Anticoagulation in Pulmonary Arterial Hypertension: Do We Know the Answer?

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Abstract: The shear stress and hypoxia in the pulmonary artery in patients with pulmonary arterial hypertension(PAH) causes endothelial dysfunction, smooth muscle proliferation and activation of thrombotic pathways leading to in situ thrombosis. Targeting the thrombotic pathways is a proposed mechanism to slow disease progression and improve survival. Over the years, the survival in patients with PAH has improved due to multiple factors with the increased use of anticoagulation as one of them. Both European Respiratory Society/European Society of Cardiology and American College of Cardiology/American Heart Association guidelines make grade II recommendations for using anticoagulation in PAH. The guidelines are based on weak observational studies with high risk of bias which have only studied warfarin as the choice of anticoagulation. In this article, we review the pathophysiology, rationale and the current literature

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investigating the role of anticoagulation in PAH. (Curr Probl Cardiol 2021;46:100738.)

Introduction

Pulmonary hypertension (PH) is defined by an increase in mean pulmonary arterial pressure (mPAP) ≥25 mm Hg at rest via right heart catheterization (RHC) or suggested by an elevation of the tricuspid regurgitant (TR) velocity of more than 2.8 m/s via echocardiography with other supporting features.[1,2] According to the World Health Organization (WHO) clinical classification, PH is divided into 5 groups, group 1 Pulmonary arterial hypertension (PAH); group 2 due to left heart disease; group 3 due to hypoxia and/or lung disease; group 4 due to pulmonary artery obstruction; and group 5 due to unclear and/or multifactorial factors. PAH is hemodynamically defined as mPAP > 25 mm Hg, Pulmonary artery wedge pressure (PAWP) <15mm Hg and pulmonary vascular resistance (PVR) >3 wood units and can be seen in groups 1, 3, 4, and 5. Postcapillary PAH is defined as mPAP >25 mm Hg, PAWP >15 mm Hg and PVR >3 wood units, notably seen in groups 2 and 5.[2] However, a new hemodynamic definition of PH was proposed in the 6th World Symposium on Pulmonary Hypertension bringing the threshold down of mean PA pressure from >25 mm Hg to >20 mm Hg.

PAH includes idiopathic (IPAH), heritable (HPAH), and drug/toxin (DPAH) induced etiologies. associated pulmonary artery hypertension (APAH), includes various causes such as schistosomiasis, chronic hemolytic conditions such as sickle cell disease, hereditary spherocytosis, thalassemia, and stomatocytosis, Human immunodeficiency virus (HIV), portal hypertension, and congenital heart disease. PAH can also be associated with connective tissue disease (CTD-PAH).

The pathophysiology of PAH includes endothelial dysfunction, remodeling leading to proliferation of endothelial and smooth muscle cells and in situ thrombi. Contemporary therapies are directed at relaxing smooth muscle via the prostacyclin, cyclic GMP/Nitric oxide and endothelin receptor pathways. There is also increased action of procoagulant factors along with other proinflammatory, and antiapoptotic mediators.[3] Recognizing the role of the procoagulant pathway in patients with PAH and the potential benefits of systemic anticoagulation therapy has been a long standing area of uncertainty.

The American College of Cardiology/American Heart Association, and European Respiratory Society (ERS)/European Society of Cardiology (ESC) offer recommendations for systemic anticoagulation (AC).[4,5]

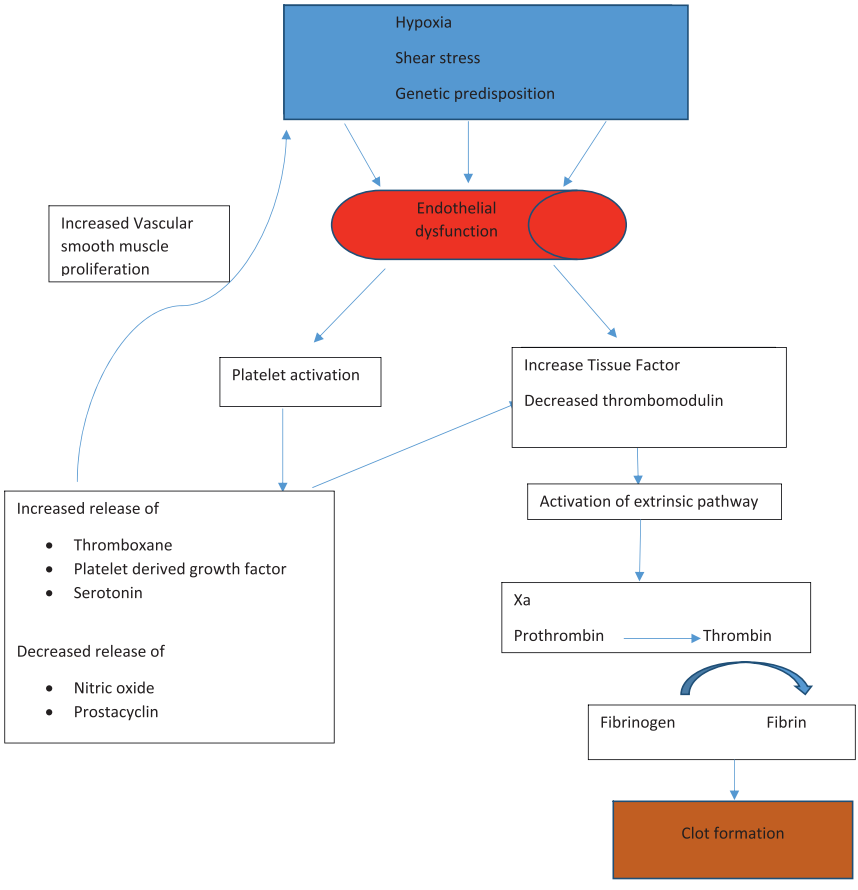

FIG 1. Proposed mechanism of increased thrombogenesis in pulmonary artery hypertension.

However, the strength of recommendations are moderate (class II) and based on limited data. We will aim to review the pathophysiology and rationale of systemic anticoagulation in PAH patients.

Thrombogenicity in PAH

It is unclear whether the hypercoagulable state noted in PAH is a cause or consequence. An autopsy series performed by the National Heart, Lung and Blood Institute in 1989 reported thrombi present in 33% of the 58 patients with IPAH.[6] There appears to be an abnormally high shear stress in the pulmonary vasculature in PAH secondary to excessive vasoconstriction leading to vascular remodeling and derangements in the

coagulation cascade and platelet function. There is a shift toward decreased fibrinolysis, increased clot formation, endothelium dysfunction, and platelet release of procoagulant, vasoactive, and mitogenic mediators (Fig 1).[7] Tissue factor (TF) which activates the extrinsic pathway is upregulated in diseased vessels, as shown in a 2007 paper by White et al.[8] TF production fluctuates with changes in blood flow and hypoxia, and can increase the production of factor Xa leading to thrombin and fibrin formation. In addition, fibrinolysis is inhibited by plasminogen activator inhibitor type I (PAI-1) which is upregulated in PAH patients. One study showed there were higher levels of PAI-1 in arterial blood suggesting an intrapulmonary presence of this enzyme.[7] Endothelial cells also overexpress von Willebrand Factor (vWF) and Endothelin-1.[9] Increased levels of vWF lead to a thrombogenic endothelial surface which in conjunction with shear stress can lead to thrombotic lesions.[10] Endothelin protein overexpression on the other hand leads to vasoconstriction and mitogenic effects by binding to pulmonary vascular smooth muscle cells leading to further vascular remodeling. Additionally, platelets also contribute to thrombogenesis by interacting with the injured endothelium within the arterial wall leading to their activation. They release serotonin, platelet derived growth factor, platelet activating factor, TGF-, and thromboxane A2. TXA2 has been shown to stimulate platelet aggregation promoting thrombogenesis.[11]

Review of Literature

A literature review was performed using PubMed to identify relevant articles through March 1, 2020 for studies evaluating the use of anticoagulation in PAH. We sought to identify Randomized Control Trials (RCTs), retrospective studies, systematic reviews and case series. A total of 14 studies from 1984 to 2018 were identified of which 10 were cohort studies, 3 systematic reviews and 1 case series (Table 1). *No RCT was identified*.

As early as 1984 Fuster et al[12] performed a retrospective chart review of 120 patients who were diagnosed with IPAH at Mayo Clinic from 1955 to 1977 and followed up to 1983. Mean age at diagnosis was 34 years with 73% females. Only 24 patients survived until 5 years with median time of death from the time of diagnosis being 1.9 years (range 6 months to 16 years). Around 57% of patients who underwent autopsy had evidence of pulmonary vascular thrombosis on autopsy. The major cause of death was right heart failure in 63% patients. There was improved 3-

TABLE 1. Cohort studies and systematic reviews of anticoagulant use in PAH

Article	Study design	Type of PAH (n)	Intervention	Background PAH therapy	Outcomes
Fuster et al (1984)[12]	Retrospective cohort	IPAH(n = 115)	Warfarin vs control (78 vs 37)	NA	Improved 3 year overall survival
Rich et al (1992)[13]	Prospective Cohort	IPAH(n = 64)	Warfarin vs control (35 vs 29)	CCBs	Improvement in survival at 1,3 and 5 years
Ogata et al (1993)[14]	Retrospective cohort	IPAH(n = 20)	Warfarin (+isoproterenol/ nifedipine) vs control(7 vs 13)	Isoprotrenol Nifedipine	Improved 5 year survival
Frank et al (1997)[15]	Retrospective cohort	Anorexigen PAH(n = 104) IPAH(n = 69)	Warfarin vs control Anorexigen PAH (56 vs 48) IPAH(24 vs 45)	NA	Improvement in survival (anorexigen PAH group) No difference in IPAH group
Roman et al (2002)[16]	Case Series	IPAH(n = 44)	NA	CCBs	Improvement in 5 patients on anticoagulation
Kawut et al (2005)[17]	Retrospective cohort	IPAH(n = 66) Familial PAH(n = 14) Anorexigen(n = 4)	Warfarin vs control (79 vs 5)	CCBs Bosentan Trepostinil Epoprostenol	Improved transplant free survival
Johnson et al (2006)[18]	Qualitative systematic review	IPAH(n = 488)	NA	NA	Anticoagulation maybe effective in PAH
Johnson et al (2012)[19]	Retrospective cohort	IPAH(n = 155) SSc-PAH(n = 275)	Warfarin vs control IPAH(33 vs 33) SSc-PAH(49 vs 49)	CCBs ER Antagonist	Low probability that warfarin improves

(*continued on next page*)

TABLE 1. (*continued*)

Article	Study design	Type of PAH (n)	Intervention	Background PAH therapy	Outcomes
				PDE inhibitor Prostaglandin analog	survival in SSc-PAH and IPAH
Ngian et al (2012)[20]	Prospective cohort	CTD-PAH(n = 117) SSc-PAH(n = 98)	Warfarin vs control (36 vs 81)	Bosentan (88%) Sildenafil (32%) Sitaxentan (15%) Inhaled Iloporst(13%)	Warfarin was found to be protective factor when administered with advanced PAH therapy.
Olsson et al (2014)[21]	Prospective cohort	IPAH(n = 800) Other types (n = 483)	Anticoagulants vs no anticoagulant IPAH(528 vs 272) SSc-PAH(104 vs 104)	ER Antagonist PDE inhibitor Prostaglandin analog	Improved survival benefit in IPAH. No survival benefit in SSc-PAH.
Preston et al (2014)[22]	Prospective cohort	IPAH(n = 288 SSc-PAH(n = 86)	Warfarin vs control IPAH(144 vs 144) SSc-PAH(43 vs 43)	ER antagonist PDE inhibitor Prostaglandin analog	No survival benefit in IPAH or SSc-PAH.
Caldeira et al (2014)[23]	Systematic Review	All types of PAH	NA	NA	31% decrease in mortality in anticoagulation group.
Ascha et al (2017)[24]	Prospective cohort	All types of PAH IPAH(n = 425) SSc-PAH(n = 100) Other types (n = 335)	Warfarin vs control 590 vs 270	Trepostinil	No significant effect on survival in type of PAH.
Khan et al (2018)[25]	Systematic Review	All types of PAH	NA	NA	Improved survival in IPAH group and worsening survival in SSc-PAH

CCB, calcium channel blockers; CTD-PAH, connective tissue disease-related pulmonary artery hypertension; ER, endothelin receptor antagonist; IPAH, idiopathic pulmonary artery hypertension; NA, not applicable; PDE, phosphodiesterase; SSc-PAH, systemic sclerosis-related pulmonary artery hypertension.

year survival in patients who had received AC vs who had not ($P < 0.02$).

In 1992, Rich et al[13] performed the first prospective cohort study which included 64 patient with IPAH referred to University of Illinois between July 1985 and March 1991 with follow up until October 1991. Thirty-five of the 64 patients received warfarin after a nuclear perfusion scan showed nonuniform pulmonary blood flow. After controlling for baseline hemodynamic variables and response to calcium channel blockers (CCBs), survival was better in those treated with warfarin ($P < 0.025$). Significant improvement in survival at 1, 3, and 5 years was seen for patients who did not respond to CCBs.

In 1993, Ogata et al[14] reported a study of 20 IPAH patients of which 7 were treated with warfarin in conjunction with vasodilator therapy (Isoproterenol or nifedipine) vs 13 who were not. There was an improved survival in patients on AC in patients with IPAH over 5 years ($P < 0.025$). However, the primary endpoint of the study was to assess the effect of vasodilator therapy plus warfarin and not warfarin alone, suggesting confounding bias.

Frank et al[15] published the first study evaluating use of AC in anorexigen induced PAH along with IPAH. A total of 56 patients (87% females) in anorexigen PAH and 24 (70% females) in IPAH group were anticoagulated. The study had a long follow up showing improved 5(63% vs 38%) and 10 years (39% vs 20%) survival in anorexigen induced PAH especially for those started on warfarin within 2 years of symptom onset. Cause of death in majority of the patients was right heart failure and there were no adverse effects to warfarin. Roman et al[16] in 2002 reported a retrospective case series of 44 patients in Spain where 5 patients reported improvement after use of warfarin and CCBs.

In another retrospective cohort review by Kawut et al,[17] evaluating 84 patients over 6 months in 1994, of which 66 had IPAH, 14 HPAH, and 4 had anorexigen related PAH. Sixty-eight (81%) patients were females with a mean age of 42 years. Seventy-nine patients were treated with warfarin. Multivariate analysis indicated association of warfarin use with increased transplant free survival ($P < 0.05$). The most common documented contraindication to be a history of gastrointestinal bleeding which was seen in 16 patients.

Ngian et al[20], evaluated 117 patients across 6 PAH centers in Australia of which 86(84%) had systemic sclerosis-related PAH (SSc-PAH). The mean age of study participants was 62 years with 105 (90%) females. Seventy-five percent of the patients belonged to functional class NYHA III. All patients were on specific PAH therapy with only 36 receiving

TABLE 2. Recommendation for anticoagulation in pulmonary arterial hypertension

	ACC guidelines[4] and updated algorithm from Fifth WSFP, Nice[27]		ESC and ERS guidelines[5]	
PAH etiology	Class of recommendation[a]/ level of evidence[b]	Target INR	Class of recommendation[a]/ level of evidence[b]	Target INR
Idiopathic	IIa/C	1.5-2.5	IIb/C	2.0-3.0
Heritable	IIa/C		IIb/C	
Anorexigens	IIa/C		IIb/C	
APAH Connective tissue disease	IIb/C		IIb/C	
HIV			III/C	
Portal hypertension			III/C	

ACC, American College of Cardiology; APAH, associated pulmonary hypertension; ESC, European society of cardiology; ERS, European respiratory society; HIV, human immunodeficiency virus; INR, International normalized ratio; PAH, Pulmonary artery hypertension; WSPH, World symposium on Pulmonary Hypertension.

aClasses of recommendations: I = Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; II = Conflicting evidence and/or a divergence of opinion about usefulness/efficacy of the given treatment or procedure; IIa = Weight of evidence/ opinion is in favor of usefulness/efficacy; IIb = Usefulness/efficacy is less well established by evidence/opinion; III = Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

bLevel of evidence: A = data derived from multiple randomized control trials or meta-analysis; B = data derived from a single randomized clinical trial or large nonrandomized studies; C = consensus of opinion of experts and/or small studies, retrospective studies, or registries.

warfarin. On multivariate analysis warfarin was associated with improved survival along with specific PAH therapy. ($P < 0.02$)

In 2014, Olsson et al[21] evaluated the effect of AC in 1283 patients of the COMPERA registry in which 41 PH centers across 7 European countries were participating. IPAH group had 800 participants of which 528 (66%) were anticoagulated and the CTD-PAH group had 483 patients of which 210(43%) patients received AC. The median age of all PAH patients was 68 years and 64 % of them were females. In the IPAH group, initial PAH medications were comparable in both the groups but combination therapies were used more frequently in AC group. The survival was significantly higher at 1,2 and 3 years in the group which was anticoagulated ($P = 0.017$) in IPAH but not significant in the CTD-PAH group.

In 2015, Preston et al[22] evaluated the effect of AC in 288 patients with IPAH and 86 patients with SSc-PAH as a part of REVEAL registry which was based out of 51 institutions in United States. No significant survival advantage in the IPAH group was seen. ($P = 0.17$). In the SSc-PAH group unadjusted analysis showed decreased survival in AC group ($P = 0.03$)

but when adjusted for REVEAL registry risk score, there was no significant difference ($P = 0.15$). Interestingly almost two thirds of patients had discontinued warfarin (65.3% and 62.8% for IPAH and SSc group, respectively) before the last assessment.

Discussion

Despite the improved survival and advances in pharmacologic therapies and the development of specialized PH centers, PAH remains a very deleterious condition that can result in significant multiorgan failure and mortality. PAH is a disease with complex pathophysiology in an extremely heterogeneous population.[26] Increased thrombogenesis plays an important role in the pathogenesis of PAH, thereby suggesting anticoagulation in PAH is warranted.[7,10] Both European and American societies recommend anticoagulation in PAH but at best as a consideration because of the limited quality of evidence (Table 2). All 3 systematic reviews suggest that use of anticoagulation in IPAH likely favors survival.[18,23,25] Conversely, Khan et al note increasing mortality in patients with SSc-PAH. Studies to date were of low quality because of suboptimal study design, small sample size and introduce the high risk of bias. No RCTs have been done so far. The lack of RCTs creates difficulty establishing a strong recommendation for or against it.

Anticoagulation is not devoid of harm particularly in patients with PAH who have limited cardiopulmonary reserve. Bleeding event rates were 5.4 per 100 patient-years for patients with IPAH, 19 per 100 patient-years for CTD-PAH who were treated with warfarin.[28] Notably, there are known interactions of warfarin with other anti-PAH treatment modalities. Endothelin receptor antagonists (ERAs) interfere with CYP2C9, hence increasing warfarin levels. Also ERAs have been linked with anemia as an adverse effect thereby making anticoagulation in these patients a challenge.[29] Sitaxsentan was withdrawn from the market after reports of drug induced liver injury and bleeding diathesis.[30] Prostacyclin

TABLE 3. Take home message

- Thrombotic pathway could be a potential target in PAH therapy.
- Recommendations for anticoagulation in PAH are based on weak evidence from observational studies.
- Well-designed RCT is needed to answer questions surrounding this treatment modality but there are many barriers.
- Clinicians should weigh risk and benefits of anticoagulation in this high risk population on a case by case basis.

analogues have been shown to cause abnormal platelet function and thrombocytopenia.[31,32] Ogawa et al reported increased risk of alveolar hemorrhage in patients with PAH on chronic epoprostenol therapy and warfarin.[33] High discontinuation rates of anticoagulation in the REVEAL registry also point towards poor tolerance to anticoagulation in PAH patients.

Future Directions

PAH treatment has made major advancements in the last 2 decades with the approval of multiple medications targeting different pathways. The 1-year mortality has improved from ~32% in 1987 to ~ 15% in 2010 but it still continues to be high.[34,35] As we are developing new therapies for PAH targeting the prostacyclin, endothelin, and nitric oxide pathway, one other potential target could include the thrombotic pathway. Unfortunately, studies showing survival benefit of anticoagulation in PAH are observational studies with most of them conducted in 1980s and 90s when advanced PAH therapies were not available.

Well-developed RCTs are needed to answer questions surrounding this treatment modality in PAH but there are many barriers (Table 3). Major barriers include (1) heterogeneous phenotype of PAH patients; (2) inability to use survival as an end point because of rarity of the disease and high mortality; (3) finding adequate surrogate end point for survival.[36,37] Currently to the authors' knowledge no randomized control clinical trials are being conducted to specifically to study the effect of anticoagulation on PAH. Atrial fibrillation, a well-known risk factor for thromboembolic events such as stroke, has led to development of $CHA2DVASc_2$ score to help guide the physicians to prescribe anticoagulation.[38] Hopefully, one day after sifting through the complexities and heterogeneous populations of PAH a similar score can be developed.

In conclusion, the recommendation of anticoagulation in PAH is based on a limited body of evidence which mostly evaluated use of warfarin. We hope to ignite an interest in the development of well-conducted RCT including traditional Vitamin K antagonist and direct oral anticoagulants that can answer the questions of the contemporary role of systemic anticoagulation in PAH and which patients will derive benefit or unfortunately incur harm in this very heterogeneous population. At the present time, however, clinicians need to weigh the relative risks of thrombosis vs bleeding to make individual decisions on warfarin vs off-label use of other agents in these relatively high-risk patients.

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