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Original Article

Cardiac findings and long-term thromboembolic outcomes following pulmonary embolism in children: a combined retrospective-prospective inception cohort study

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Abstract In paediatric pulmonary embolism, cardiac findings and thromboembolic outcomes are poorly defined. We conducted a mixed retrospective-prospective cohort study of paediatric pulmonary embolism at the Children's Hospital Colorado between March, 2006 and January, 2011. A total of 58 consecutive children – age less than or equal to 21 years – with acute pulmonary embolism were enrolled. Data collection included clinical and laboratory characteristics, treatments, serial echocardiographic and electrocardiographic findings, and outcomes of pulmonary embolism non-resolution and recurrence. The median age was 16.5 years ranging from 0 to 21 years. The most prevalent clinical risk factors were oral contraceptive pill use (52% of female patients), presence of a non-infectious inflammatory condition (21%), and trauma (21%). Thrombophilias included heterozygous factor V Leiden in 21%; antiphospholipid antibody syndrome was established in 31% overall. Proximal pulmonary artery involvement was present in 34%. At presentation, nearly half of the patients had hypoxaemia and 37% had tachycardia. The classic electrocardiographic finding of S1Q3T3 was present in 12% acutely; tricuspid regurgitation greater than 3 metres per second, septal flattening, and right ventricular dilation were each present on acute echocardiogram in 25%. Nearly all patients received therapeutic anticoagulation, with initial systemic tissue plasminogen activator administered in 16% for occlusive iliofemoral deep venous thrombosis and/or massive pulmonary embolism. Pulmonary embolism resolution was observed in 82% by 6 months. Recurrent pulmonary embolism occurred in 9%. There were no pulmonary embolism-related deaths. Right ventricular dysfunction was rare in follow-up. These data indicate that acute heart strain is common, but chronic cardiac dysfunction is rare, following aggressive management of acute pulmonary embolism in children.

Keywords: Heart strain; ventricular dysfunction; cardiogram; pulmonary hypertension

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VENOUS THROMBOEMBOLISM, INCLUDING DEEP VENOUS thrombosis and pulmonary embolism, is a rare event in the paediatric population. Nevertheless, it is increasing in frequency.[1] Furthermore, a recent paediatric retrospective series suggests that, in the setting of pulmonary embolism, mortality may be as high as 21%.[2]

We are not aware of any published prospective cohort studies in paediatric pulmonary embolism; as such, high-quality observational evidence on long-term outcomes remains limited. Whereas numerous studies have described acute cardiac manifestations including right ventricular dysfunction,[3–6] and have

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established its predictive capacity for adverse outcomes in adults with pulmonary embolism,[7,8] cardiac findings and their potential prognostic importance have received little attention in children. We therefore sought to determine acute and chronic cardiac findings and long-term thromboembolic outcomes following acute pulmonary embolism in children, via an institution-based combined retrospective-prospective inception cohort study.

Methods

Subjects

With the approval of the Colorado Multiple Institutional Review Board (05-0339), consecutive children who ranged in age from birth to 21 years and who had received a diagnosis of acute pulmonary embolism were enrolled and followed up in this mixed retrospective-prospective inception cohort study at the Children's Hospital Colorado between March, 2006 and January, 2011, with the exception of 11 patients diagnosed with acute pulmonary embolism before March, 2006 – for whom data were retrospectively collected before this date and prospectively thereafter. Signed informed consent – and child assent, as appropriate – was provided. There were no exclusion criteria beyond the aforementioned eligibility criteria.

Data collection

The following clinical data were prospectively collected: demographics; presenting signs, including tachycardia and hypoxaemia, as defined by room-air oxygen saturation of less than 90%; thromboembolism characteristics, including pulmonary arterial distribution and presence/absence of concomitant deep venous thrombosis; thromboembolic risk factors, including trauma, sepsis, oral contraceptive pill use, presence of a central venous catheter, prolonged immobility – other than for trauma – congenital heart disease, congenital stenosing vascular anomaly, inflammatory conditions, malignancy, and inherited and acquired thrombophilias; antithrombotic treatments, administered in accordance with the 7th and 8th American College of Chest Physicians guidelines,[9,10] or institution-based clinical care pathways in the case of lytic interventions; serial imaging findings for pulmonary embolism, performed clinically at 3–6 months post event and again at 1 year if persistent at 3–6 months; recurrent thromboembolism; and death. Thrombophilia testing was performed as previously described.[11]

The criteria for administration of systemic tissue plasminogen activator for massive pulmonary embolism included the presence of echocardiographic criteria of severe right ventricular dysfunction or the presence of haemodynamic instability, as defined by requirement for any inotropic support in a patient without underlying primary cardiac disease or the requirement for any new/increase in inotropic support in a patient with underlying primary cardiac disease. Discontinuation of the tissue plasminogen activator infusion occurred when there was no further evidence of severe right ventricular dysfunction seen by echocardiogram or when 96 hours post-initiation of the infusion had been reached or if major bleeding concerns, severe headache, or neurologic changes were present.

The criteria for administration of local tissue plasminogen activator for deep venous thrombosis included the presence of a completely veno-occlusive proximal limb thrombus with either phlegmasia cerulean dolens – tense oedema accompanied by inability to walk or move the limb because of pain – or adversely prognostic plasma biomarkers – the combination of plasma factor VIII activity greater than or equal to 150 units per decilitre and D-dimer concentration greater than or equal to 500 nanograms per millilitre. Dosage and more specific information on the route of administration of thrombolytic therapies has been described in detail in two previous publications.[12,13] At the Children's Hospital Colorado, an institution-wide, electronic medical record-based diagnostic evaluation and management pathway is used for patients with suspected acute pulmonary embolism. Within this clinical pathway, echocardiographic evidence of right ventricular dysfunction is defined by the following parameters: tricuspid regurgitation velocity (greater than 3 metres per second or estimates of right ventricular pressure greater than 50% of systemic blood pressure), presence of septal flattening, and presence of right ventricular dilation. Serial echocardiographic data were reviewed retrospectively with a paediatric cardiologist (Shelley D. Miyamoto). Echocardiogram and 12-lead electrocardiogram data were grouped by time into acute (less than 72 hours), sub-acute/early chronic (1–6 months), and late chronic (greater than 1 year) time periods, with the first study within each time period uniformly chosen for analysis. The tricuspid regurgitation velocity was measured by Doppler when present, except in cases of trivial tricuspid regurgitation where a complete Doppler signal could not be obtained. Electrocardiogram findings of interest with regard to right ventricular dysfunction were ST/T segment changes, the classic S1Q3T3 phenomenon (S wave in lead 1 greater than 1.5 millimetres, Q wave in lead III greater than 1.5 millimetres, and negative T wave in lead III), and voltage criteria for right ventricular hypertrophy. Echocardiogram and electrocardiogram data of patients with congenital heart disease were excluded.

Statistical methods

Summary statistics were reported descriptively, using non-parametric methods. Distributions of data were compared between groups by Mann–Whitney U-test. Frequencies (proportions) were compared by chi-square or Fisher's exact test, as appropriate. Inferential statistics employed two-sided testing, with a p-value of less than 0.05 considered to be statistically significant. All statistics were performed using SAS version 9.1 statistical software (SAS Institute, Cary, North Carolina, United States of America).

Results

Demographic and presenting characteristics

The cohort comprised 58 consecutively enrolled children with acute symptomatic pulmonary embolism. Table 1 summarises demographic data and clinical findings at acute pulmonary embolism presentation. The median age was 16.5 years ranging from birth to 21 years. Gender distribution was balanced. In all, 23% of patients were obese, as defined by a body mass index greater than or equal to the 95th percentile. Acute pulmonary embolism presentation included hypoxaemia in 23 patients (45%) and tachycardia in 19 patients (37%). Concurrent deep venous thrombosis was identified in 19 patients (33%). Symptoms of pulmonary embolism included acute onset/worsened shortness of breath, pleuritic chest pain, haemoptysis, and/or unexplained new/increased oxygen requirement, but were not systematically collected or scored given the absence of a validated tool for the same.

Prothrombotic clinical risk factors

The most prevalent prothrombotic clinical risk factors included oral contraceptive pill use in 14 of 27 female patients (52%); presence of a chronic inflammatory condition in 12 patients (21%), including primary antiphospholipid antibody syndrome, systemic lupus erythematosus, ulcerative colitis, and others; and trauma in 12 patients (21%). Additional diagnoses included congenital stenosing vascular anomaly (May–Thurner anomaly or Paget–Schroetter syndrome in five patients, that is, 9%), presence of a central venous catheter in four patients (7%), congenital heart disease in four patients (7%), and sepsis in four patients (7%), among others.

Laboratory thrombophilia testing

Plasma D-dimer levels were obtained at presentation in 48 patients (83%) and were found to be elevated in 39 (81%) of these. The complete results of D-dimer and thrombophilia testing are shown in Table 1. Heterozygous factor V Leiden was identified in 11 patients (21%), and 17 (31%) of the patients met the criteria for antiphospholipid antibody syndrome.[14] It is noteworthy that only seven patients (13%) had acute antiphospholipid antibodies, such that a considerable number of cases of the syndrome were characterised by a delayed onset of these antibodies. Of the 14 female patients (50%) on oral contraceptive pills, seven had factor V Leiden and five (36%) had antiphospholipid antibody syndrome. A total of 30 patients (58% of those tested) had acutely elevated factor VIII levels. Of these patients (33%) in whom initial elevated factor VIII levels were found, 17 had persistently elevated factor VIII on subsequent laboratory testing.

Imaging characteristics

Nearly all patients were diagnosed with acute symptomatic pulmonary embolism via spiral computed tomography pulmonary angiography; two patients with known underlying cardiac disease – one patient with hypoplastic left heart syndrome following the Norwood procedure and one with tetralogy of Fallot with stenosis of a right ventricular outflow tract stent – were diagnosed by cardiac catheterisation obtained owing to worsening oxygen saturations and respiratory distress. In all, 19 patients (34%) had proximal pulmonary artery involvement and 39 (70%) had bilateral pulmonary embolism.

Antithrombotic treatment

Nearly all patients received therapeutic anticoagulation. A total of 15 patients (26%) underwent acute thrombolysis with tissue plasminogen activator. Of the patients, seven received systemic tissue plasminogen activator only, six received local tissue plasminogen activator only via catheter-directed pharmacomechanical thrombolysis, and two received initial systemic tissue plasminogen activator followed by local salvage therapy. Acute anticoagulation consisted of intravenous unfractionated heparin in 44 patients (76%) and low-molecular-weight heparin by twice-daily subcutaneous injection in 14 patients (24%). Sub-acute treatment consisted of warfarin in 45 patients (78%), low-molecular-weight heparin in 12 patients (20%), and aspirin monotherapy in one patient (2%) with underlying cardiac disease; a combination of aspirin and anticoagulation was used in three patients (5%). There were seven patients (12%) who underwent inferior vena caval filter placement, including three retrievable filters.

Serial echocardiographic and electrocardiographic findings

Among the 24 patients who underwent echocardiography in the acute period (first 72 hours post event),

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Table 1. Demographic data and clinical findings among 58 children with acute pulmonary embolism.

(a) Patient characteristics and venous thromboembolism risk factors	
Age (years)	
Median	16.5
Range	0–20.5
Gender (%)	
Male	31/58 (53)
Female	27/58 (47)
Race/ethnicity	
White	37/58 (64)
White/Hispanic or Latino	4/58 (7)
Other/Hispanic or Latino	6/58 (10)
Black/African American	5/58 (9)
Asian	1/58 (2)
Other	1/58 (2)
Not reported	4/58 (7)
Body mass index percentile	
Median	63
Range	3–99.1
Number of patients with body mass index ⩾95th percentile	12/53 (23)
Tachycardia at presentation (%)*	19/51 (37)
Hypoxaemia at presentation (%)†	23/51 (45)
Deep venous thrombosis (%)	19/58 (33)
Clinical venous thromboembolism risk factors (%)	
Oral contraceptive pill use in females	14/27 (52)
Inflammatory condition‡	12/58 (21)
Trauma	12/58 (21)
Congenital stenosing vascular anomaly§	5/58 (9)
Congenital heart disease‖	4/58 (7)
Central venous catheter	4/58 (7)
Sepsis	4/58 (7)
Malignancy¶	2/58 (3)
Other prolonged immobility (not trauma)**	2/58 (3)
Inherited thrombophilia††,‡‡	
Factor V Leiden heterozygote	11/53 (21)
Acquired thrombophilia	
Positive D-dimer at diagnosis	39/48 (81)
Transient increased factor VIII	13/52 (25)
Persistent increased factor VIII	17/52 (33)
Transient lupus anticoagulant	7/55 (13)
Persistent lupus anticoagulant (antiphospholipid antibody syndrome)	17/55 (31)
Transient increased fibrinogen	15/56 (27)
Persistent increased fibrinogen	0/56 (0)
Transient positive anticardiolipin antibody immunoglobulin M	3/56 (5)
Persistent positive anticardiolipin antibody immunoglobulin G	1/56 (2)
Transient antithrombin deficiency	5/56 (9)
Transient protein C deficiency	5/56 (9)
Transient protein S deficiency	3/56 (5)
(b) Thrombus characteristics and antithrombotic treatments	
Thrombus characteristics§§	
Proximal pulmonary artery involvement	19/56 (34)
Bilateral pulmonary embolism	39/56 (70)
Antithrombotic treatments	
Acute‖‖	
Unfractionated heparin	44/58 (76)
Low-molecular-weight heparin	14/58 (24)
Sub-acute	
Low-molecular-weight heparin	12/58 (20)
Warfarin	45/58 (78)
Aspirin	4/58 (7)
Inferior vena cava filter placement¶¶	7/58 (12)
Tissue plasminogen activator	15/58 (26)
Recurrence of pulmonary embolism	5/58 (9)
Pulmonary embolism unresolved within 6 months	7/38 (18)

*Tachycardia as defined by age and heart rate range from Pediatric Emergency Guidelines at the Children's Hospital Colorado
†Hypoxaemia as defined by room-air saturation of less than 90% in a paediatric population in Colorado at higher elevation
‡Inflammatory condition: one patient with autoimmune lymphoproliferative syndrome, one patient with Stevens–Johnson syndrome, three patients with systemic lupus erythematosis, five patients with antiphospholipid antibody syndrome, two patients with inflammatory bowel disease
§Congenital stenosing vascular anomaly: four patients with May–Thurner syndrome and one patient with Paget—Scroetter syndrome
‖Congenital heart disease: one patient with atrial septal defect, one patient with hypoplastic left heart syndrome, one patient with bicuspid aortic valve, and one patient with tetralogy of Fallot
¶Malignancy: one patient with acute lymphoblastic leukaemia with recent asparaginase, one patient with T-cell leukaemia
**Other prolonged immobility: one patient with orthopaedic surgery (tibial realignment) and one patient with meningomyelocele and chronic immobility
††Prevalence of inherited protein S, Protein C or antithrombin deficiency, and prothrombin gene mutation was each 0%
‡‡Not all patients had undergone testing for all aspects of the thrombophilia panel as evidenced by denominators in data collection
§§There were two patients whose acute imaging was unavailable
‖‖First agent used in the acute period is shown
¶¶3/7 inferior vena cava filters were retrievable

14 patients had a measurable tricuspid regurgitation velocity with a median tricuspid regurgitation velocity of 2.9 metres per second ranging from 2.1 to 4.2 metres per second; Table 2. Parameters of acute right heart dysfunction – tricuspid regurgitation velocity greater than 3 metres per second, septal flattening, and right ventricular dilation – were each present in six (25%) of these children. Of the 24 patients, four (17%) had only one echocardiographic parameter of acute right heart dysfunction, five (21%) had two echocardiographic parameters, and one patient (4%) had all three parameters. During the sub-acute and early chronic periods (1–6-month follow-up interval post event), among the 11 patients studied, five had a measurable tricuspid regurgitation velocity with a median tricuspid regurgitation velocity of 2.3 metres per second ranging from 2.1 to 4.2 metres per second. Tricuspid regurgitation velocity greater than 3 metres per second, septal flattening, and right ventricular dilation were present during this time period in two (18%), three (27%), and four (36%) patients, respectively. Among the 15 patients evaluated in the

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Table 2. Natural history of echocardiographic and electrocardiographic findings over time in children after acute pulmonary embolism.

Echocardiographic data organised by time to echocardiogram	
Less than 72 hours	
Number of patients (%)	24/58 (41)
Median tricuspid regurgitation velocity in m/s (range)*	2.85 (2.1–4.2)
Tricuspid regurgitation >3 m/s (%)	6/24 (25)
Septal flattening (%)	6/24 (25)
Right ventricular dilation (%)	6/24 (25)
1–6 months	
Median time period to echocardiogram in days (range)	101 (24–210)
Number of patients (%)	11/58 (19)
Median tricuspid regurgitation velocity in m/s (range)	2.3 (2.06–4.2)
Tricuspid regurgitation >3 m/s (%)	2/11 (18)
Septal flattening (%)	3/11 (27)
Right ventricular dilation (%)	4/11 (36)
1 year plus	
Median time period to echocardiogram in days (range)	554 (360–1636)
Number of patients	15/58 (26)
Median tricuspid regurgitation velocity in m/s (range)	2.4 (1.84–2.78)
Tricuspid regurgitation >3 m/s	0/15 (0)
Septal flattening	2/15 (13)
Right ventricular dilation	2/15 (13)
Electrocardiographic data organised by time to electrocardiogram	
Less than 72 hours	
Number of patients	32/58 (55)
ST/T segment changes	13/32 (41)
S1Q3T3†	4/32 (12)
Right ventricular hypertrophy	2/32 (6)
1–6 months	
Median time period to electrocardiogram in days (range)	38 (23–146)
Number of patients	6/58 (10)
ST/T segment changes	1/6 (16)
S1Q3T3	0/6 (0)
Right ventricular hypertrophy	3/6 (50)
1 year plus	
Median time period to electrocardiogram in days (range)	565 (347–956)
Number of patients	4/58 (7)
ST/T segment changes	0/4 (0)
S1Q3T3	0/4 (0)
Right ventricular hypertrophy	1/4 (25)

*Median tricuspid regurgitation velocity: not all patients had a measurable tricuspid regurgitation velocity (some patients had physiologic/trivial tricuspid regurgitation)

†S1Q3T3 criteria used: S wave in lead 1 = first negative deflection after R wave greater than 1.5 millimetres, Q wave in lead III = first negative deflection after P wave and before any R wave greater than 1.5 millimetres, associated with negative T wave in lead III

late chronic period – greater than 1 year post event – seven patients had a measurable tricuspid regurgitation velocity, none had a tricuspid regurgitation velocity greater than 3 metres per second, and septal flattening and right ventricular dilation were each present during this time period in 13% of the patients.

With regard to electrocardiogram findings (Table 2), of the 32 patients studied in the acute period 13 patients (41%) had ST/T segment changes, four patients (12%) showed the classic S1Q3T3 pattern (Fig 1), and two patients (6%) met voltage criteria for right ventricular hypertrophy. Of the 32 patients, nine (28%) had only one electrocardiographic finding of acute right heart strain, five (16%) had two findings, and none of the 32 patients had all three electrocardiographic findings. Electrocardiography was infrequently performed in long-term follow-up.

Overall, 20 of the 58 patients (34%) had either echocardiogram or electrocardiogram findings of right heart dysfunction in the acute time period, seven (12%) had findings in the sub-acute and early chronic time period, and only three (5%) had

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Table 3. Characteristics of patients with recurrence and non-resolution of pulmonary embolism within 6 months as compared with those without recurrence and with resolution of pulmonary embolism within 6 months.

Characteristics	Recurrence/non-resolution within 6 months	No recurrence/resolved within 6 months
Clinical venous thromboembolism risk factors		
Trauma/sepsis	1/10	11/28
Oral contraceptive pill use	3/10	6/28
Central venous catheter	0/10	1/28
Congenital heart disease*	0/10	2/28
Congenital stenosing vascular anomaly†	1/10	3/28
Inflammatory condition‡	*6/10*	*5/28*
Inherited thrombophilia§		
Factor V Leiden heterozygote	2/10	7/26
Acquired thrombophilia		
Positive D-dimer at diagnosis	7/7	18/23
Transient increased factor VIII	4/10	6/28
Persistent increased factor VIII	2/10	11/28
Transient lupus anticoagulant	2/10	2/28
Persistent lupus anticoagulant (antiphospholipid antibody syndrome)	5/10	8/28
Transient increased fibrinogen	2/10	8/28
Persistent increased fibrinogen	0/10	0/28
Transient positive anticardiolipin antibody Immunoglobulin M	1/10	2/28
Persistent positive anticardiolipin antibody Immunoglobulin G	1/10	0/28
Transient antithrombin deficiency	1/10	2/28
Transient protein C deficiency	1/10	1/28
Transient protein S deficiency	1/10	2/28
Clot characteristics		
Proximal pulmonary artery involvement	5/10	7/28
Bilateral pulmonary embolism	8/10	20/28

*Congenital heart disease: one patient with atrial septal defect, one patient with hypoplastic left heart syndrome, one patient with bicuspid aortic valve, and one patient with tetralogy of Fallot
†Congenital stenosing vascular anomaly: four patients with May–Thurner syndrome and one patient with Paget–Schroetter syndrome
‡Inflammatory condition: one patient with autoimmune lymphoproliferative syndrome, one patient with Stevens–Johnson syndrome, three patients with systemic lupus erythematosis, five patients with antiphospholipid antibody syndrome,
two patients with inflammatory bowel disease
§Prevalence of inherited protein S, Protein C or antithrombin deficiency, and prothrombin gene mutation were each 0%
Italicised text indicates statistically significant differences $p < 0.05$

findings in the late chronic time period. The percent agreement between abnormal electrocardiogram findings – any of the three aforementioned findings – and abnormal echocardiogram findings – any of the three aforementioned parameters – for acute right heart dysfunction was low, at 24%.

Of the patients who had proximal pulmonary artery involvement and underwent acute echocardiograms, 50% had right ventricular dilation versus only 7% of patients without proximal pulmonary artery involvement (Fisher's p-value is equal to 0.04). There was no significant association with proximal pulmonary artery involvement and other acute echocardiographic or electrocardiographic parameters of interest.

A total of 38 patients had an echocardiogram performed. The seven patients (18%) who had studies in the non-acute time period had a prior paired acute echocardiogram performed. There was only one patient who had all three time period echocardiogram studies. A total of 37 patients had an electrocardiogram performed. The five patients (14%) who had studies in the non-acute time period had a prior paired acute electrocardiogram performed. No patient had an electrocardiogram in all three study periods.

Outcomes

The median follow-up duration was 13.3 months ranging from 0.5 to 56 months. There were no pulmonary embolism-related deaths. The overall mortality was 1.6%, representing one child with a history of meningomyelocele and prolonged immobility whose cause of death was indeterminate and occurred at least

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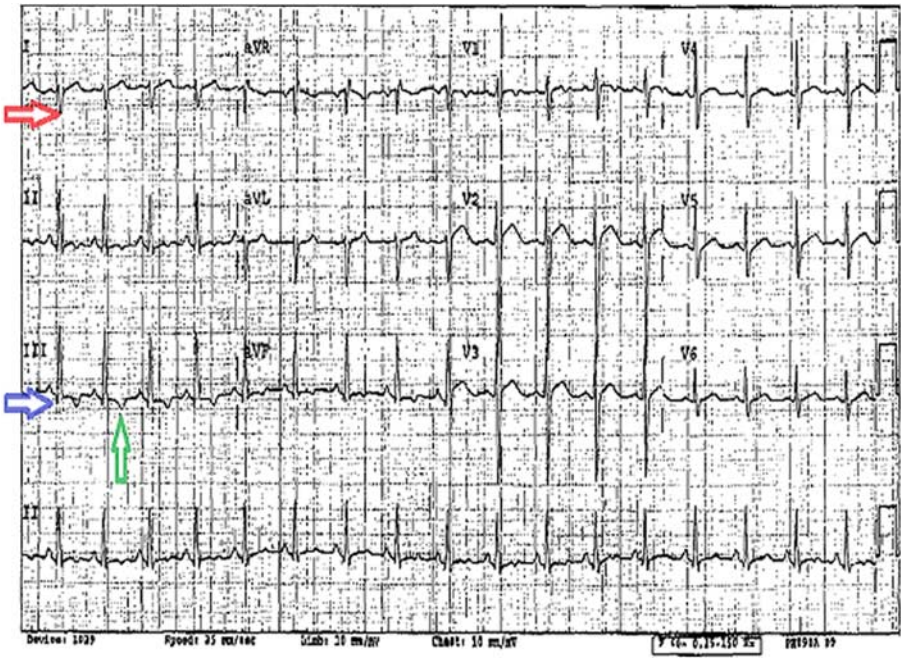

Figure 1.
Classic S1Q3T3 pattern on an electrocardiogram in a child with acute pulmonary embolism in whom right heart strain was evident at presentation. Red arrow denotes S wave in lead 1 greater than 1.5 millimetres. Blue arrow denotes Q wave in lead III greater than 1.5 millimetres. Green arrow denotes negative T wave in lead III.

3 years after pulmonary embolism diagnosis. There were five patients (9%) who developed symptomatic recurrent pulmonary embolism in follow-up, two of whom also had non-resolution of pulmonary embolism on repeat imaging at 6 months post event. An additional five patients showed non-resolution of pulmonary embolism 6 months post event, among 38 patients with repeat imaging during this period (overall risk of non-resolution, 18%). Findings of evaluation for putative prognostic factors for recurrence/non-resolution of pulmonary embolism are displayed in Table 3, and the presence of an underlying non-infectious chronic inflammatory condition – lupus, ulcerative colitis – was identified as an adverse prognostic indicator, with a prevalence of 60% among patients with recurrence/non-resolution versus 18% among those with resolution and no recurrence (p-value less than 0.05). None of the laboratory thrombophilias, and neither echocardiogram nor electrocardiogram findings of right heart dysfunction, was found to be associated with these thromboembolic outcomes.

Discussion

In the present work, we describe the natural history of acute and chronic cardiac findings and long-term thromboembolic outcomes following acute pulmonary embolism in children via a mixed retrospective-prospective cohort study. The findings demonstrate that in paediatric pulmonary embolism, acute right heart strain is common, but death and chronic cardiac dysfunction both appear to be rare following aggressive antithrombotic management, which included thrombolysis in 16% of patients for occlusive iliofemoral deep venous thrombosis and/or massive pulmonary embolism. Symptomatic recurrent pulmonary embolism occurred in 9% of the patients, and non-resolution of pulmonary embolism was determined at 6 months in 18%; these thromboembolic outcomes were significantly associated with the presence of an underlying non-infectious chronic inflammatory condition such as lupus or ulcerative colitis.

The rates of recurrent pulmonary embolism and non-resolution of pulmonary embolism determined here are similar to those in a recent paediatric series by Biss et al[2] from the Hospital for Sick Children. At the same time, in considering outcomes in our cohort, it is important to note that acute thrombolytic therapy was instituted in a large minority (26%) of children, and nearly all children received anticoagulant therapy for a minimum of 3 months. In addition, the underlying demographic characteristics and pulmonary embolism risk factors in our cohort differ somewhat from that of Biss et al[2], in that median age was higher, an indwelling central venous catheter was less common, and oral contraceptive pill use was more frequent. The latter two risk factors were similar in frequency, however, to a recent report of paediatric pulmonary

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embolism by Rajpurkar et al[15]. Lastly, with regard to thrombophilic abnormalities, the frequencies of factor V Leiden and antiphospholipid antibody syndrome were each higher than reported by Biss et al[2], and may represent important pulmonary embolism risk factors among children without indwelling central venous catheters, particularly adolescent females taking estrogen-containing oral contraceptives.

Echocardiographic parameters of interest for right ventricular dysfunction in the setting of adult pulmonary embolism include right ventricular enlargement and hypokinesis, septal flattening, evidence of pulmonary hypertension by tricuspid regurgitation velocity, and myocardial Doppler tissue imaging including the measurement of the right ventricular myocardial performance index.[8] In the present paediatric cohort study, each of the three echocardiographic parameters of right heart dysfunction employed in the hospital-wide clinical care pathway for acute pulmonary embolism at the Children's Hospital Colorado (tricuspid regurgitation velocity greater than 3 metres per second, septal flattening, and right ventricular dilation) was found to be present acutely in 25% of children with pulmonary embolism, but was infrequent in follow-up. Although numerous adult studies have discussed acute and chronic cardiac sequelae of pulmonary embolism,[3–8,16–23] we can find no such published data in children by which to compare our findings. Rydman et al[5] and co-workers reported that right ventricular dysfunction is common acutely following onset of pulmonary embolism in adults but normalises by 3 months' follow-up. Similarly, Hsiao et al showed frequent abnormalities of right ventricular systolic and diastolic function in adults with acute pulmonary embolism using myocardial Doppler tissue imaging and the right ventricular myocardial performance index, which normalised with optimisation of anticoagulant therapy.[3,4]

Several adult studies have also investigated the prognostic value of the electrocardiogram in the setting of pulmonary embolism.[19,21–23] Electrocardiogram findings useful in the diagnostic evaluation for acute pulmonary embolism in adults include right bundle branch block and S wave in lead I, a Q wave in lead III, and inverted T wave in lead III; these comprise the classic S1Q3T3 pattern, which was observed in 12% of our cohort acutely. Vanni et al[23] evaluated the prognostic value of the electrocardiogram among patients with acute pulmonary embolism and normal blood pressure, and found that a right ventricular strain pattern on the electrocardiogram was associated with adverse short-term outcome and added prognostic value to echocardiographic signs of right ventricular dysfunction.

Strengths of the present study include the prospective nature of patient follow-up and non-cardiologic data collection in the cohort, and the adjudicated review of all echocardiogram studies with a paediatric cardiologist. Limitations of the current work include the single-institutional setting of the cohort, the relatively small number of children in whom follow-up echocardiographic imaging and electrocardiogram was performed, and the retrospective nature of the echocardiographic and electrocardiographic data extraction. We did not evaluate the prognostic value of acute echocardiogram and electrocardiogram findings because of the fact that findings of acute heart strain often triggered more aggressive therapy (thrombolytic), which serves as a confounding factor with respect to thromboembolic outcomes. In addition, we restricted our outcomes analysis to death and thromboembolic end points (resolution and symptomatic recurrence); functional end points (pulmonary function testing, 6-minute walk) or quality-of-life assessments were not included, given the limited experience in the use of these measures, particularly in a paediatric pulmonary embolism population. Lastly, sudden death secondary to pulmonary embolism may have been missed because of one or more of the following: pulmonary embolism was not suspected; pulmonary embolism was suspected, but confirmatory testing could not be performed before death; and/or autopsy was not performed or data were not available. Future studies should seek to systematically employ the above-mentioned additional clinically relevant functional end points/outcomes, once standardised and validated.

Notwithstanding its limitations, this study is important in describing acute and chronic cardiac findings and thromboembolic outcomes following pulmonary embolism in children. It is unique in identifying potential prognostic factors for adverse thromboembolic outcomes. Further prospective studies are warranted to longitudinally evaluate functional end points in paediatric pulmonary embolism, in order to inform the development of future risk-stratified therapeutic approaches designed to optimise long-term outcomes.

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