale HHT center showed that arterial oxygen saturation often decreases during EST, most likely due to increased extraction of oxygen and decrease in systemic mixed venous oxygen content (24). However, the reliability and reproducibility of EST and 6MWT have yet to be demonstrated.

The primary hypothesis of this project is that the exercise stress test (EST) and 6-minute walk test (6MWT) are reproducible and reliable in patients with PAVMs. Secondarily, if both of these standard tests are shown to be reliable and reproducible in patients with all types of PAVMs, then EST and 6MWT:

1) may become a surrogate for adolescent and adult patients with small PAVMs after quantification with non-contrast CT,
2) may replace contrast echocardiography in asymptomatic HHT children under 12 or if parents are concerned since the data on contrast echocardiography indicates grade 1 or less would not warrant treatment.
3) If serial EST and 6MWT demonstrate no worsening of shunts after a patient's

PAVMs are repaired, EST and 6MWT could be used as routine follow-up tools for the assessment of PAVM recurrence or enlargement.

Thus, this could lead to reduction of the use of chest CT and, ultimately, decrease the financial and radiation burden on individual patients while continuing to monitor for the presence of clinically significant PAVMs in HHT patients and providing reassurance to their families. The reason for validating two different exercise tests is because the 6MWT is familiar to adult pulmonologists and often used for adult pulmonary disease, whereas, the cycle ergometry EST is frequently employed by pediatric cardiologists. Therefore, patients may be seen by a pulmonologist or a cardiologist for follow-up.

Subjects and Methods

Subject selection

Twenty-two subjects were included in this study. All patients at the Yale HHT center undergoing either evaluation before transcatheter embolotherapy or follow-up after transcatheter embolotherapy for previously identified PAVMs were offered participation in the study. A detailed history of present illness, past medical history, family history, and physical exam were performed in office. Physical exam findings that were noted include telangiectasias, clubbing, and/or cyanosis. Standing oxygen saturations were obtained by finger clip blood oxygen sensor at the initial office visit.

Most patients in the study have at least one prior unenhanced chest CT for confirmation of PAVM. In addition, some have contrast echocardiography performed at Yale and interpreted into grades 1 to 4 by experienced readers. Some patients also have pulmonary angiography from their transcatheter embolization on file. A few patients also

have MRIs with gadolinium of the brain with note of any aneurysms. Patients were evaluated for HHT status through genetic testing. Results of positivity and HHT type were recorded.

Each patient performed one EST followed by one 6MWT after 30 minutes of rest. The second 6MWT followed after another 30 minutes of rest. Lastly, patients performed one more EST following the second 6MWT and another 30 minutes of rest. Therefore, in total, patients performed two EST and two 6MWT on the same day in the order of first EST, first 6MWT, second 6MWT, and second EST.

Participating patients were all in stable clinical condition and were New York Heart Association class I. A physician was present at all times during the exercise studies. This research protocol was approved by the Yale-New Haven Hospital Human Investigation Committee.

6-minute walk test protocol

6MWT was conducted under direct physician supervision and according to the guidelines published by the American Thoracic Society and the American Heart Association (33). The 6MWT is a practical test that requires a 30-meter long, flat, straight, enclosed, hard-surfaced hallway but no exercise equipment or advanced training for technicians. The test is self-paced and assesses functional capacity. Patients choose their own intensity of exercise and allowed to stop and rest during the test, though none of the subjects in this study chose to do so.

Before the test began, patients sat at rest in a chair located near the starting position. There was no “warm-up” period before the test. At the start of the test, resting

heart rate and oxygen saturation were measure using a Nellcor N-20 pulse oximeter (Nellcor Puritan Bennett LLC, Boulder, CO), which was placed on the patient's index finger. The monitor was then removed to prevent inaccurate readings due to considerable motion artifact during the walk. In addition, patients were asked to rate their baseline dyspnea and fatigue on the Borg scale (34). As the timer for six minutes starts, patients were instructed to walk as much as they can up and down the 30-meter hallway. No one walked with the patient, and patients were not coached during the test.

After six minutes, patients were instructed to stop. At this time, heart rate and oxygen saturation were measured once again using a Nellcor N-20 pulse oximeter placed on the index finger. The total distance walked was recorded. In addition, patients were asked to rate their post-test dyspnea and fatigue on the Borg scale (34).

Exercise stress test protocol

EST was conducted under direct physician supervision in the Yale-New Haven Hospital Pediatric Cardiology Exercise Laboratory and in accordance with the consensus statement by the American College of Cardiology (35).

Patients were instructed to wear or bring comfortable exercise clothing, preferably shorts, T-shirt, and athletic shoes. In preparation for the test, the patient is fitted with 10 electrodes so that a continuous 12-lead ECG tracing can be obtained during testing. Before the test begins, resting heart rate was measured by electrocardiographic monitoring, and oxygen saturation was measured using Nellcor OxiMax N-600 oximeter with Max-Fast adhesive forehead reflectance sensor with headband (Nellcor). Participants underwent continuous electrocardiographic, oxygen saturation, and heart rate

monitoring while undergoing cycle ergometry (Marquette Electronics, Milwaukee, WI) with step-wise increases of 30 watts of resistance every 2 minutes while maintaining a continuous cadence of 60–65 revolutions per minute.

EST was concluded when participants experienced leg fatigue, shortness of breath, or reached 85% of their predicted maximum heart rate. At EST conclusion, patient heart rate and oxygen saturation were measured, and cycle ergometry resistance was decreased to 15 watts. Participants were instructed to peddle slowly until their heart rate reached within 10% of baseline.

Statistical analysis

Descriptive statistics were listed as means with standard deviations. Intraclass Pearson correlation coefficients (r_is), with 95% confidence intervals (CIs) were calculated to assess test–retest reliability for the following variables for the 6MWT and EST respectively:

1. Baseline heart rate,
2. Post test heart rate,
3. Baseline oxygen saturation,
4. Post test oxygen saturation,
5. Difference between baseline and post test oxygen saturation.

In addition, the level of resistance in watts on the cycle ergometer that the patient was able to achieve by the end of EST was recorded as well.

Bland–Altman plots were used to assess agreement between 6MWT and EST at baseline and at the end of each test for oxygen saturation. Oxygen saturation changes

during 6MWT and EST were compared with a repeated-measures analysis (adjusted for patient age, sex, weight, and height) and listed as means with standard errors. Significance was established with alpha < 0.05. Data were analyzed using Microsoft Excel 2008 for MAC version 12.0 (Microsoft, Seattle, WA) and SAS 9.2 (Cary, NC).

Results

Patient Characteristics

Twenty-two patients were recruited for the study (Table 1). There were 16 females and 6 males, corresponding to previous literature regarding the female predominance of HHT. We tested both children and adults, with the oldest patient at 74 years of age. 8 patients were under the age of 18. The average resting oxygen saturation among all patients was 93.9%.

With the exception of two patients who had only positive contrast echocardiograms, all other patients had positive chest CT findings for PAVMs. PAVM status among this cohort included the following: 10 focal (<4 PAVMs), 4 multifocal, 4 diffuse, and 10 previously embolized. All participants completed both sets of 6MWT and EST without adverse events, and all participants reached 85% of their predicted maximum exercise tolerance on EST, independent of their baseline and peak exercise oxygen saturation status.

Reproducibility of 6MWT

The reproducibility of 6MWT was determined by examining intraclass correlation coefficients with 95% confidence intervals (Table 2). All patients performed two 6MWT

during the day. With the exception of oxygen saturation difference $r_i = 0.659$ (95% CI 0.346-0.841), all parameters including baseline heart rate, post test heart rate, baseline oxygen saturation, post test oxygen saturation, distance walked showed reproducibility significance ($p < 0.05$) as seen by high intraclass correlation coefficients (r_i).

The mean baseline heart rates for all patients were 94.5 and 95 respectively in the two 6MWTs. The r_i for baseline heart rate was 0.829 (95% CI = 0.630-0.925). The mean post test heart rates were 108.3 and 106.5 respectively, with an r_i of 0.940 (95% CI = 0.863-0.975). The mean baseline oxygen saturations were 93.9% and 94.3%, with an r_i of 0.989 (95% CI = 0.975-0.996). The post test oxygen saturations were 92.2% and 93.0%, with an r_i of 0.973 (95% CI = 0.933-0.989). The differences in oxygen saturation between the baseline and post test values were calculated to determine how much desaturation occurred with exercise. The values are 1.7% and 1.2% respectively for the first and second 6MWT, with r_i of 0.659 (95% CI = 0.346-0.841). The 6MWT distance walked was similar between the two tests at 471.1 and 477.5 meters, with r_i of 0.942 (95% CI = 0.867-0.975).

Reproducibility can also be seen on Bland-Altman plot of the parameters of the 6MWT. The plot compares exact same parameters between the first and second 6MWT for each patient. Each patient appears as a point on the graph. The point (x, y) uses the average of two post test oxygen saturations for each patient for the x-grid point and the difference between them as the y-grid point. The primary application of the Bland-Altman plot is to compare two measurements, and the limits of agreement is specified as average difference ± 1.96 times standard deviation of the difference.

For instance, the graph of end oxygen saturation of 6MWT compares the values

of each individual patient's oxygen saturation at the end of the 6MWT from the first test to that of the second test (Figure 2). Almost all points are within limits of agreement for end oxygen saturation.

In addition, the Bland-Altman plot of decrease in oxygen saturation in the two 6MWTs shows good correlation with all but one point inside the limits of agreement (Figure 3).

Reproducibility of EST

In addition to the 6MWT, reproducibility was investigated for EST also by examining intraclass correlation coefficients with 95% confidence intervals (Table 3). Patients performed two EST; therefore, each patient possesses two distinct values for each parameter. All measurements from the EST showed significant reproducibility ($p < 0.05$) including baseline heart rate, post test heart rate, baseline oxygen saturation, post test oxygen saturation, the difference between oxygen saturations pre and post test, and work in watts on the ergometer.

The mean baseline heart rates for all patients were 90.5 and 91.8 respectively, with r_i of 0.871 (95% CI = 0.717-0.944). The mean post test heart rates were 159.0 and 158.5 respectively, with an r_i of 0.941 (95% CI = 0.865-0.975). The mean baseline oxygen saturations were 95.3% and 95.1%, with an r_i of 0.979 (95% CI = 0.950-0.991). The post test oxygen saturations were 91.8% and 92.3%, with an r_i of 0.993 (95% CI = 0.982-0.997). The difference in oxygen saturations between the baseline and post test values were 3.5% and 2.9% respectively for the first and second ESTs, with r_i of 0.836 (95% CI = 0.647-0.928). The work in watts that patients were able to pedal to were

114.5 and 113.2 respectively, with r_i of 0.941 (95% CI = 0.864-0.975).

Bland-Altman plots for end oxygen saturation of EST is shown comparing the values of each individual's oxygen saturation at the end of the first EST to that of the second EST (Figure 4). All except two points lie within the limits of agreement, which is the mean difference ± 1.96 times standard deviation of the difference.

Furthermore, decreases in oxygen saturation from each EST is also shown on a Bland-Altman plot with limits of agreement (Figure 5). Only one patient representation point is outside the limits of agreement for the decrease in oxygen saturation in EST.

Comparison of 6MWT and EST

The 6MWT and EST parameters were compared with each other. For each patient, the oxygen saturation at the end of the first 6MWT was compared to the oxygen saturation at the end of the first EST (Figure 6). The mean of all differences between each set of two numbers was 0.4, and the standard deviation was 2.5. The limits of agreement are 5.4 and -4.5. The Bland-Altman is shown with all points lying between the limits of agreement, showing consistent correlation of the 6MWT and EST.

The second parameter that was compared between the two exercise tests was decrease in oxygen saturation during the tests (Figure 7). The mean difference was 1.8, and the standard deviation was 2.2, with limits of agreement at 6.1 and -2.4. Once again, all patient data points were between the limits of agreement, exhibiting high correlation of the EST and 6MWT.

Lastly, the average of all baseline oxygen saturations and end oxygen saturations were compared between the two tests (Figure 8). The average change in oxygen

saturation for 6MWT was -1.5 with a standard error of 0.7. For EST, the average change in oxygen saturation from beginning to end of exercise was -3.3 with a standard deviation of 0.7. A larger drop in oxygen saturation occurred during EST than during 6MWT.

Discussion

Current study shows reproducibility of exercise testing

All twenty-two patients recruited for the current study completed all testing, including two 6MWTs and two ESTs, without complications. For the 6MWT, distance walked, heart rate at baseline, heart rate at end of test, and oxygen saturations at the beginning and end were all reproducible as shown by high Pearson correlation coefficients. For the EST, heart rate at beginning and end of test, oxygen saturations at the beginning and end of test, and maximum resistance achieved by the patient were all reproducible as well. Therefore, we have shown that in patients with known PAVMs the 6MWT and EST provide reliable measurements of physiologic parameters by comparing the test to itself in the same patients. Both tests are physiologic measures of shunt fractions. Importantly, while not diagnostic of the presence or absence of shunting, the previous results from Murphy et al. using the EST in patients with diffuse PAVMs indicated stability of exercise testing mirrored clinical status. Those who had enlargement of PAVMs exhibited a change in their exercise study or showed new symptoms such as fatigue and dyspnea.

When comparing the two tests, all parameters across the two were highly correlated with large correlation coefficients as well as Bland-Altman plots. When examining oxygen saturation changes during EST and 6MWT, it appears that oxygen

saturation decreased more during EST than 6MWT (Figure 8). This is likely due to EST causing more oxygen extraction during exercise as it is a more strenuous test, where patients move against increasing resistance.

There were some limitations to this study. First, the sample size was small though enough power was obtained through statistical measures with significance. Secondly, testing was obtained during routine outpatient clinic visits, and 6MWT and EST were not correlated with chest CT, pulmonary angiography, or contrast echo results. Some patients were returning for follow-up after their transcatheter embolization, and some have not had repair of their PAVMs. Furthermore, some patients had focal PAVMs while others had diffuse disease. A strength of the study was that it demonstrated reliability in patients with treated and untreated, focal and diffuse PAVMs. This has led to our hypotheses, not yet proven, about the potential value of exercise testing above.

Future directions

The next stage in this investigation may include examining longitudinal changes in oxygen saturation measurements on EST and 6MWT for each patient; in essence, using the patient as his or her own control to evaluate the use of exercise testing in follow-up of PAVMs. The hypothesis would be that once a baseline exercise test has been performed, any further decreases in exercise tolerance and oxygen saturation may predict recurrence or enlargement of clinically significant PAVM. At that point, a chest CT would be performed. This obviates radiation exposure due to CT scans up to once or twice a year for some patients. Hence, the radiation burden and increased cancer risk may be decreased in this population that has relied heavily on imaging thus far.

Furthermore, the exercise test parameters, namely oxygen desaturation amount, may be correlated to the number of unrepaired or newly diagnosed PAVMs.

Ultimately, this study has demonstrated that EST and 6MWT are reliable measures of exercise capacity, oxygen saturations, and oxygen decreases during the tests in patients with existing PAVMs. Benefits of exercise testing include non-invasiveness and low radiation exposure, especially important in children. Reproducibility of both tests means HHT patients may seek care from pulmonologists or cardiologists, who are familiar with each of these respective tests. In addition, the 6MWT is a less strenuous test, which may be useful for the elderly or severely ill patient who cannot perform the EST due to fatigue. In short, exercise testing may become an important surrogate for CT in the continued follow-up of 1) asymptomatic pediatric patients, 2) adult patients with small PAVMs not requiring embolotherapy, and 3) patients post-embolotherapy after CT has demonstrated involution of the treated PAVM.

Importance of screening and follow-up in patients with PAVMs

Patients may present to an HHT center through a variety of routes. They may have already experienced one of the complications of HHT, including stroke, brain abscess, hemoptysis, hemothorax, gastrointestinal bleeding, and so on (36). They may also have shown persistent symptoms common in HHT, including epistaxis, clubbing, dyspnea on exertion, and cyanosis (6,37,38).

In the 1990s, various genetic mutations have been shown to exist in HHT. Endoglin and activin receptor-like kinase proteins, ENG and ACVRL1 genes respectively, have been described in HHT type 1 and type 2 (39,40). In addition, Smad4

protein mutations cause an overlap syndrome of juvenile polyposis and HHT (41). In addition to those, hundreds of other genetic mutations have been described in HHT (42). After one family member has been diagnosed with HHT, he or she should receive testing to identify the proband. After the family's particular genetic mutation is initially identified, other members can be tested (43). Therefore, many pediatric patients may present to HHT centers after DNA testing.

The value of screening for PAVMs lies in the prevention of potential complications that may occur. Currently, patients may receive grade-based contrast echocardiography to determine their probability for having PAVMs (44). After contrast echocardiography is shown to be positive, many patients will undergo a non-contrast chest CT to detect PAVMs (45). The unenhanced chest CT provides information on the number and location of PAVMs, the size of feeding arteries for each PAVM, and whether the PAVMs are diffuse or focal (46).

Patients may require follow-up once diagnosed for many reasons. First of all, patients who have received transcatheter embolotherapy must follow-up 6 months after treatment with a chest CT to ensure involution of the PAVM. Secondly, patients with PAVMs with feeding arteries less than 3mm in diameter are not recommended for embolotherapy because complications have known to occur in PAVMs with larger feeding arteries (14,18). These patients with unrepaired PAVMs require follow-up in case of enlargement of the malformations. This is especially true in the pediatric population because growth of PAVMs is known to occur during puberty and pregnancy (47). Due to the availability of genetic mutation testing, patients may be completely asymptomatic but harbor the gene for HHT. These patients, whether adults or children,

may benefit from non-invasive follow-up methods without radiation exposure.

Treatment of PAVMs in children

No current guidelines exist regarding treatment and follow-up of PAVMs in children. There are a number of reasons behind the reservations for treating children with PAVMs, including both reperfusion after and complications during transcatheter embolotherapy.

Observations suggest high degree of reperfusion post-therapy in children, irrespective of device and approach. Extensive studies have found and categorized the causation of reperfusion following embolotherapy (13,48–51). Most studies have found persistence or reperfusion of embolized PAVMs in a small numbers of patients and lesions, typically from 0% to 10% (13,48–51). In a Yale series examining 393 treated PAVMs, reperfusion was identified in 2.8% or 11 out of 393 PAVMs (14). Reasons for the residual embolized PAVMs included recanalization (n = 7), accessory feeding artery (n = 1), collateral perfusion of distal feeding artery from small pulmonary artery branches (n = 1), and systemic bronchial artery collateral perfusion (n = 2) (14). This series was comprised of 155 patients, with a mean age of 45, and only 7 patients were children younger than 18 years of age (14).

Studies show the higher reperfusion rate in children as an estimated 15% most likely due to the higher rate of collateral perfusion development in the pediatric population (52). In a pediatric series of the 23 children who experienced reperfusion, collateral perfusion (n = 12), recanalization (n = 11), and missed accessory (n = 8) were contributing factors (52). Collateral perfusion occurs in a growing lung and resembles

the collateralization in high flow peripheral arteriovenous malformations.

In addition to reperfusion, some rare complications estimated at 2% can happen during transcatheter embolotherapy (14,53,54). Complications include angina, transient ischemic attack, and pleurisy (14,53). A meta-analysis of PAVMs in 130 children between 1966 and 2000 showed that complications from PAVMs did not occur in children under 12 years of age who were not cyanotic or clubbed (55). Clinical features indicative of sizable PAVMs in children can appear as cyanosis, growth failure, pseudoasthma, or pulse oximetry consistently below 97%.

Because of this higher reperfusion rate and rare procedural complications along with the lack of complications in those without symptoms, many asymptomatic children may be followed conservatively. In recent years, the approach for diagnosis in children has veered away from blood gases and shunt studies toward standing pulse oximetry and contrast echocardiography.

Screening for PAVMs

Since the majority of patients with PAVMs have HHT and are at risk of developing new PAVMs throughout their lifetime, the search for a sensitive and safe screening tool is critical and ongoing. At present, several screening tests are used to detect the presence of PAVMs. The initial screenings tests include transthoracic contrast echocardiography (Figure 1) and unenhanced spiral chest computed tomography. Three-dimensional helical CT permits a detailed evaluation of PAVMs without contrast injection, thus preventing accidental intravenous air entry as well. In a series of 37 PAVMs, analysis of the angioarchitecture of 28 PAVMs (76%) was provided by 3D

reconstructions, while addition of transverse sections to the interpretation led to accurate evaluation of 35 PAVMs (95%) (56). Other benefits of unenhanced CT over pulmonary angiography include its noninvasive nature and no contrast requirement.

In recent years, contrast echocardiography has been compared to unenhanced spiral CT. Agitated saline solution transthoracic contrast echocardiography was shown to have a sensitivity of 92% to 100% in the detection of PAVMs (57,58). In comparison to the unenhanced CT, contrast echocardiography is much more sensitive; in fact, it is the most sensitive test for detection of PAVMs (57,58). It requires minimal invasiveness in terms of intravenous saline injection but does not expose patients to radiation. In addition, increased shunt grade seen as microbubbles seen in the left ventricle after a certain number of cardiac cycles can be used to predict the probability of PAVMs (19).

Four HHT centers, including ones in Italy, Spain, Toronto, and the Netherlands, have validated the contrast echocardiography in its predictive value of PAVMs (45,58–60). In the initially validation study at the Toronto center, the positive predictive value of grades 1, 2, 3, and 4 for the presence of a PAVM were determined to be 0.02, 0.25, 0.56, and 1.0 respectively (19). The Dutch HHT center investigated echocardiography only in three grades with the positive predictive value of shunt grade for the presence of PAVMs on chest high-resolution CT scans as 0.229 for grade 1, 0.348 for grade 2, and 0.830 for grade 3 respectively (59). Lastly, the Italian center showed an extensive quantitative analysis of shunt size according to contrast echocardiography degree of opacification of the left chambers of the heart (45). The overall diagnostic performance of contrast echocardiography had sensitivity of 1.00, specificity of 0.49, positive predictive value of 0.32, and negative predictive value of 1.00 (45). The positive predictive value for the

different grades was 0.00 for grade 1, 0.56 for grade 2, 1.00 for grade 3 (45). The negative predictive value of grade 0 was 1.00 (45).

However, contrast echocardiography is not useful after treatment due to positivity after repair. In a prospective study, 29 patients underwent contrast echocardiography prior to and after transcatheter embolization (20). In all patients, contrast echo was positive prior to therapy. After all PAVMs with feeding vessels greater than 3 mm were successfully occluded based on completion angiography, 48% of patients showed no detectable residual PAVMs while others had PAVMs smaller than 3 mm remaining (20). After repair, 90% of patients showed positive contrast echo results (20). In the subset of patients with no remaining PAVMs on angiography, 80% continued to show positive echo results (20). This indicates residual PAVMs too small to be seen on angiography. The persistence of positive contrast echo results has important implications for the follow-up and management of HHT patients.

Current international guidelines for the diagnosis and management of HHT recommends either transthoracic contrast echocardiography at a center of excellence with expertise in reading echocardiography studies or unenhanced multidetector thoracic CT with thin-cut of 1–2mm reconstructions (17). While the contrast echocardiography does not expose patients to radiation, it only provides the probability of PAVM existence in a patient. The unenhanced chest CTs exposes patients to radiation, which for pediatric patients can accumulate to a high amount over the years (61). There have not been clear guidelines for safe and effective screening in the pediatric population. Therefore, HHT centers employ a combination of clinical evaluation, supine and upright pulse oximetry, contrast echocardiography, or unenhanced CT.

Effects of radiation exposure from imaging techniques

In the past few years, the risk of radiation from diagnostic imaging has been increasingly studied. Because of the ease of use, CT scans have increased dramatically. An estimated 62 million CT scans are now completed annually in the United States compared to 3 million in 1980 (61). The postulated mechanism of biological damage is through formation of hydroxyl radicals from x-ray interactions with water molecules, and these radicals may interact with nearby DNA causing strand breaks or base damage (61).

In a study of nearly 1 million nonelderly adults in the United States, approximately 70% of the population underwent at least one medical imaging procedure with radiation exposure in the three-year study period (62). This resulted in mean effective doses double what would be expected from natural sources. Generalized to the population, an estimated 4 million Americans receive effective doses that exceed 20 mSv per year (62).

Much of the epidemiological data regarding radiation exposure comes from the cohort of atomic bomb survivors (63–65). The mean dose in this subgroup was about 40 mSv, almost tantamount the organ dose from a typical CT scan involving two to three scans in an adult (65). In addition, radiation-induced cancer risks have been shown in a large-scale 15-country study of 400,000 radiation workers in the nuclear industry (66,67). The workers sustained an average of 20 mSv (66). A significant association was found between mortality from cancer in both these cohorts (64,67). Through epidemiologic extrapolation, 1.5 to 2.0% of cancers in the United States today may be caused by radiation from CT studies (61).

Because of they carry the diagnosis of HHT, patients and their families have reported countless instances of receiving CT scans at outside hospitals, most often in the emergency department. The importance of radiation exposure is paramount in the pediatric population as cancer risk increases with lower age of exposure due to the latency periods for solid tumors are typically decades (61) (Figure 9). Children have more dividing cells and are therefore more radiosensitive, and this is very important for our pediatric HHT population as they may receive multiple chest CTs to follow PAVMs.

Exercise testing obviates radiation exposure risks associated with CT scans. The HHT center at Yale piloted exercise testing in the diffuse PAVM group. Annual exercise testing was found to be a reasonable method to follow this high risk group of patients. The pilot study also exhibited the safety of performing EST in patients with PAVMs (24). Having a large pediatric population in our HHT center and having shown the reproducibility of EST and 6MWT, we hope to use these exercise methods to follow asymptomatic pediatric patients and assure parents regarding their children's exercise capacity. Exercise testing can also be used in adults who are post-repair or have small PAVMs that have not been treated.

Manifestations of PAVMs in children with HHT

Children who have complications resulting from PAVMs often show clinical signs of cyanosis, clubbing, or dyspnea on exertion. In a complete literature review of 130 children under age 18 with PAVMs from 1966 to 2000, some patients experienced complications of hemoptysis or hemothorax (14/130), cerebral abscess (7/130), and stroke (5/130) (55). However, no child under age 12 had serious complication unless he

or she was showing signs of cyanosis or clubbing (52).

In a literature search of reports since 2000, two main case series were found. In one long-term study over 16 years, eight children with PAVMs from age 1 day to 12 years were included (68). The most frequent presenting symptoms were pulmonary (n = 6), including dyspnea on exertion and hemoptysis. The others showed neurologic complications at initial presentation. The complications from PAVMs included hemoptysis/hemothorax (n = 6), cerebral abscess (n = 5), and stroke (n = 1). Importantly, on clinical examination, all children showed signs of cyanosis (n = 8). Some showed dyspnea on exertion (n = 6) and/or clubbing (n = 3). Their measured oxygen saturations ranged from 59% to 80%.

In a separate case series, six children under 12 years old were reported (69). Five of these patients initially presented with cyanosis and were treated with transcatheter embolotherapy. One patient presented with hemoptysis, though oxygen saturation and other clinical signs of low oxygen were not reported. In summary, all children under 12 years of age that have had complications showed signs of cyanosis, clubbing, or dyspnea on exertion. The clinical characteristics of 149 children under age 18 reported in literature until 2007 have been summarized (Table 4).

Cerebral manifestations of HHT in children

Children from families with HHT are screened for existence of PAVMs, and conversely children with PAVMs should be screened for HHT. The hereditary aspect of HHT means family members of those with HHT also need screening for HHT. Although PAVMs cause morbidity and mortality, many other organ systems are also affected by

HHT.

Cerebral arteriovenous malformations (CAVMs) occur in the brain with a prevalence of 5% to 20% in adults and children affected by HHT (8,70). Morgan et al. reported on several cases of intracranial hemorrhage secondary to CAVMs in infants and children (70). None of the nine children, who presented with intracranial hemorrhage secondary to cerebral AVM, were suspected of having HHT before the hemorrhage despite family history of the disease (70). All cases were confirmed through autopsy, imaging studies, or surgery to have been CAVMs causing intracranial hemorrhage (70). The youngest of these children was a neonate born at 38.5 weeks with low Apgar scores and dilated pupils, and he was found to have a massive left parietal occipital hemorrhage (70). In six of nine families, the endoglin mutation for HHT type 1 was found (70). The other three children came from families containing relatives with HHT diagnoses using the Curacao criteria (70). No clinical indications of CAVM existed prior to intracranial hemorrhage, which resulted in death of five children, cognitive and motor impairment in three, and hemiparesis in one (70).

In the series from Yale, five of 34 children showed a CAVM on brain imaging (55). Two of five were treated with surgery (55). Eight children were not screened (55). Of these, two developed intracranial hemorrhage, resulting in one with hemiparesis and one who fully recovered (55).

Most often patients are asymptomatic before intracranial hemorrhage occurs. If symptomatic, patients may experience migraine headaches, visual changes, mental status changes, seizures, intracranial hemorrhages, transient ischemic attacks, and strokes (70–73). Intracranial hemorrhages from CAVMs are devastating and have been reported as

the leading cause of death in the pediatric HHT population (74). If the patient survives, he or she may suffer from significant neurological deficits in later life (70). Infants and children with a family history of HHT are at risk for sudden and catastrophic intracranial hemorrhage.

The prevalence of CAVMs larger than 10 mm in diameter is estimated to be 12% and 11% by two respective studies by Willemse et al. and Fulbright et al (8,75). Although the risk of massive hemorrhage in children with HHT is uncertain, some estimates from 2% to 4% per year in the pediatric populations affected by HHT (70). A prevalence rate of greater than 10% for larger CAVMs along with a risk of hemorrhage support the screening for CAVMs in all patients with HHT in order to help identify and prevent severe sequelae. One standard gadolinium-enhanced brain MRI is used to screen the presence of CAVMs in HHT patients.

Gastrointestinal manifestations of HHT in children

Fewer than two percent of HHT patients present with gastrointestinal symptoms prior to 30 years of age (76). Gastrointestinal bleeding usually appears in 20% of HHT patients at a mean age of 50-60 (76–79). Gastrointestinal manifestations are the initially presentation of HHT in less than 1% of HHT patients (76). Bleeding is often painless and may arise from arteriovenous malformations or telangiectasias throughout the GI tract. Bleeding from telangiectasias has been reported in four children from 1 to 5 years of age (80).

In addition, hemobilia is rare in children; however, Bross et al. reported on a 21-month-old child who presented with gastrointestinal bleeding due to hemobilia secondary

to hepatic and biliary arteriovenous malformations (81). A 14-year-old girl with an HHT positive family history was reported to have persistent bright red blood per rectum (76). No findings were evident on colonoscopy and esophagastroduodenoscopy (76). A right-sided ileocolectomy was performed, and typical lesions were found on pathology (76). Endoscopic findings typically include multiple well-defined erythematous flat nodules in the stomach, duodenum, small bowel, or colon that may require eletrocoagulation, which is not helpful in the long-term (81–83).

Previously, juvenile polyposis (JP) and HHT were considered clinically very distinct diseases caused by mutations in SMAD4 and BMPR1A, for JP, and endoglin and ALK1, for HHT (47,84–86). Recently, a combined syndrome of JP-HHT was described that is also caused by mutations in SMAD4 (87). Any mutation in SMAD4 can cause JP-HHT (88). Therefore, any JP patient with a SMAD4 mutation is at risk for GI manifestations of HHT and any HHT patient with SMAD4 mutation is at risk for early onset gastrointestinal cancer (87,88). In short, a patient who tests positive for a SMAD4 mutation should be monitored accordingly with regard to risks for the combined JP-HHT syndrome.

Yale algorithm for children under 12

The evidence from extensive review of all pediatric cases at Yale prior to the year 2000 and review of literature on pediatric HHT cases post 2000 shows that no asymptomatic child under 12 years of age has had a complication from PAVM (52,55,68,69). Children who have had complications showed signs of low oxygenation whether cyanosis or low pulse oximetry (52,55,68,69).

The Yale algorithm for children with HHT was developed based on previous literature and past experience at our center. All patients are given an initial 90-minute history and physical clinical appointment, during which careful examination for telangiectasia is performed along with a standing pulse oximetry. Patients are recommended for genetic testing as PAVMs occur in all genotypes associated with HHT. The crucial piece of imaging that all children and adults need is a brain MRI with gadolinium. Brain MRI is performed due to the silent nature of CAVMs as previously mentioned, and patients may develop an intracranial bleed at any age (70).

Next, an exercise test is performed to obtain baseline oxygenation during activity. If patients show a standing pulse oximetry above 98% with no symptoms of dyspnea, cyanosis, clubbing, and no desaturation is observed during the exercise test, then further investigation including contrast echocardiography and unenhanced CT would be discouraged. Sometimes, at the insistence of parents, contrast echocardiography would be performed.

However, if desaturation occurs or the patient shows symptoms of low oxygenation, a contrast echo is warranted. If contrast echocardiography reveals grade 2 or above, an unenhanced chest CT would be performed to search for PAVMs. In the case of a family member having recent brain abscess, contrast echocardiography would be recommended to an asymptomatic child. With a grade 1 echo result, no further investigation is warranted. Due to the rarity of GI manifestations in children, it is not part of the algorithm to screen for arteriovenous malformations in the GI tract or liver.

Once again, there are no guidelines for screening and follow-up in the pediatric HHT population. Our center proposes to expand exercise testing and encourage

participation from other centers in the validation and use of the exercise protocols shown to be reproducible here.

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Figure 1. Contrast echocardiography grading scale for PAVMs.
Echocardiography grading shows increased shunt grade seen as microbubbles in the left ventricle after a certain number of cardiac cycles can be used to predict the probability of PAVMs (19).

Figure 2. Oxygen Saturation at End of 6MWT.
The Bland-Altman plot of oxygen saturation at the end of both 6MWTs with limit of agreement defined as mean ±1.96 SD is presented here. The mean difference (solid line) was -0.8, and the standard deviation was 2.0. Therefore, the limits of agreement (dotted lines) are 3.2 and -4.8.

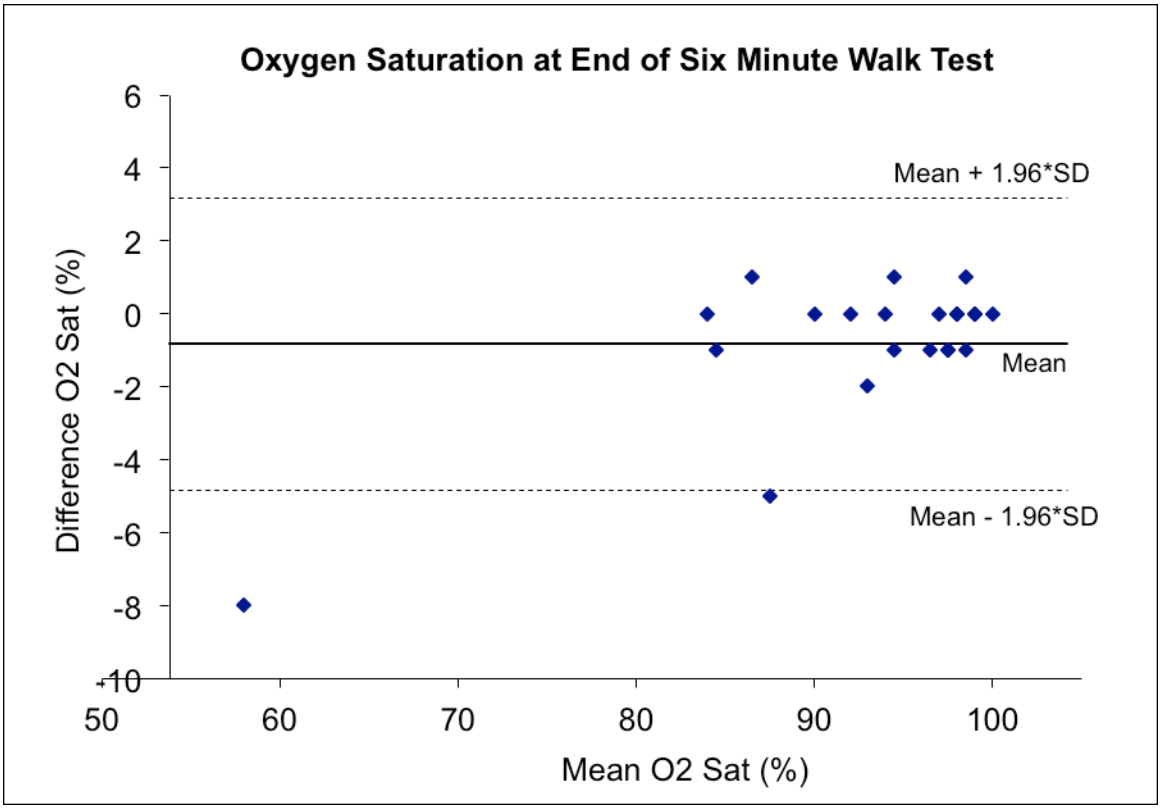

Figure 3. Decrease in Oxygen Saturation during Six Minute Walk Test.
The Bland-Altman plot of decrease in oxygen saturation during 6MWTs with limits of agreement defined as mean ±1.96 SD is presented here. The mean difference (solid line) was -0.5, and the standard deviation was 1.7. Therefore, the limits of agreement (dotted lines) are 3.0 and -3.9.

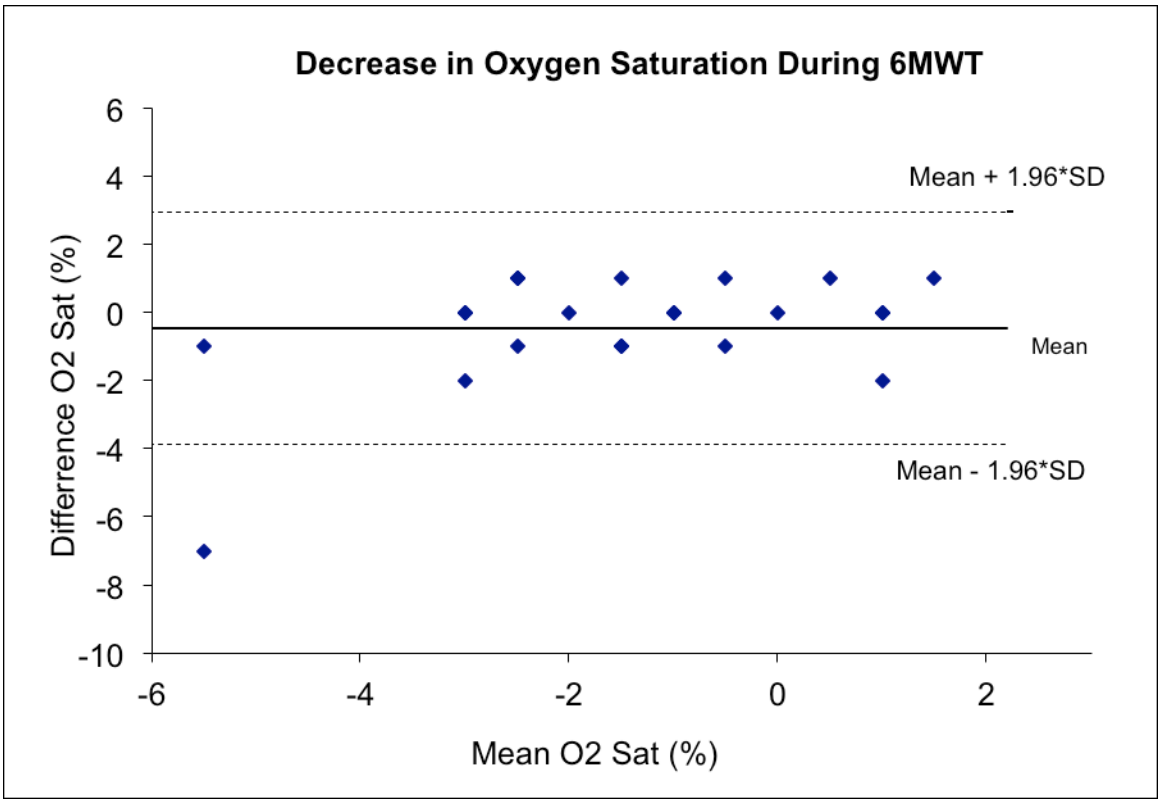

Figure 4. Oxygen Saturation at End of Exercise Stress Test.
The Bland-Altman plot of oxygen saturation at end of ESTs with limits of agreement defined as mean ±1.96 SD is presented here. The mean difference (solid line) was -0.5, and the standard deviation was 1.0. Therefore, the limits of agreement (dotted lines) are 1.5 and -2.4.

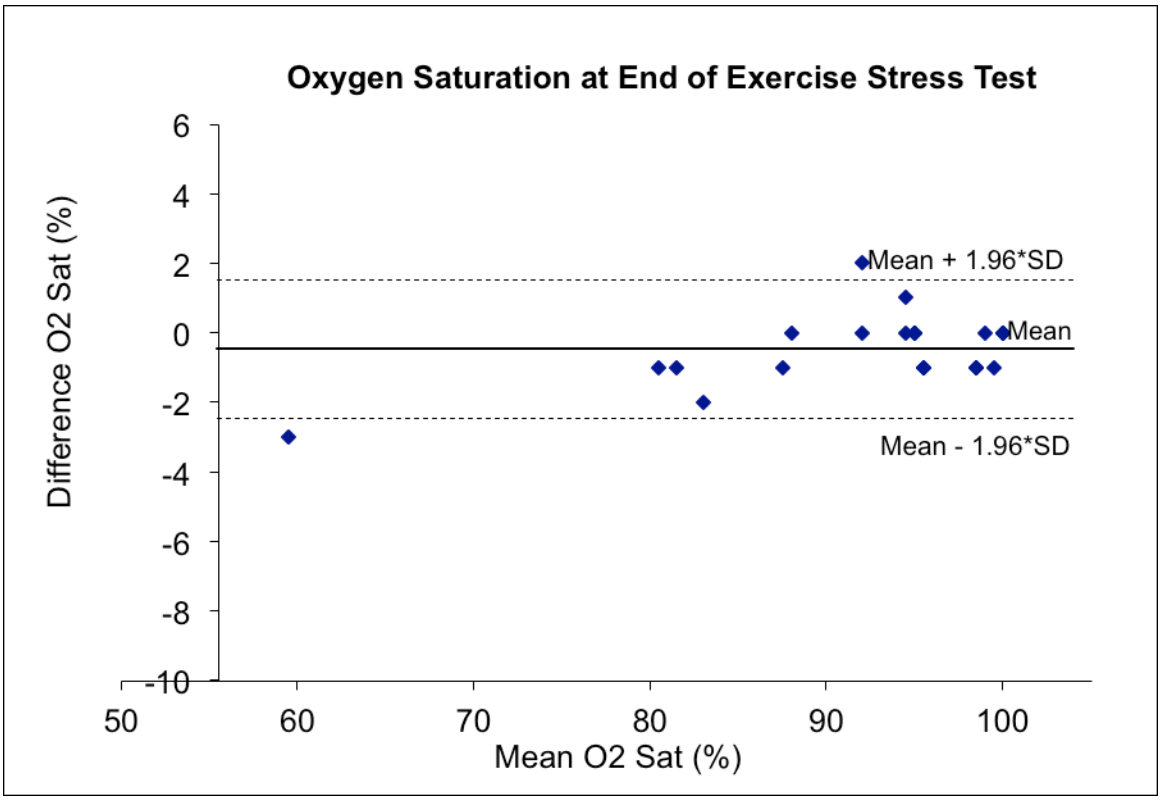

Figure 5. Decrease in Oxygen Saturation During EST.
The Bland-Altman plot of decrease in oxygen saturation during ESTs with limits of agreement defined as mean ±1.96 SD is presented here. The mean difference (solid line) was -0.6, and the standard deviation was 1.9. Therefore, the limits of agreement (dotted lines) are 3.1 and -4.3.

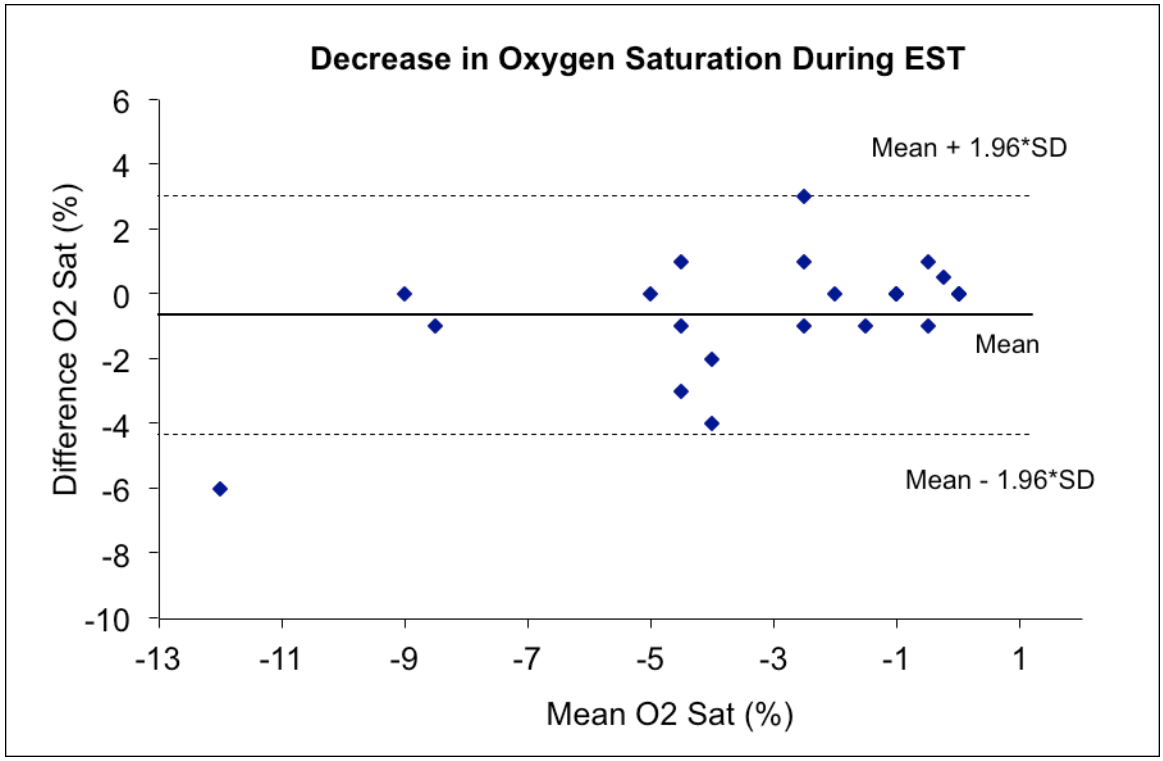

Figure 6. Oxygen Saturation Measured at End of 6MWT and EST.
The Bland-Altman plot of oxygen saturation at the end of 6MWT compared with end of EST with limits of agreement defined as mean ±1.96 SD is presented here. The mean difference (solid line) was 0.4, and the standard deviation was 2.5. Therefore, the limits of agreement (dotted lines) are 5.4 and -4.5.

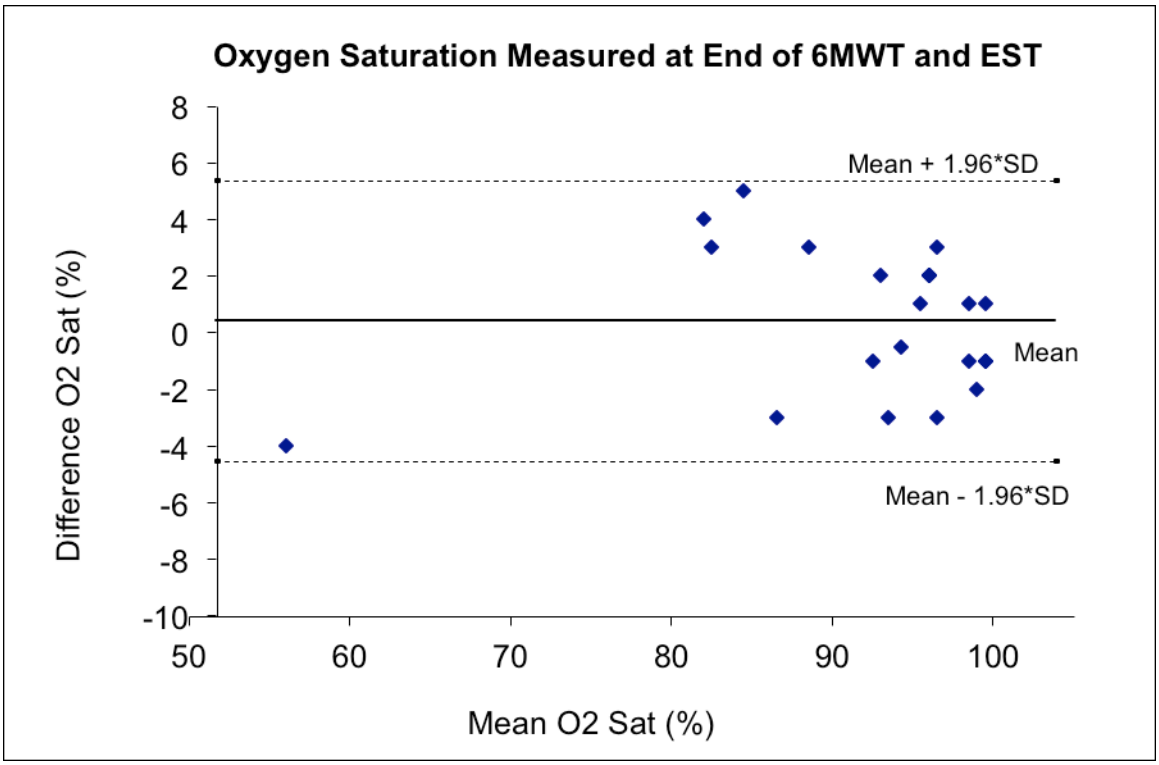

Figure 7. Decrease in Oxygen Saturation During 6MWT and EST.
The Bland-Altman plot of the decrease in oxygen saturation during 6MWT compared with during EST with limits of agreement defined as mean ±1.96 SD is presented here. The mean difference (solid line) was 1.8, and the standard deviation was 2.2. Therefore, the limits of agreement (dotted lines) are 6.1 and -2.4.

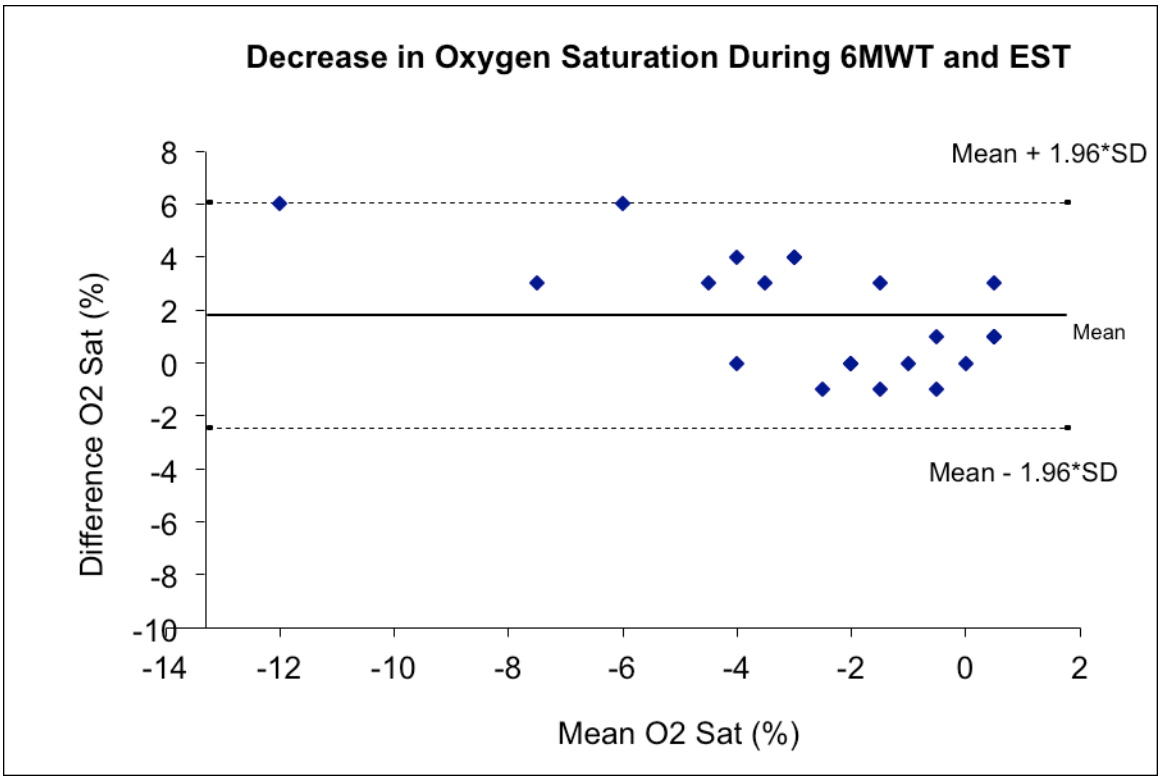

Figure 8. Response of Oxygen Saturation to 6MWT and EST.

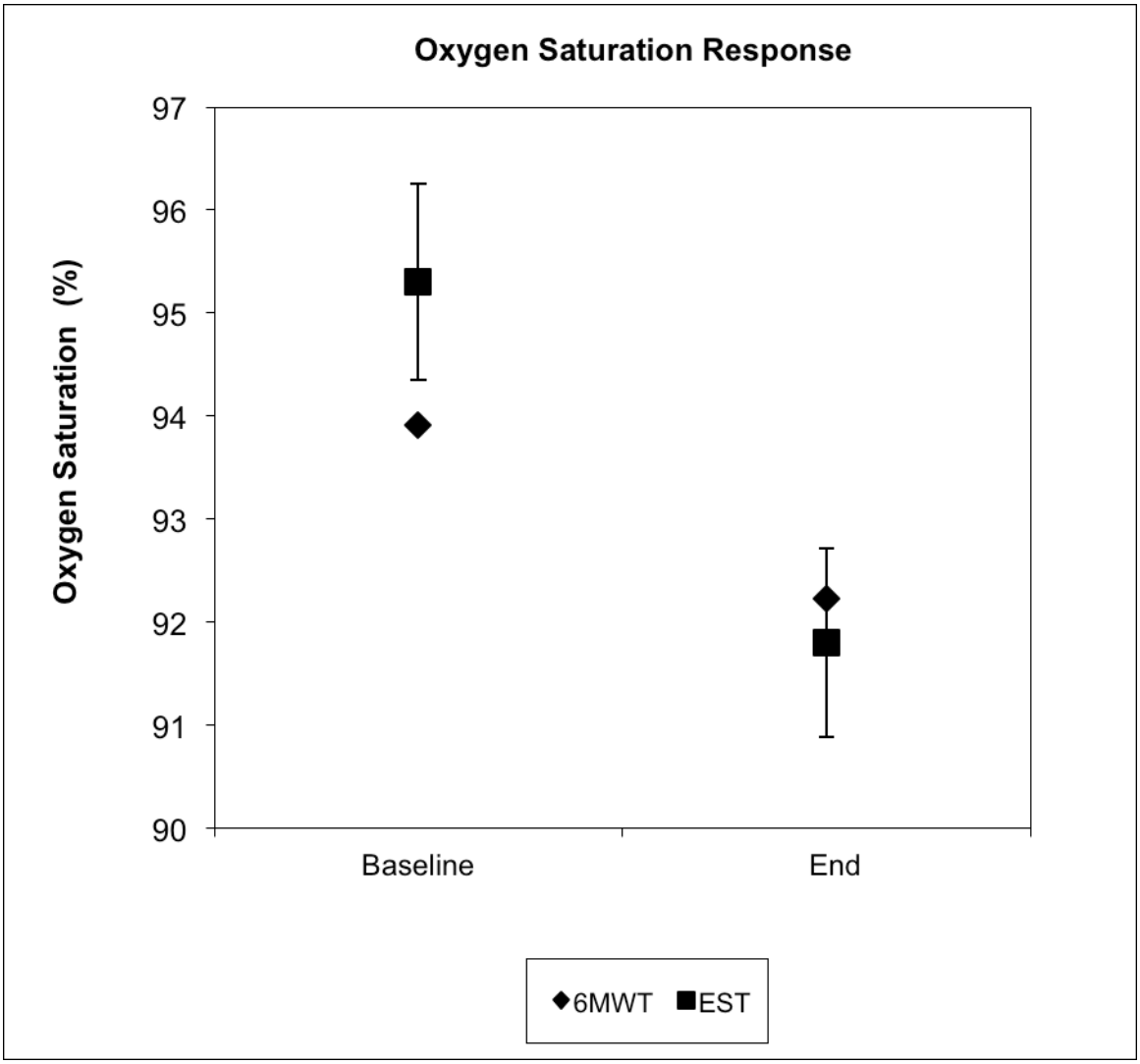

Figure 9. Estimated Dependence of Lifetime Radiation-Induced Risk of Cancer Versus Age at Exposure (61).

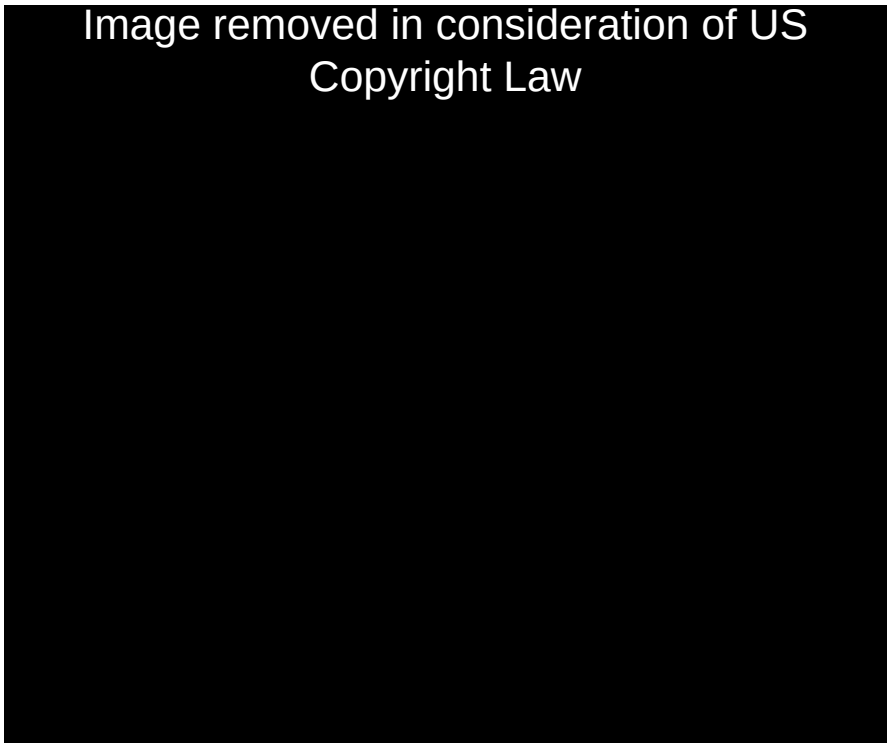

Table 1. Patient characteristics.
Data for twenty-two patients who participated in this study is presented with average sex, age, weight, height, and resting oxygen saturation levels shown. (a) In parentheses, the minimum and maximum numbers are entered for each category.

Sex (F/M)	16/6
Age (y)	28.2 (8.8, 74.3)[a]
Weight (kg)	64.8 (29.0, 133.8)[a]
Height (m)	1.6 (1.3, 1.9)[a]
Resting oxygen saturation (%)	93.9 (63, 100)[a]

[a]

Table 2. Mean values with standard deviations (SD) and intraclass correlation coefficients (r_i) with 95% confidence intervals (CI) for 6MWT.

Parameter	Mean test no. 1 (SD)	Mean test no. 2 (SD)	r_i (95% CI)
Baseline 6MWT HR (bpm)	94.5 (14.6)	95.0 (15.7)	0.829 (0.630–0.925)
Post 6MWT HR (bpm)	108.3 (17.4)	106.5 (20.4)	0.940 (0.863–0.975)
Baseline 6MWT O_2 saturation	93.9 (7.9)	94.3 (7.6)	0.989 (0.975–0.996)
Post 6MWT O_2 saturation	92.2 (9.9)	93.0 (8.4)	0.973 (0.933–0.989)
6MWT O_2 saturation difference	1.7 (2.5)	1.2 (1.7)	0.659 (0.346–0.841)
6MWT distance (m)	471.1 (84.2)	477.5 (71.7)	0.942 (0.867–0.975)

Table 3. Mean values with standard deviations (SD) and intraclass correlation coefficients (r_i) with 95% confidence intervals (CI) for EST.

Parameter	Mean test no. 1 (SD)	Mean test no. 2 (SD)	r_i (95% CI)
Baseline EST HR (bpm)	90.5 (15.4)	91.8 (14.8)	0.871 (0.717–0.944)
Post EST HR (bpm)	159.0 (15.7)	158.5 (15.9)	0.941 (0.865–0.975)
Baseline EST O_2 saturation	95.3 (6.2)	95.1 (6.9)	0.979 (0.950–0.991)
Post EST O_2 saturation	91.8 (9.7)	92.3 (9.1)	0.993 (0.982–0.997)
EST O_2 saturation difference	3.5 (3.8)	2.9 (2.8)	0.836 (0.647–0.928)
EST work (W)	114.5 (42.1)	113.2 (41.3)	0.941 (0.864–0.975)

Table 4. Clinical Characteristics of 144 Children with PAVMs Reported in Literature under age 18.

Signs and Symptoms of PAVMs	Number reported/Total Children	Percent
Dyspnea	73/149	49%
Cyanosis	113/149	78%
Clubbing	75/149	50%
Complications of PAVMs		
Transient Ischemic Attack	4/149	3%
Stroke	3/149	2%
Cerebral Abscess	13/149	9%
Hemoptysis	15/149	10%
Hemothorax	3/149	2%