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Pulmonary thromboembolism in congenital heart defects with severe pulmonary arterial hypertension

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ABSTRACT

Introduction: Congenital heart defect (CHD) with shunt can lead to severe, even irreversible pulmonary arterial hypertension (PAH); in extreme form to Eisenmenger syndrome (ES). Despite relatively good long-term survival, these patients often suffer from cyanosis and multisystemic dysfunction; where pulmonary artery thrombosis can be a potentially fatal complication. Together with bleeding these are the most frequent causes of non-cardiac death in patients with severe PAH due to CHD.
Patients and methods: Prospective study of 40 patients with severe PAH due to CHD (28 female/12 male, median age 41.5 years) was performed, with the aim to analyze the presence of pulmonary artery thrombosis and correlating anatomical and laboratory risk factors.
Results: Previous thrombosis and/or thromboembolic event was found in 7 patients (17.5%). Significant difference in cyanotic versus non-cyanotic patients were in red blood count parameters: median hemoglobin level – 195 vs 141 ($p < 0.0001$), median erythrocytes count 6.62 vs 4.88 × 10^{12}/l ($p < 0.0001$), median hematocrite 0.58 vs 0.44 ($p < 0.0001$). Laboratory findings causing increased risk for thrombosis were: increased thrombocytes aggregation in 15 patients (37.5%), hypercoagulation in 5 patients (12.5%) and endothelial dysfunction in 8 patients (20%). Anatomical risk factor – severe pulmonary artery dilatation (> 40 mm in female and > 45 mm in male) was found in 19 patients (51.4%).
Conclusions: Patients with severe PAH due to CHD represent a high-risk group for pulmonary artery thrombosis with morphological and flow pathology combined with secondary erythrocytosis and coagulation abnormalities. A relatively high incidence of platelet hyperaggregability shown in our study would propose that aspirin therapy might be considered in some highly selected patients with severe PAH due to CHD. Further studies though are needed to support this data.

SOUHRN

Úvod: Skratové vrodené srdcové chyby môžu viesť k vzniku ťažkej až ireverzibilnej pľúcnej artériovej hypertenzii (PAH), v extrémnom prípade k Eisenmengerovmu syndrómu (ES). Napriek relatívne dobrému dlhodobému prežívaniu títo pacienti často trpia cyanózou a multiorgánovým poškodením. Trombóza pulmonálnej artérie predstavuje u nich pomerne častú a potenciálne fatálnu komplikáciu a spolu s krvácaním tvorí najčastejšiu príčinu nekardiálneho úmrtia u pacientov s ES.

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Pacienti and metódy: Prospektívne bolo sledovaných 40 pacientov s ťažkou PAH pri vrodenej chybe srdca (28 žien a 12 mužov, medián veku 41.5 rokov), s cieľom analyzovať prítomnosť trombózy pulmonálnej artérie a súvisiacich anatomických a laboratórnych rizikových faktorov.
Výsledky: Anamnestický údaj o trombóze a/alebo tromboembolickej príhode bol prítomný u 7 pacientov (17,5 %). Signifikantný rozdiel v parametroch červenej zložky krvného obrazu bol prítomný u cyanotických v porovnaní s necyanotickými pacientmi: medián hodnoty hemoglobínu 195 vs 141 g/l ($p < 0,0001$), medián počtu erytrocytov 6,62 vs 4,88 × 10^{12}/l ($p < 0,0001$) a medián hodnoty hematokritu 0,58 vs 0,44 ($p < 0,0001$). Laboratórny nález zvyšujúci riziko trombózy: zvýšená agregabilita trombocytov bola prítomná u 15 pacientov (37,5 %), hyperkoagulácia u 5 pacientov (12,5 %) a endotelová dysfunkcia u 8 pacientov (20 %). Anatomický rizikový faktor – závažná dilatácia pulmonálnej artérie (> 40 mm u žien a > 45 mm u mužov) bola prítomná u 19 pacientov (51,4 %).
Záver: Pacienti s ťažkou PAH pri vrodenej chybe srdca predstavujú rizikovú skupinu pre výskyt trombózy v dôsledku morfologických a prietokových anomálií pulmonálnej artérie, kombinovaných so sekundárnou erytrocytózou a poruchami koagulácie. Relatívne vysoký výskyt hyperagregability trombocytov, ktorý sme dokázali v našej práci, dáva na zváženie liečbu kyselinou acetylosalicylovou u niektorých vysoko selektovaných pacientov so závažnou PAH pri vrodenej chybe srdca. Potrebné sú však ďalšie štúdie na potvrdenie týchto údajov.

Klíčová slova:
Cyanóza
Dilatácia pľúcnej artérie
Eisenmengerov syndróm
Pľúcna artériová hypertenzia
Trombóza pľúcnej artérie
Vrodené chyby srdca

Introduction

The presence of a hemodynamically significant congenital heart defect (CHD) with shunt can lead to increased pulmonary arterial flow and pressure. The onset and severity of pulmonary arterial hypertension (PAH) are quite variable according to the type of CHD, and in an extreme form can lead to Eisenmenger syndrome (ES) with irreversible PAH [1–2], contraindicated to any further correction.

Pulmonary arterial chances in PAH are closely studied but still not completely understood. Endothelial dysfunction and histomorphological changes in small pulmonary arterial vessels are the releasing factors of PAH [1]. Due to the increased pulmonary arterial pressure and resistance a secondary dilatation of proximal pulmonary artery is seen, with thrombosis in situ also described [1]. Even pulmonary artery dissection or rupture is sometimes reported [3,4].

ES represents a unique group among patients with PAH. The long-term survival of these patients is traditionally described as much better compared to other types of severe PAH [1,2,5]; despite the presence of extreme pulmonary arterial pressure, which can be systemic or even suprasystemic. This is usually contributed to the well preserved right ventricular (RV) function [5–8]. The presence of the defect is supposed to serve as a "pop-off valve", enabling the severely overloaded RV decompression and so preventing its decompensation and failure. This is why patients with a late CHD closure usually do much worse than before surgery or compared to patients with persistent cardiac shunting.

On the other hand, this RV "protection" in ES is paid with the cost of right-to-left shunting through the defect that leads to mixing of desaturated blood to systemic circulation and resulting in patient's cyanosis. Cyanosis and systemic hypoxemia lead again to compensatory secondary erythrocytosis, changes in hemocoagulation and also in most of the body organs [5,9,10].

So, in ES, patients have complications resulting not only from the CHD and PAH but also from cyanosis and multisystemic dysfunction [9,10]. Therefore there are combined several risk factors for possible pulmonary arterial thrombosis (Fig. 1).

On the other hand, these patients often suffer from severe bleeding complications as well. Both these complications are the most common cause of "non-cardiac" death in ES, as frequently as in 20% [11].

The necessity or the appropriateness of anticoagulation therapy is often discussed and until now is not solved. In patients with PAH it is usually recommended [1] but in ES subgroup of patients the use of anticoagulation is a controversy [2,11–14], with no real benefit proven; also in the guidelines there is no expert consensus on this point. On the contrary, often secondary fatal bleeding complications with or without anticoagulation therapy are described.

Aims of the study

The aim of the study was to analyze patients with severe PAH due to CHD for the presence of pulmonary artery thrombosis and risk factors, as pulmonary arterial dilatation, and establishing possible correlations with cyanosis, secondary erythrocytosis and coagulation abnormalities. The aim was to define high-risk patients where anticoagulation therapy would be most profitable.

Patients

The patients analyzed were 40 patients with severe PAH due to CHD, 28 female (70%) and 12 male (30%), with median age 41.5 years (23–78 years). Age groups were as follows: there were 16 patients ≤ 40 years of age (40%), 17 patients between 40 and 60 years (42.5%) and 7 patients ≥ 60 years (17.5%).

23 patients (57.5%) had a simple shunt lesion (atrial septal defect, ventricular septal defect or persistent arterial duct) and 7 patients (17.5%) had a combined shunt and 10 patients (25%) a complex heart defect. Nine (22.5%) patients had a previous defect closure without a residual shunt. All patients had an invasively confirmed

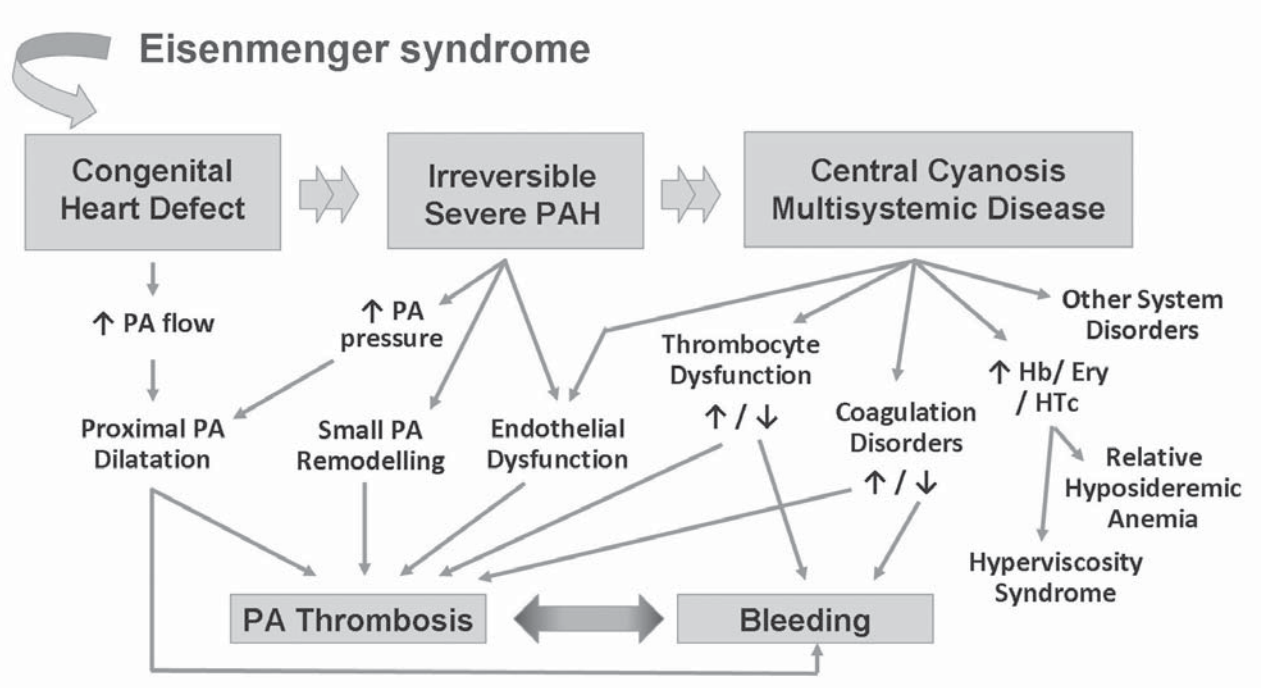

Fig. 1 – Complex pathological situations that can lead to pulmonary artery thrombosis and/or bleeding in patients with Eisenmenger syndrome.

severe PAH (mean pulmonary artery pressure > 45 mmHg; and systolic pulmonary pressure > 2/3 of systemic systolic arterial pressure).

Eight patients (20%) were not on anticoagulation therapy due to previously present major bleeding event; 9 patients (22.5%) were on full anticoagulation (desired INR 2–2.5) therapy due to other risk factors (as atrial fibrillation and/or previously reported thromboembolic event); and the other 23 patients (57.5%) were on low-dose anticoagulation (desired INR 1.8–2.0).

Methods

Patients were evaluated prospectively and partially retrospectively. Medical history, clinical status, laboratory and echocardiographic findings were evaluated in all patients; computer tomography (CT) or magnetic resonance imaging (MRI) was performed and analyzed in 23 patients (in some it was impossible due to their mental disability (Down syndrome), or due to their refusal or other technical problems.

Medical history was obtained from his/her health card and during personal interview. Objective clinical status was evaluated, dominantly signs of cyanosis and clubbing.

Routine laboratory evaluation of blood count and capillary oxygen saturation was performed. At specialized hematology laboratory a detailed analysis of hemocoagulation parameters, thrombocytes count, thrombocytes aggregation assessment and endothelial dysfunction evaluation was performed [15,16]. Platelet aggregation was investigated by light transmission aggregometry without stimulation (i.e. spontaneous aggregation), and after induction by arachidonic acid 0.5 mg/mL, adenosine diphosphate (ADP) 20 µmol/L, collagen 10 µmol/L, epinephrine 300 µmol/L and ristocetin 1.0 µmol/L, as well as after three concentrations of low-dose platelet inducers ADP (2 µmol/L, 1 µmol/L, 0.5 µmol/L) and epinephrine (10 µmol/L, 1 µmol/L, 0.5 µmol/L). All blood collections were carried out between 08:00 and 09:00 AM after an overnight fasting with minimal trauma from antecubital vein. The samples were treated immediately, at least up to 2 h after blood collection. Plasma von Willebrand factor (vWF) and plasminogen activator inhibitor type 1 (PAI-1) were used as indicators of endothelial dysfunction and/or damage. Plasma for blood coagulation and endothelial parameters were immediately separated by centrifugation and analyzed, or frozen at –80 °C until tested.

Echocardiography was performed with Philips iE33 ultrasound system or GE Vivid 7, both with digital archive system. The studies were obtained from standard projections; measurements of the main pulmonary artery (MPA) were taken from the parasternal short axis view; measured was 3 times and the mean value was taken. CT or MRI measurements of the main pulmonary artery were performed and the presence/absence of pulmonary artery thromboembolic finding was analyzed.

Statistical analysis

Continuous data are presented as median and range; nominal data as percentage. Statistical analysis was performed using Windows Microsoft Excel 2007 and software package JMP 5.0.1 (SAS Institute Inc., Cary, NC). Univariate analysis was performed to analyze correlation be-

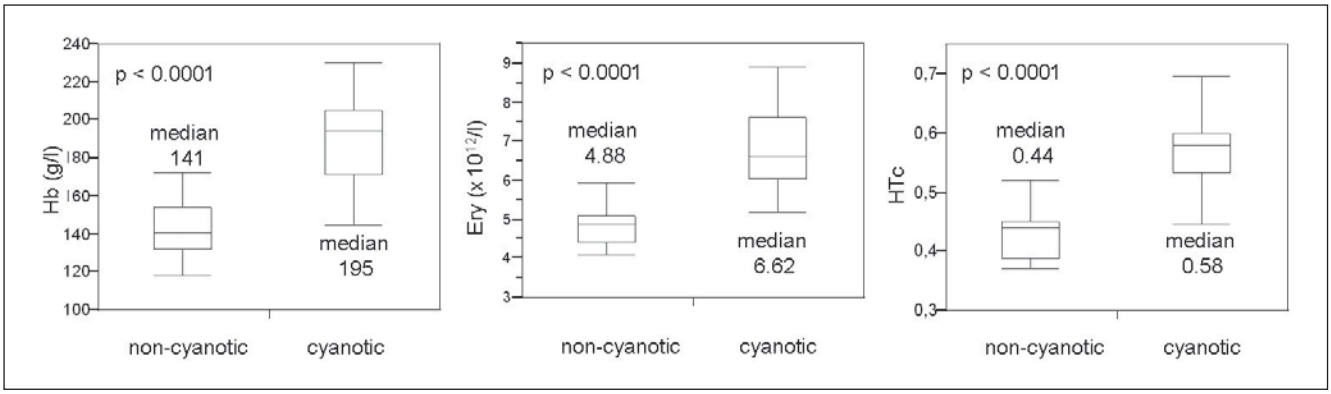

Fig. 2 – Laboratory findings – comparison of hemoglobin, erythrocytes and hematocrite in cyanotic versus non-cyanotic patients (Hb – hemoglobin, Ery – erythrocytes, HTc – hematocrite).

tween parameters. In case of continuous data T-test and non-parametric Wilcoxon test was used, in case of nominal data contingence tables. A *p*-value < 0.05 was considered significant.

Results

Anamnestic finding of previous pulmonary thromboembolic event (PTE), deep venous thrombosis or embolism (systemic – central nervous or other) was found in 7 patients (17.5%) – Table 1. In 7 patients (17.5%) lower extremities varicosity was found.

Clinically apparent cyanosis with clubbing and also laboratory finding of systemic hypoxemia (O_2 saturation < 90%) were present in 24 patients (60%).

The presence of PTE was significantly more frequently occurring in older patients (59 vs 40 years, $p = 0.0093$), where all PTEs were present after 40 years of age. PTEs were more frequent in female 21.4% vs 8.3% in male, though this was not statistically significant. Type of the congenital heart defect or the presence of cyanosis did not show statistical significant correlation with the presence of PTE.

Blood count showed increased red count levels: median hemoglobin (Hb) was in male 181 g/l (141–218) and in female 169 g/l (118–230), median erythrocyte (Ery) count in male 6.0 × 10^{12}/l (5–8.2), in female 5.6 × 10^{12}/l (4.1–8.9), with 21 patients (52.2%) with severely increased red blood count. Median hematocrite (Htc) was in male 0.55 (0.44–0.66) and in female 0.51 (0.37–0.73); with only 3 patients (7.5%) who had the hematocrite above 0.65. On the other hand, only in one of these patients (2.5%) a clinically marked hyperviscosity syndrome was present.

Table 1 – Thromboembolic events in our patients.

Anamnestic clinical event	No of pts.	(%)
• Pulmonary artery thrombo/embolism	3 pts.	(7.5%)
• Ischemic/embolic central nervous event	3 pts.	(7.5%)
• Deep venous thrombosis	3 pts.	(7.5%)
• Intracardiac (right atrial) thrombus	1 pt.	(2.5%)

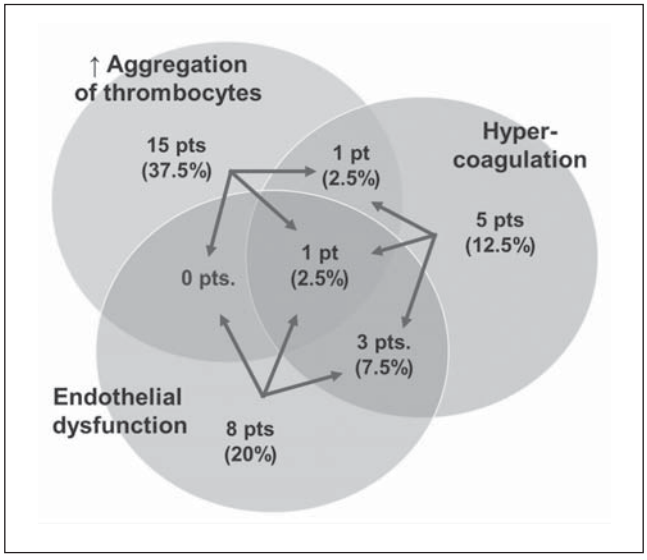

Fig. 3 – Presence of pathological laboratory findings (pts – patients).

There was a significant difference in cyanotic versus non-cyanotic patients in red count parameters (Fig. 2): median Hb 195 g/l (145–230) versus 141 g/l (118–173) ($p < 0.0001$), median Ery 6.62 × 10^{12}/l (5.19–8.9) versus 4.88 × 10^{12}/l (4.1–5.95) ($p < 0.0001$), median HTc 0.58 (0.45–0.73) versus 0.44 (0.37–0.52) ($p < 0.0001$).

Detailed hemocoagulation analysis showed increased risk for thrombosis (Fig. 3): (1) increased thrombocytes aggregation in 15 patients (37.5%), (2) hypercoagulation in 5 patients (12.5%) and (3) endothelial dysfunction in 8 patients (20%). At least one of these pathologies was present in 23 patients (57.5%), two combined pathologies in 4 patients (10%), and all three hemocoagulation abnormalities were found in 1 patient (2.5%). No correlation of laboratory increased risk of thrombosis and cyanosis or increased red blood count was found.

At least mild pulmonary artery dilatation (MPA > 25 mm) was found in all patients and the dilatation was progressive with age ($p = 0.04$). Severe MPA dilatation (> 40 mm in female and > 45 mm in male) (Fig. 4) was found in 19 patients (51.4%). While in patients < 40 years of age

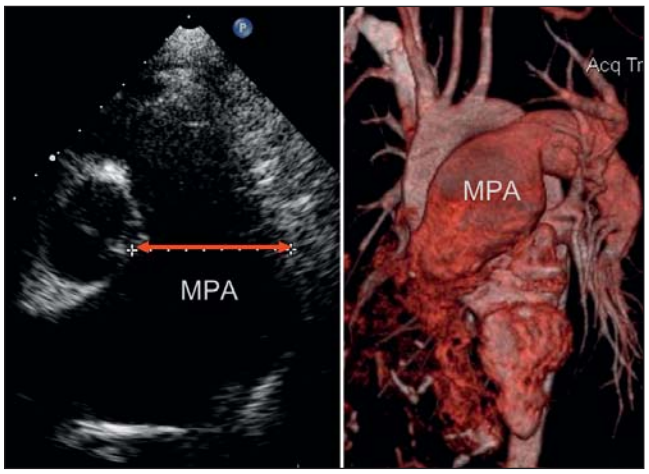

Fig. 4 – Echocardiographic and CT findings of severe central pulmonary artery dilatation (MPA – main pulmonary artery).

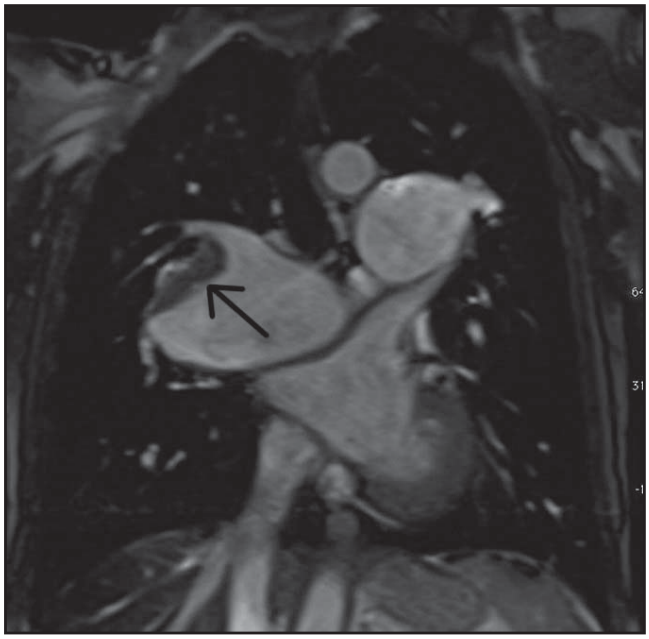

Fig. 5 – MRI finding of central pulmonary artery embolus in a patient with Eisenmenger syndrome.

only 26.7% had severe AP dilatation, in the age group 40–60 years it was 66.7% and > 60 years it was 71.4% of patients (p = 0.04). Sex or type of the congenital heart defect nor the presence of cyanosis did not correlate with MPA dilatation. CT or MRI signs of pulmonary thromboembolism were present in 3 patients (7.5%); previously known distal type embolus were present in 2 female patients (5%) and newly found asymptomatic proximal embolus in 1 male patient (2.5%) (Fig. 5).

When analyzing the risk factors for pulmonary thrombosis (MPA dilatation and hemocoagulation abnormalities) – at least one of these factors were found in 31 patients (77.5%), and both of these risk factors were present in 11 patients (27.5%). There was no correlation found between hemocoagulation abnormalities and/or MPA dilatation and the clinical presence of PTEs.

Discussion

The pathological and pathophysiological mechanisms leading to pulmonary artery thrombosis in severe PAH and Eisenmenger syndrome constitute a very complex problem, where more issues have to be taken into account, complicated even more by the fact that they may be combined together quite variably.

Isolated red component of the blood count showed typical increase in cyanotic compared to non-cyanotic patients. This was proving compensatory erythrocytosis that enables them best possible oxygen delivery in a general hypoxemic status. This fact has to be taken into account when dealing with a cyanotic patient. It seems to be an evident matter but sometimes it is not so obvious in everyday clinical practice, especially in some types of CHDs (as in persistent arterial duct where cyanosis is only the lower half of the body, or in atrial septal defects where clinical manifestation of desaturation sometimes occurs only after physical activity); or simply because a less experienced doctor is involved, so the cyanosis is missed and/or oxygen saturation is not established. So, while dealing with these patients, one always has to know what is the "normal", i.e. the usual hemoglobin level of such a patient; so as not to miss a serious, especially rapid fall in its level, for this may mean for a cyanotic patient a life-threatening situation (i.e. due to bleeding).

Laboratory pro-thrombotic findings may be represented by activated coagulation factors, increased thrombocytes aggregation and also by endothelial dysfunction (which is a risk factor for both arterial and venous thrombosis). At least one of these abnormalities was present in more than half of our patients (51.4%), but there were present combined abnormalities too (Fig. 3), increasing the potential risk for thrombosis even more.

Despite the presence of various hemocoagulation pathology (hypercoagulation and/or increased thrombocytes aggregation and/or endothelial dysfunction) in our patients there was no correlation with cyanosis and/or increased red cell blood count; and also no correlation with clinical manifestation of thrombosis was found.

On the other hand, these patients tend also to thrombocytopenia and/or thrombocytes dysfunction which may contribute to opposite types of problems as well – to more or less severe bleeding. This was also found in our patients though not included and presented in this study. It is therefore very important to be very careful when and how to propose anticoagulation therapy in these patients.

There was a surprisingly high incidence of increased thrombocytes aggregation found in our patients (37.5%) which is usually not described in literature and would need a further detailed hematological study. But when pathological thrombocytes aggregation is present, and especially isolated (which was up to 30% in our group) without any other clinical or laboratory pathology, it would then perhaps rationalize aspirin therapy instead of the use of warfarin. Though, no such proposal can be found in the literature so far. And, on the other hand, of course, aspirin might again cause an increased risk of bleeding complications, so these therapeutic considerations have to be evaluated very carefully.

Severe (even aneurysmatic) pulmonary artery dilatation represents a serious finding in patients with severe PAH, appears to be very frequent (in more than 50% of patients) and is progressive with age, as shown in our study. This dilatation is the result of the patient's hemodynamic situation (severe pulmonary pressure and flow overload). Other factors like pulmonary arterial wall morphological and functional changes and pathological blood flow patterns, as well as coagulation abnormalities most probably also play an important role. They are surely contributing to the increased risk of pulmonary artery thrombosis, but there is still very little information on the topic.

A relatively low incidence of clinically manifest thromboembolic events (especially newly developed) in our patients may be due to the anticoagulation strategy at our center (especially in patients with other indications for anticoagulation, as atrial fibrillation). On the other hand, of course, some silent pulmonary thromboembolic findings might have been missed in our study, as we were not able to perform CT and/or MRI in all patients, despite the fact that the central part of the pulmonary arteries was also well scanned by echocardiography and no thromboemboli were detected.

Despite the fact that we could not prove a significant correlation between the occurrence of clinical thromboembolic event and MPA dilatation or hemocoagulation abnormalities, we still consider these patients as a very high-risk group, especially when the above mentioned factors are combined. In the presence of pulmonary artery aneurysm (especially when giant) anticoagulation therapy may be perhaps indicated. On the other hand, it is extremely important to take into consideration any clinical presence of bleeding, especially hemoptysis or any laboratory pathology consistent with increased risk of bleeding complications, as these may be life-threatening for the patient. So it is necessary to be strictly individual.

Conclusions

Patients with severe PAH due to CHD, and especially Eisenmenger syndrome, represent a very high-risk group of patients for pulmonary artery thrombosis. These patients suffer from histo-morphological and functional pathology of distal small arterioles combined with severe proximal vessel dilatation due to pathological hemodynamic situation with extreme flow and pressure overload, even more often combined with secondary erythrocytosis and coagulation changes. On the other hand, these patients very often tend to major bleeding episodes as well. Both of these complications (thrombosis and bleeding) may be fatal for them. The question of anticoagulation therapy is therefore still open and has to be considered strictly individually; also taking into account all other accessory clinical findings (i.e. atrial fibrillation with the need of higher anticoagulation level or on the contrary, the presence of bleeding events where any treatment might be too risky). A special topic may represent a surprisingly high incidence of platelet hyperaggregability, as shown in our study. Especially when found without any other clinical or laboratory pathology it would perhaps propose that aspirin therapy could be considered in some highly selected patients with PAH and CHD. Further data though are needed to support this theory.

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