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Pulmonary Arterial Thrombosis in Eisenmenger Syndrome Is Associated With Biventricular Dysfunction and Decreased Pulmonary Flow Velocity

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Objectives This study sought to determine what factors are associated with pulmonary artery thrombi in Eisenmenger patients.

Background Pulmonary artery thrombosis is common in Eisenmenger syndrome, although its underlying pathophysiology is poorly understood.

Methods Adult patients with Eisenmenger syndrome underwent computed tomography pulmonary angiography, cardiac magnetic resonance imaging, and echocardiography. Measurement of ventricular function, pulmonary artery size, and pulmonary artery blood flow were obtained. Hypercoagulability screening and platelet function assays were performed.

Results Of 55 consecutive patients, 11 (20%) had a detectable thrombus. These patients were older ($p = 0.032$), but did not differ in oxygen saturation, hemoglobin, or hematocrit from those without thrombus. Right ventricular ejection fraction by magnetic resonance imaging was lower in those with thrombus (0.41 ± 0.15 vs. 0.53 ± 0.13, $p = 0.017$), as was left ventricular ejection fraction (0.48 ± 0.12 vs. 0.60 ± 0.09, $p = 0.002$), a finding corroborated by tissue Doppler and increased brain natriuretic peptide. Those with thrombus also had a larger main pulmonary artery diameter (48 ± 14 mm vs. 38 ± 9 mm, $p = 0.007$) and a lower peak systolic velocity in the pulmonary artery ($p = 0.003$). There were no differences in clotting factors, platelet function, or bronchial arteries between groups. Logistic regression showed pulmonary artery velocity to be independently associated with thrombosis.

Conclusions Pulmonary arterial thrombosis among adults with Eisenmenger syndrome is common and relates to older age, biventricular dysfunction, and slow pulmonary artery blood flow rather than degree of cyanosis or coagulation abnormalities. Further work to define treatment efficacy is needed. (J Am Coll Cardiol 2007;50:634–42)

The high incidence of pulmonary artery (PA) thrombosis and hemoptysis in patients with Eisenmenger syndrome is well documented, although the underlying basis for this association is poorly understood. Dr. Eisenmenger's index case report described PA thrombi at autopsy in a patient who died of hemoptysis (1). In Wood's (2) seminal necropsy series, PA thrombi were present in roughly one-fourth of patients. More recent retrospective studies have confirmed these early observations (3,4). However, despite decades of recognition of the problem, there has been little to no

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advancement in our understanding of pathophysiology, prognostic implications, or effectiveness of treatment.

The growing use of pulmonary angiography by computed tomography (CTPA) has renewed interest in this issue by easily showing the lesions in vivo (5) with an overall prevalence of approximately 20% (6). Thrombi are reportedly more common in women and in those with lower oxygen saturation, although no differences were shown in hemoglobin, platelet count, PA diameter, or right ventricular dysfunction by echocardiography (6). Other studies have stirred interest in the potential relationship between hemoptysis and bronchial artery enlargement. Thus many questions remain unanswered, in particular the relationship between thrombosis and hemoptysis, because this has great implications for treatment.

This study investigated possible variables associated with PA thrombosis and hemoptysis in Eisenmenger patients to better understand the pathophysiological mechanisms and rationale for treatment.

Methods

We designed a prospective cross-sectional study of consecutive adults with Eisenmenger physiology seen at the Royal Brompton Hospital. Portions of the study have been previously reported (7). The protocol was approved by the institutional ethics committee, and all patients signed informed consent before participation. Patients with Down syndrome or learning disabilities were eligible to participate, and were asked to sign consent together with their parent or guardian.

Patients. Eisenmenger syndrome was defined as all of the following: 1) known intracardiac or great artery shunt; 2) increased PA pressure (tricuspid regurgitation velocity >4 m/s or measured mean PA pressure >50 mm Hg); and 3) reversed or bidirectional shunt resulting in hypoxemia (cutaneous oxygen saturation <92% at rest or <87% with exercise). Patients with an atrial septal defect <3.0 cm and no other shunt were not included (2). For patients with differential cyanosis, eligibility was based on oxygen saturation measured at the toe. Patients with impaired renal function (creatinine >1.5 mg/dl), pregnancy, or significant comorbidity (decompensated heart failure, active hemoptysis, recent surgery, or current infection) were excluded.

All studies were performed at the Royal Brompton Hospital within a 24-h period and according to accepted clinical standards. A complete history and physical examination were performed initially. Significant hemoptysis was defined as any episode producing at least 1/4 cup of bright red blood. Oxygen saturation was measured in the finger or toe after a minimum of 5 min rest in sitting position. Saturation also was measured after 5 min of supplemental oxygen via nonrebreather mask (15 l/min), and then again on room air after 6 min of brisk walking. Distance walked in 6 min was also recorded (8).

Blood samples. A peripheral venous catheter was inserted, and blood samples were obtained for measurement of full blood count, electrolytes, urate, and creatinine. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were also measured (monoclonal antibody assay, Shionoria, Schering, West Sussex, England). Viscosity and red cell aggregation were measured as previously described (7). After completion of all investigations, further blood samples were drawn for hypercoagulability screening. The citrate concentration was adjusted based on packed cell volume measured on the previous sample, following published guidelines (9).

Computed tomography. A CTPA scan was performed using a 4-channel multidetector scanner (Somatom Volume Zoom; Siemens, Erlangen, Germany). Ninety milliliters of contrast media (Ultravist 370, Schering, Berlin, Germany) were injected through a peripheral venous catheter via an automated injector (rate 4 ml/s). Because venous-line air filters were incompatible with the rate of injection, extra attention was made to eliminate air within the line. Bolus tracking was done using built-in software (Carebolus, Siemens, Erlangen, Germany) to determine computed tomographic density of the main pulmonary artery (MPA) (or ascending aorta in cases with truncus arteriosus). Scanning at held inspiration was begun when density reached 100 HU.

Thrombi were identified from raw axial images by an experienced radiologist blinded to any other clinical information. Diameter measurements of the MPA, right branch pulmonary artery (RPA), and left branch pulmonary artery (LPA) within the mediastinum were made in the axial plane. The largest bronchial arteries to the right and left lungs were identified, and their diameters were measured.

Magnetic resonance. Cardiovascular magnetic resonance imaging (CMR) was performed using a 1.5-T scanner (Sonata, Siemens, Erlangen, Germany) with a phased-array body coil. Steady-state free precession end-expiratory breath hold short-axis cine images (7 mm with 3-mm spacing) were obtained from base to apex. Through-plane phase contrast velocity mapping was made in the proximal MPA and proximal ascending aorta at held expiration. In patients with truncus arteriosus, in-plane flow through a cross section of the RPA and LPA was used for pulmonary flow,

Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CI = confidence interval
CMR = cardiovascular magnetic resonance
CTPA = computed tomography pulmonary angiogram
LPA = left pulmonary artery
LV = left ventricle/ventricular
MPA = main pulmonary artery
OR = odds ratio
PA = pulmonary artery
RPA = right pulmonary artery
RV = right ventricle/ventricular
RVOT = right ventricular outflow tract
VSD = ventricular septal defect

and aortic flow was measured distal to the origin of the PA branches.

Measurements of volume and flow were performed using CMR Tools software (Imperial College, London, England). Right ventricular (RV) and left ventricular (LV) volume at end diastole and end systole, indexed to body surface area, were calculated using the Simpson method with careful contouring around each trabeculation and outflow tracts as previously described (10). For patients with a ventricular septal defect (VSD), delineation between the RV and LV chambers at the defect was done using a line in direct continuity with the septum. For each patient, the diameter of the shunt was measured in 2 orthogonal planes, and these diameters were used to determine elliptical area. The diameters of the MPA, RPA, and LPA were measured from axial single-phase spin echo images.

Phase contrast velocity flow maps of the MPA were used to calculate maximum peak systolic velocity, mean systolic velocity (average velocity of each pixel in the region of interest during systole), stroke volume, and flow. Mean and maximum velocity were not determined for patients with truncus arteriosus or aortopulmonary window. For determination of maximum velocity, care was taken to avoid high-shear areas near the perimeter of the region of interest.

Echocardiography. Echocardiography was performed using a standard transthoracic approach with a Philips ultrasound imaging system (Sonos 7500, Hewlett-Packard, Andover, Massachusetts) interfaced with a multifrequency transducer. Continuous-wave Doppler was aligned through the right ventricular outflow tract (RVOT) to obtain a peak velocity. Myocardial tissue Doppler velocities were recorded using spectral pulsed Doppler from the LV free wall, septum, and RV free wall from the apical four chamber view. All 2-dimensional images, Doppler flow velocities, and tissue Doppler velocities were recorded digitally with a simultaneous electrocardiogram (lead II) and a phonocardiogram superimposed on each. EnConcert Echo Information Management System (Philips, Reigate, England) was used to analyze the stored data.

Coagulation and platelet function testing. Thrombophilia assays were all performed on an automated analyzer (MDA-180 Biomerieux, Basingstoke, England) and included antithrombin activity, protein C activity (Biomerieux), and free protein S (Diagnostica Stago, Axis Shield, Huntingdon, England). von Willebrand antigen was a total antigen measurement using a latex particle assay (Diagnostica Stago, Axis Shield, Huntingdon, England). Platelet function assays were performed using the PFA-100 (Sysmex, Milton Keynes, England), where closure time for a platelet plug to form as blood passes through an aperture is measured in seconds.

Statistical analysis. Two groups were defined based on the presence or absence of PA thrombus. Analysis was done using SPSS for Windows 11.0 (SPSS Inc., Chicago, Illinois). Normality was tested using the Kolmogorov-Smirnov method. Continuous variables were compared with Student *t* test or the Mann-Whitney *U* test as appropriate. Categorical variables were compared by chi-square or Fisher exact test. Univariate regression was done using a Pearson regression coefficient. To assess the uniqueness of association between variables, logistic regression was performed on variables that were statistically different between groups, with no more than 3 variables included in any multivariate model at any time because of the limitations of sample size. Results are expressed as mean ± SD, or median/interquartile range for non-normal variables. A value of $p < 0.05$ was considered statistically significant. No correction was made for multiple tests.

Results

Patients. Fifty-five patients were studied, 37 women and 18 men. Fifteen patients had Down syndrome or other forms of developmental delay. Eleven patients (20%, 95% confidence interval [CI] 10% to 33%) had PA thrombus. Distribution of shunt types are shown (Table 1). Seven patients had a systemic RV. For simplicity, this article will use the term LV to mean the systemic ventricle and RV for the pulmonic ventricle. Two patients had single-ventricle physiology (one with double-inlet LV, another with hypoplastic left heart/aortic atresia). Two had undergone palliative Mustard procedures without closure of the VSD. One patient developed diffuse urticaria after CTPA, which resolved completely after treatment. Another patient developed transient hand numbness immediately after the scan, which resolved in 30 min. There were no other adverse events.

General clinical characteristics of those with thrombus compared with those without are shown (Table 1). Those with thrombus were older ($p = 0.032$), but did not differ with respect to gender or heart rate. We found no difference in oxygen saturation at rest, after supplemental oxygen (91 ± 5% vs. 91 ± 7%), or after walking (60 ± 8% vs. 58 ± 9%) between patients with and without thrombus, respectively. Six-minute walk distance was not different (339 ± 62 m vs. 373 ± 114 m). Similarly, there was no difference in hemoglobin, spun hematocrit, packed-cell volume, transferrin saturation, or mean corpuscular volume (Table 1). Shunt area was not different between groups, even when analyzed separately according to shunt type.

PA size. Pulmonary artery measurements from both computed tomography and CMR are shown (Table 2). There was excellent correlation between the 2 methods for measurement of MPA, RPA, and LPA diameters ($r = 0.96$, 0.82, and 0.89 respectively; $p < 0.001$ for each). Patients with thrombus had a significantly larger diameter of the MPA, RPA, and LPA. Because of an observed tendency for preferential dilatation of the RPA, the RPA/LPA diameter ratio was calculated for each patient and was found to be significantly higher in those with thrombus than in those without (Table 3).

Table 1 General Characteristics of Patients With Pulmonary Artery Thrombus Compared With Those Without

	Thrombus (n = 11)	No Thrombus (n = 44)	p Value
Shunt type			
Atrial septal defect, n (%)	2 (100%)	0	
Ventricular septal defect, n (%)	7 (23%)	24 (77%)	
Patent ductus arteriosus, n (%)	0	7 (100%)	*
Atrioventricular septal defect, n (%)	1 (11%)	8 (89%)	
Truncus or anteroposterior window, n (%)	1 (17%)	5 (83%)	
Clinical			
Age (yrs)	46.2 ± 17.1	36.5 ± 12	0.032
Female, n (%)	6 (55%)	31 (70%)	NS
Developmental delay, n (%)	3 (27%)	12 (27%)	NS
New York Heart Association functional class III or IV, n (%)	7 (64%)	14 (32%)	NS
History of hemoptysis, n (%)	8 (73%)	19 (43%)	0.08
Aspirin use currently, n (%)	1 (9%)	13 (30%)	NS
Warfarin use currently, n (%)	5 (45%)	8 (18%)	NS
Systemic right ventricle, n (%)	2 (18%)	5 (11%)	NS
Heart rate (beats/min)	86 ± 17	83 ± 14	NS
Oxygen saturation at rest (%)	81 ± 6	81 ± 8	NS
Laboratory			
Hemoglobin (g/dl)	18.8 ± 3.6	19.9 ± 2.7	NS
Packed cell volume (%)	57 ± 10	61 ± 8	NS
Mean corpuscular volume (fl)	89 ± 7	89 ± 10	NS
Urate (mmol/l)	372 ± 111	413 ± 118	NS
Serum albumin (g/dl)	3.5 ± 7.2	3.9 ± 5	0.045
C-reactive protein (mg/l)	8 (16)	6 (6.8)	NS
Atrial natriuretic peptide (pmol/l)	25 (40)	16 (20)	NS
Brain natriuretic peptide (pmol/l)	24 (43)	10 (15)	0.034

*p = 0.028 for patent ductus versus atrial septal defect by Fisher exact test. Continuous variables are given as mean ± SD or median (interquartile range).

Ventricular function. Forty-four patients (80%) were able to undergo CMR scanning (10 patients with thrombus and 34 patients without). Reasons for not undergoing CMR included claustrophobia (n = 3), presence of an implanted pacemaker (n = 2), inability to comply with instructions (n = 3), or scanner unavailability on the study day (n = 3). No significant differences were found between those who did or did not participate in CMR.

Parameters of ventricular function measured by CMR and echocardiography are shown (Table 3). Mass index and end-diastolic volumes for RV and LV were not different between patients with thrombus and without. However, there was a significant difference in both RV and LV ejection fraction measured by CMR. Tissue Doppler peak systolic velocity of the LV free wall and septum were significantly lower in those with thrombus versus those without, although not different for the RV free wall. The diastolic E′-wave velocity of the LV and RV free walls was lower in those with thrombus versus those without, although not significantly different for the septum. Tissue Doppler A′-wave velocity was not different, nor was the E/E′ ratio.

Table 2 Pulmonary Artery Diameters

	Thrombus	No Thrombus	p Value
Computed tomography			
Main pulmonary artery (mm)	48 ± 14	38 ± 9	0.007
Right pulmonary artery (mm)	37 (10)	25 (8)	<0.001
Left pulmonary artery (mm)	33 ± 9	25 ± 7	0.006
Right/left pulmonary artery ratio	1.22 ± 0.30	1.06 ± 0.18	0.022
Pulmonary artery calcification present	8 (73%)	10 (23%)	0.002
Magnetic resonance			
Main pulmonary artery (mm)	42 (6)	34 (11)	0.016
Right pulmonary artery (mm)	38 (17)	21 (7)	0.002
Left pulmonary artery (mm)	29 (14)	19 (7)	0.006

Continuous variables are given as mean ± SD or median (interquartile range).

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Table 3 Biventricular Function and Pulmonary Flow Dynamics

	Thrombus	No Thrombus	p Value
Magnetic resonance: volumes			
RV end-diastolic volume index (ml/m^2)	92 ± 51	83 ± 34	NS
RV end-systolic volume index (ml/m^2)	57 ± 47	41 ± 24	NS
LV end-diastolic volume index (ml/m^2)	90 ± 40	77 ± 27	NS
LV end-systolic volume index (ml/m^2)	50 ± 34	32 ± 15	0.029
RV mass index (g/m^2)	64 ± 22	66 ± 26	NS
LV mass index (g/m^2)	73 ± 29	66 ± 23	NS
RV ejection fraction	0.41 ± 0.15	0.53 ± 0.13	0.017
LV ejection fraction	0.48 ± 0.12	0.60 ± 0.09	0.002
Systemic blood flow (l/min)	4.96 ± 1.26	4.82 ± 1.43	NS
Pulmonary blood flow (l/min)	4.82 ± 2.07	4.90 ± 1.84	NS
Qp/Qs	0.95 ± 0.27	1.09 ± 0.80	NS
Echocardiography: tissue Doppler			
LV free wall peak systolic velocity (cm/s)	6.1 ± 1.5	8.0 ± 1.7	0.013
LV free wall peak E′ wave velocity (cm/s)	4.2 ± 2.7	7.5 ± 3.4	0.032
Septal peak systolic velocity (cm/s)	4.3 ± 1.1	5.9 ± 1.7	0.035
Septal peak E′-wave velocity (cm/s)	3.7 ± 1.7	4.9 ± 2.3	NS
RV free wall peak systolic velocity (cm/s)	7.8 ± 1.8	10.8 ± 15.3	NS
RV free wall peak E′-wave velocity (cm/s)	3.4 ± 2.3	6.9 ± 3.3	0.012
Maximum peak systolic velocity (m/s)	0.63 ± 0.19	0.98 ± 0.23	0.003
Mean systolic velocity (m/s)	0.19 ± 0.08	0.63 ± 0.19	0.044
Main pulmonary artery cross-sectional area (cm^2)	22.3 (19.1)	9.8 (4.6)	0.004
Pulmonary artery stroke volume (ml/beat)	61 (40)	57 (37)	NS
Echocardiography: continuous-wave Doppler			
RVOT peak velocity (m/s)	1.09 ± 0.30	1.00 ± 0.34	NS
RVOT velocity time integral (cm)	14.42 ± 7.29	14.85 ± 6.40	NS
RVOT diameter (cm)	2.89 ± 0.44	2.69 ± 0.48	NS
RVOT area (cm^2)	6.7 ± 2.0	5.9 ± 2.1	NS
RVOT stroke volume (ml/beat)	98 ± 40	87 ± 56	NS

Continuous variables are given as mean ± SD or median (interquartile range).
LV = left venriuclar; RV = right ventricular; RVOT = right ventricular outflow tract.

Both ANP and BNP levels were above the normal range (Table 1, normal values are <11 and <4 pmol/l, respectively). There was a significantly higher BNP level in those with thrombus than without (Table 1), whereas ANP levels did not differ.

Pulmonary flow dynamics. Those with thrombus had a significantly larger measured cross-sectional area of the MPA, as expected given the diameter differences described (Table 2). The maximum and mean peak systolic velocities were both significantly lower in those with thrombus than those without (Table 3). Stroke volume was not different. By continuous-wave Doppler echocardiography, there was no difference in peak velocity or velocity–time integral through the RVOT. Cross-sectional area of the RVOT based on measured diameter also was not different. There was no difference in similar parameters for the LV outflow tract or aorta using either echocardiography or CMR.

Hypercoagulability screening and platelet function. Twenty-eight patients were included in the hypercoagulability analysis (Table 4). Patients were excluded because of warfarin or aspirin use, or inadequate blood samples (insufficient blood volume, hemolysis, or clotted sample). There were no differences in antithrombin III, protein C, free protein S, or von Willebrand factor levels. There was no evidence of lupus anticoagulant in any patient. Homocysteine levels were within normal limits. Platelet function assays were

Table 4 Coagulation Screening and Platelet Function Assays

	Thrombus	No Thrombus	p Value	Normal Range
Platelet count (10^9/l)	175 ± 53	139 ± 59	0.071	150–400
Platelet function assay (collagen/adenosine diphosphate) (s)	163 ± 46	200 ± 70	NS	68–121
Platelet function assay (collagen/epinephrine) (s)	212 ± 72	238 ± 74	NS	85–140
Antithrombin III (IU/dl)	81 ± 14	88 ± 16	NS	70–130
Protein C (IU/dl)	83 ± 24	101 ± 27	NS	70–130
Free protein S (%)	85 ± 26	113 ± 20	NS	65–130
von Willebrand factor (IU/dl)	163 ± 91	168 ± 55	NS	50–150

consistently abnormal, with longer closure times in our patients than the normal range, yet no differences were found between those with and without thrombus. There was a nonsignificant trend toward higher platelet count in those with thrombus, however.

Bronchial arteries and hemoptysis. Diameters of the right and left bronchial arteries were not different between those with and without thrombus (3.4 ± 1.3 mm vs. 2.6 ± 1.3 mm and 2.9 ± 1.0 mm vs. 2.5 ± 1.2 mm for the right and left bronchial arteries, respectively). Bronchial artery diameter did not correlate with pulmonary blood flow, oxygen saturation, hemoglobin, or hematocrit. Although 78% of patients with thrombus also reported prior significant hemoptysis, this did not reach statistical significance compared with those without thrombus (Table 1). There also was no difference in bronchial artery diameter in those with (n = 13) versus without (n = 42) a history of significant hemoptysis.

Logistic regression. By logistic regression analysis, the variables with the strongest association with thrombus were LV ejection fraction (p = 0.0065, odds ratio [OR] 0.89, 95% CI 0.82 to 0.97), age (p = 0.04, OR 1.054, 95% CI 1.01 to 1.087), and peak systolic PA velocity by CMR (p = 0.013, OR 0.163, 95% CI 0.006 to 0.419). When these 3 variables were compared in a multivariate model, peak systolic PA velocity was the only variable significantly associated with thrombosis (p = 0.034). The LV ejection fraction did not correlate with age or resting oxygen saturation. In a model comparing only age and LV ejection fraction, LV ejection fraction was independently associated with thrombosis (p = 0.007), whereas age was not.

Discussion

Prevalence. This prospective study confirms the relatively high prevalence (20%, 95% CI 10% to 33%) of PA thrombus in Eisenmenger syndrome. In Wood's classic series, 29% of patients died of massive hemoptysis, the cause of which "was usually pulmonary infarction from arterial thrombosis" (2). Several retrospective studies concur (3,4). Perloff et al. (5) showed moderate to massive thrombi in 29% of 31 patients, and Silversides et al. (6) reported thrombi in 21% of 34 patients.

In our study, thrombus formation was not dependent on the severity of right-to-left shunt as measured by oxygen saturation, degree of secondary erythrocytosis, or shunt area measured by CMR. This was in contrast to the results of Silversides et al. (6), who found lower resting oxygen saturation in those with thrombus but no difference in hemoglobin or hematocrit. Others have shown that oxygen saturation does not correlate with age or survival (11). Patients with thrombi in our study were older, also different from the findings of Silversides et al. (6), although the mean age for both study populations was not different. Because of the potential relationship between age and ventricular function, we compared these in a logistic regression model and found that age was not uniquely associated with thrombus. Silversides et al. (6) found more thrombi in women, whereas we found no gender difference. No patients with thrombus were using oral contraception in the Toronto series (6) nor in our own. Menstruating women may be more prone to iron deficiency (7), although iron deficiency was not associated with thrombosis in our dataset.

Mechanism of thrombosis. Four possible etiologies of PA thrombi in Eisenmenger syndrome can be hypothesized. Thrombi may arise from: 1) local vascular injury from progressive pulmonary hypertension; 2) hypercoagulability secondary to cyanosis-related factor deficiencies or platelet dysfunction; 3) sluggish flow in the pulmonary arteries promoting red cell aggregation; or 4) embolic sources rather than form in situ. We interpret the laminar position (12) and the successive layers of clot formation (Fig. 1) to indicate the later hypothesis is unlikely.

The first hypothesis is supported by the finding of extensive calcification in the pulmonary arteries (Fig. 2) in those with thrombus from both our data and the study by Silversides et al. (6). We found no evidence of systemic inflammation in those with thrombus as gauged by C-reactive protein (Table 1), although we did not study more specific markers of endothelial injury. Medial hypertrophy and intimal proliferation have been described in Eisenmenger syndrome, with destruction of the elastica interna believed to be "the end result of trauma to the pulmonary vessels from the elevated pulmonary pressure" (13). Based on such work, Wood (2) postulated that thrombosis was secondary to atherosclerosis, although not

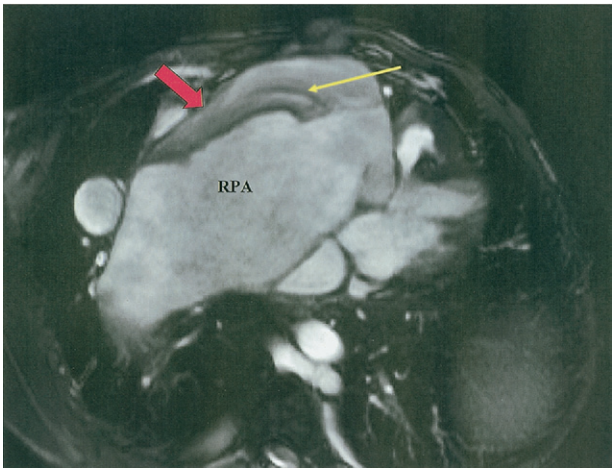

Figure 1 **Cardiac MRI SSFP Image in Oblique Axial Plane**

The patient has an aneurismal right pulmonary artery (RPA) with a laminar thrombus along its anterior wall **(red arrow)**. Several different signal intensities within the thrombus **(yellow arrow)** suggest successive laminar build-up in situ rather than an embolic origin. MRI = magnetic resonance imaging; SSFP = steady state free precession.

Please see the Appendix for accompanying video.

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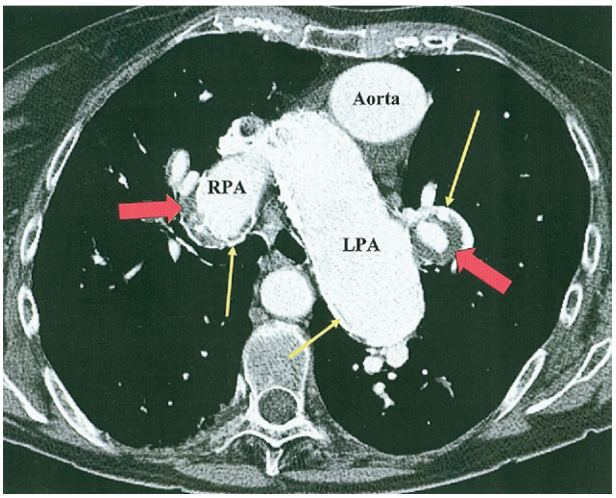

Figure 2 **Computed Tomographic Pulmonary Angiogram**

This scan from a patient with a double-inlet left ventricle and large ventricular septal defect shows extensive calcification of the left and right pulmonary arteries **(yellow arrows)** with circumferential thrombi **(red arrows)**. LPA = left pulmonary artery; RPA = right pulmonary artery.

all agree (5). Overall, we find the theory that small intimal tearing contributes to local thrombogenesis very plausible.

We found no evidence of significant clotting factor deficiencies traditionally associated with hypercoagulability that could explain PA thrombosis. Deficiencies in clotting factors synthesized by the liver have been shown in cyanotic heart disease (14,15) but without hypercoagulation. Such deficiencies may be subclinical and unrelated to thrombosis (15).

Abnormal flow properties secondary to PA dilatation is another possible contributor to thrombogenesis. We found a highly significant difference in PA diameter, preferential dilatation of the RPA compared with the LPA, and slower PA flow velocity in those with thrombus. Slow propagation of pulsatile flow can be appreciated visually with CMR (Fig. 3, Online Video). Deceleration of fluid flowing through a larger cross-sectional area is a well-understood principle of fluid dynamics, and slow-moving blood promotes the formation of aggregates. Red cell aggregation index at low shear, which we measured and recently described elsewhere (7), tended to be higher in those with thrombus (13.03 ± 2.52 vs. 10.92 ± 2.41, $p = 0.059$), although not statistically significant. Thus, our interpretation of these findings is that patients with Eisenmenger syndrome may be vulnerable to local thrombogenesis similar to Fontan patients with right atrial enlargement. However, our data do not prove a cause-effect relationship between flow and thrombosis, and it is also plausible that thrombus is the primary cause of other abnormalities shown.

Biventricular dysfunction. Biventricular systolic dysfunction is present in those with thrombi. Ventricular systolic dysfunction may contribute to relative slowing of PA flow (Fig. 3). There was a weak correlation between LV ejection fraction and PA maximum velocity ($r = 0.33$, $p = 0.08$) that, although not statistically significant, adds credibility to this theory, although again, a cause-effect relationship is not proven. Both the RV and the LV contribute to PA flow in patients with a VSD (including atrioventricular septal defect and truncus arteriosus), and face similar loading conditions. Thus an interventricular functional relationship is not surprising. There was a strong correlation between RV and LV ejection fraction in this series ($r = 0.74$, $p < 0.001$), a common phenomenon in congenital heart disease (16), although not necessarily in other forms of pulmonary arterial hypertension.

The BNP level is increased by 12 times the normal concentration in patients with cyanosis (17). The higher BNP level in those with thrombus in our series supports the possible pathogenic relationship between biventricular systolic dysfunction and PA thrombus. The lower E′ wave tissue Doppler velocity may indicate possible diastolic dysfunction of the RV or LV, although we found no difference in the E/E′ ratio or mitral/tricuspid valve inflow patterns to confirm this. We found no difference in estimated PA pressure by echocardiography between groups, which is not surprising when considering the limitations of accuracy in patients with pulmonary hypertension (18).

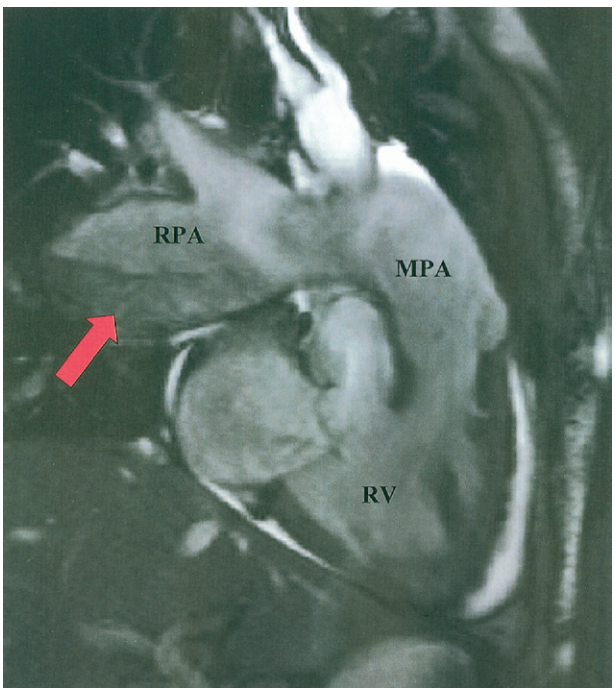

Figure 3 **Cardiac MRI SSFP Image in Oblique Coronal Plane**

The patient has a ventricular septal defect and severe biventricular dysfunction. The RPA is dilated and a large mural thrombus is present along its inferior wall **(red arrow)**. By cine imaging, sluggish flow in the pulmonary artery is visible. MPA = main pulmonary artery; RV = right ventricle; other abbreviations as in Figure 1.

Please see the Appendix for accompanying video.

Bronchial artery hypertrophy. We also hypothesized that patients with prior hemoptysis would have larger bronchial arteries, as has been shown in other congenital patients with pulmonary vascular disease (19). This is the first study we know of to investigate bronchial artery diameter critically in Eisenmenger syndrome. Although the majority of our patients had significant dilatation of the bronchial arteries (normal diameter is <1.5 mm), we were unable to show any difference between those with or without hemoptysis, nor between those with or without thrombus, even after indexing for body size. Thus the role of the bronchial arteries in the etiology of hemoptysis remains uncertain. Coil embolization of the bronchial arteries is sometimes considered as a treatment approach for uncontrolled hemorrhage, although usually as an empiric last resource (20).

Clinical implications. Although this study does not address the efficacy of anticoagulation in prevention of either thrombosis or hemoptysis, it does attempt to clarify the relationship between these coexisting problems in Eisenmenger patients. This is crucial for determining optimal therapy, because treatment of one may worsen the other (12). Based on the belief that PA thrombi lead to microinfarction, which then causes hemoptysis, Wood (2) believed that anticoagulation was warranted, which is supported by findings of fibrinoid necrosis in the PA (21). Since then, however, there have been virtually no clinical data published to either validate or refute his recommendation.

Anticoagulation would likely be recommended by most clinicians today when thrombus is identified, although this is not based on data (6), and legitimate arguments against warfarin have been raised (5). Anticoagulation can provoke significant hemoptysis (12), which occurs in 20% of patients (22) and is the cause of death in roughly 8% (2–4,23). However, a history of hemoptysis does not necessarily carry prognostic weight (3,11,22,23). All available data are retrospective, with no standardization regarding how hemoptysis is defined. Further, anticoagulation in cyanotic patients requires citrate adjustment for accurate international normalized ratio quantification (9), and improper monitoring has lead to warfarin-related deaths in Eisenmenger syndrome (24). Finally, patients with idiopathic pulmonary arterial hypertension are routinely anticoagulated, but are distinctly different from Eisenmenger patients (2,23,25,26). Thus, empiric application of this same anticoagulation strategy in patients with Eisenmenger syndrome may be questioned. Clearly, prospective data must be obtained for this issue to be resolved.

Study limitations. The sample size of our population gave >80% power to show differences in the major findings of PA size, LV ejection fraction, and peak systolic velocity in the PA. Therefore a type I error is unlikely. Power to avoid a type II error with hypercoagulability data is limited. Based on the sample variation, our study was powered to detect a 33% difference in protein C, which is typically considered clinically deficient at 60% of normal. Thus it is unlikely that smaller differences would be clinically relevant. We were not able to measure all potential factors that might play a role in thrombophilia. Our sample size did not allow for comparison between shunt types. For example, 0 of the 7 patients with a patent ductus arteriosus had thrombi, but both patients with an atrial septal defect did. We cannot conclude whether a physiological difference accounts for this finding or whether this is attributable to chance. Because this was designed as a cross-sectional study, the clinical indications for warfarin varied, and no conclusions regarding warfarin efficacy can be made. None of the patients using warfarin were doing so because of previously detected risks for hypercoagulation. There are additional important questions that our data do not answer, such as the pathogenesis and timing of PA dilatation, the precise etiology of biventricular dysfunction, and the cause-effect relationship between PA velocity and thrombosis. Larger studies may shed additional light on the mechanisms of thrombosis and hemoptysis and on the potential effects of anticoagulation therapy.

Conclusions

In situ thrombosis in the PA of patients with Eisenmenger syndrome is common and associated with older age, biventricular dysfunction, dilatation of the pulmonary arteries, and concomitantly decreased pulmonary flow velocity. Neither degree of cyanosis nor large differences in clotting factors were associated with intrapulmonary thrombosis. Prospective data to establish the potential treatment effect of anticoagulation in this patient group are greatly needed.

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APPENDIX

For accompanying videos, please see the online version of this article.