

Idiopathic pulmonary fibrosis co-morbidity: thromboembolic disease and coronary artery disease

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Abstract Over the past decade, it has been increasingly recognized that patients with idiopathic pulmonary fibrosis (IPF) are at risk of both venous thromboembolic disease (VTE) and coronary artery disease (CAD). When present, these co-morbid conditions negatively affect outcomes. For this disease without effective therapy to improve survival, increased diagnosis and treatment of these co-morbid processes may improve outcomes. Better understanding of the mechanisms that place IPF patients at increased risk of VTE and CAD may also ultimately lead to novel therapeutic interventions.

Keywords Idiopathic pulmonary fibrosis · Pulmonary fibrosis · Venous thromboembolism · Thromboembolic disease · Pulmonary embolism, deep venous thrombosis · Coronary artery disease · Atherosclerosis · Epidemiology

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial lung disease of unknown etiology that primarily affects older individuals [1, 2•]. To date, no therapy other than lung transplantation has been proven effective for lengthening survival of IPF patients [2•].

Over the last decade, researchers have become increasingly aware that both venous thromboembolic disease (VTE) and coronary artery disease (CAD) are common in patients with IPF and may significantly affect survival [3, 4]. It is hypothesized that the occurrence of VTE and CAD in IPF results from the aberrant wound-healing and pro-fibrotic mechanisms underpinning the development of pulmonary fibrosis.

Our understanding of the pathogenesis of IPF has evolved; once regarded as a chronic inflammatory state, IPF is now believed to be a disease of abnormal wound healing [2•]. In normal wound healing, coagulation and fibrinolysis cascades are activated in a tightly regulated manner to promote repair via the formation and timely degradation of fibrin and fibrin clots. Increasing evidence suggests that during the aberrant wound healing process in IPF, the alveolar space becomes pro-coagulant and anti-fibrinolytic, leading to the persistent deposition of fibrin and fibrin clots, worsening fibrosis, and increasing the risk of thromboembolic disease. Besides hypoxia and other physiological disorders, increased

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circulating cytokines and growth factors may accelerate atherosclerotic disease in patients with IPF. Herein, we examine the hypothesized mechanisms for, and review the data regarding, the increased risk of VTE and CAD reported for patients with IPF.

Epidemiological and clinical evidence: the association between IPF and VTE

Several epidemiological studies have found an increased risk of VTE among patients with IPF. This association has been reported before and after diagnosis of IPF, at the time of death, and in the post-transplant period.

Using a longitudinal primary care database from the UK, Hubbard et al. [5] conducted a case-control study and cohort analysis to assess the risk of cardiovascular outcomes, including deep venous thrombosis (DVT), both before and after diagnosis of IPF. A total of 920 index cases of IPF were compared with 3,592 age and community-matched controls; those with IPF were twice as likely as controls to have had a diagnosis of DVT before their diagnosis of IPF (2 % vs. 1 %; odds ratio (OR)=1.98; 95 % confidence interval (CI)=1.13–3.48). Results of the cohort analysis revealed that, compared with controls, IPF subjects had an even larger risk of DVT after diagnosis of IPF; the incidence of DVT was 5.9 per 1,000 person-years within approximately the first three years of diagnosis of IPF, versus 2.1 per 1,000 person-years for controls (relative risk (RR)=3.39; 95 % CI=1.57–7.28).

Sode et al. [6] analyzed 7.4 million records from a Danish patient registry to assess the association between VTE, diagnosed at any time during a patient's history, and incident idiopathic interstitial pneumonias (IIPs), including IPF. They found that patients with a history of VTE had a significantly increased risk of developing IIP; the age-standardized incidence of IIP was 0.70 per 10,000 person-years for those without VTE, compared with 1.60 per 10,000 person-years for those with a history of VTE (RR=1.8; 95 % CI=1.7–1.9), 2.49 per 10,000 person-years for those with a history of pulmonary embolism (PE) (RR=2.5; 95 % CI=2.4–2.7), and 1.08 per 10,000 person-years for those with a history of DVT (RR=1.3; 95 % CI=1.2–1.4). Similarly to Hubbard et al. these researchers found that VTE events occurred both before and after diagnosis of IIP. Regarding VTE events before diagnosis of IIP, Sode et al. hypothesized that perhaps subclinical ILD was present at the time of the VTE or, alternatively (but in our opinion less probably), that an undiagnosed pro-coagulant state resulted in chronic, clinically unnoticed pulmonary emboli leading to progressive lung fibrosis.

Given these results [5, 6], our group attempted [7•] to determine the prevalence of VTE at the time of death for IPF patients, and to compare it with the general population (those dying of causes other than IPF) and with people dying

of lung cancer or COPD—two populations previously identified as having underlying pro-coagulant states [8, 9]. By analyzing death certificate data in the US from 1992 through 2007 (in total, approximately 47 million records), we found that the risk of VTE at the time of death from IPF was higher than that for the background population (OR=1.34; 95 % CI=1.29–1.38) and, surprisingly, that the risk of VTE associated with IPF was higher than that for either COPD (OR=1.44; 95 % CI=1.39–1.49) or lung cancer (OR=1.54; 95 % CI=1.49–1.59). Further, the VTE in IPF seemed to be clinically significant: those with VTE and IPF died at a younger age than those with IPF alone. The results were the same regardless of gender: both men and women with VTE and IPF died at younger ages than comparators with lone IPF (men: 72.0 versus 74.4 years, $p < 0.0001$; women: 74.3 versus 77.4 years, $p < 0.0001$).

Additional data suggest patients with IPF may be at higher risk than other groups for VTE after lung transplant. Nathan et al. performed a retrospective analysis of 72 lung transplant recipients at a tertiary center lung transplant program [10]. All of the patients with a symptomatic post-transplant PE had a diagnosis of IPF (six of 23 patients (27 %) versus 0 % of all other transplant recipients, $p < 0.001$). Similar findings were reported for patients receiving transplants at a European center between 1999 and 2009: of 280 patients undergoing lung transplantation, all five cases of PE were in those undergoing transplant for IPF (1.78 %) [11].

Overview of the coagulation cascade and fibrinolysis

To better understand the function of the coagulation cascade and fibrinolysis in IPF, a brief overview of these pathways is provided. Activation of the coagulation cascade results in a sequence of proteolytic steps, which ultimately lead to the generation of fibrin and cross-linked fibrin. After tissue injury, the coagulation cascade is activated via the extrinsic pathway (Fig. 1). When tissue factor (TF), which is normally expressed on non-vascular or activated endothelial cells, is exposed to plasma-derived coagulation proteins via vascular injury, it binds to coagulation factor VII (FVII), forming the TF/FVIIa complex. The TF/FVIIa complex then activates factors X (FXa) (and the “common” pathway) and IX (FIXa) (part of the intrinsic pathway of coagulation). FXa and activated factor V (FVa) then catalyze the conversion of prothrombin to thrombin, which in turn catalyzes the conversion of fibrinogen to fibrin. Fibrin is ultimately covalently cross-linked via activated factor XIII (FXIIIa). Thrombin, like the TF/FVIIa complex, can assist the clotting process via the intrinsic pathway by activating factors IX and VIII [12, 13].

Activation of anticoagulation factors occurs coincidentally with activation of coagulation factors; this limits both the temporal and spatial scope of the coagulation cascade. The

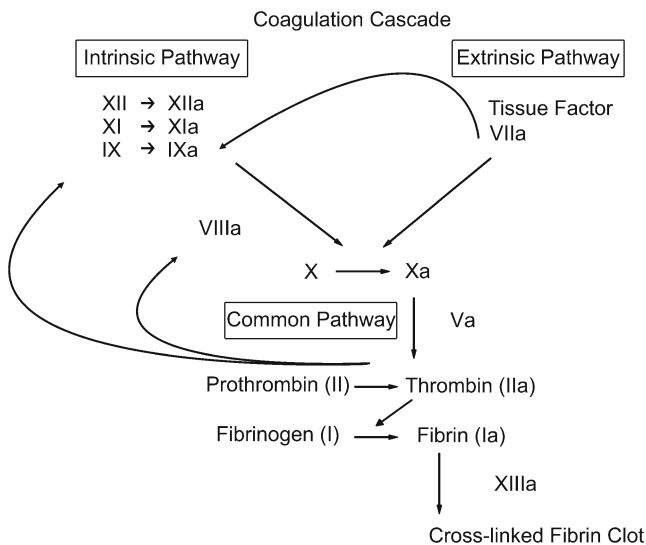


Fig. 1 Overview of the coagulation cascade. In idiopathic pulmonary fibrosis, evidence suggests that tissue factor is up-regulated, thereby activating the extrinsic pathway of the coagulation cascade and ultimately resulting in fibrin and cross-linked fibrin clot. Once this pathway is activated, there are several positive feedback mechanisms whereby the intrinsic pathway also becomes activated. (Adapted from [13])

primary inhibitor of the extrinsic pathway is tissue factor pathway inhibitor (TFPI), which acts on the TF/FVIIa complex. Antithrombin III (ATIII) acts on thrombin and inhibits conversion of fibrinogen to fibrin. Thrombin ultimately activates the vitamin K-dependent anticoagulant, activated protein C, which inhibits both FVa and FVIIIa [12, 13] (Fig. 2).

As fibrin and cross-linked fibrin clots form, the fibrinolysis pathway is activated with the objective of dissolving the thrombus (Fig. 3). Plasmin is derived from the proteolytic cleavage of the zymogen plasminogen by the two primary

plasminogen activators: tissue type (tPA) and urokinase type (uPA). tPA is the primary activator in the intravascular space, whereas uPA acts primarily in the extravascular environment, including the parenchyma and alveolar space of the lung. The primary function of plasmin is cleaving cross-linked, insoluble fibrin polymers, rendering them soluble [12–14].

The fibrinolytic system, like the anticoagulation system, is tightly regulated; inhibitors of this system include plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2, respectively). PAI-1, the main inhibitor of the two, is secreted from smooth muscle, endothelium and liver, and inhibits the formation of plasmin (and therefore fibrinolysis). Both α 2-antiplasmin (A2PI) and thrombin-activatable fibrinolysis inhibitor (TAFI) inhibit fibrinolysis via inhibition of plasmin [12, 13] (Fig. 3).

Mechanism of disease: evidence of activation of the coagulation cascade in IPF

Several important studies have revealed evidence of coagulation abnormalities as a causative explanation for alveolar fibrin deposition in patients with interstitial lung disease (ILD), and specifically in patients with IPF. These abnormalities at the alveolar level may ultimately result in the increased risk of VTE reported from epidemiological studies.

Evidence of activation of extrinsic arm of the coagulation pathway

TF does not seem to be expressed in normal lung tissue, but it does seem to be up-regulated in IPF [15, 16]. Imokawa et al.

Fig. 2 Inhibitors of the coagulation cascade. Once the coagulation pathway is activated, several anticoagulation factors are activated to limit coagulation, including tissue factor pathway inhibitor, activated protein C, and antithrombin III. (Adapted from [13])

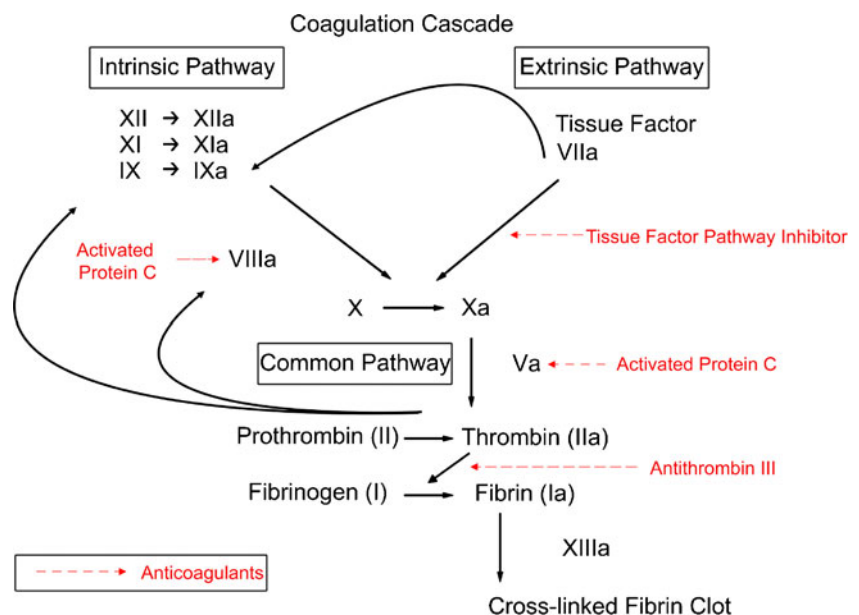
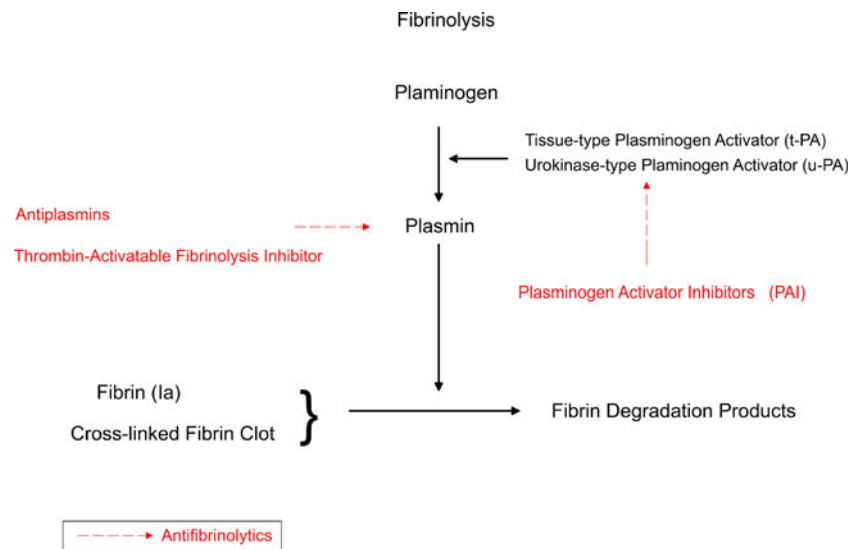


Fig. 3 Overview of fibrinolysis. In the alveolar space and lung parenchyma, urokinase-type plasminogen activator cleaves plasminogen to form plasmin, which then cleaves fibrin. Inhibitors of fibrinolysis include plasminogen activator inhibitors, antiplasmins, and thrombin-activatable fibrinolysis inhibitor, which thereby favor fibrin and clot persistence. (Adapted from [13])



[15] conducted a series of experiments on lung tissue from patients with IPF and other ILDs, including systemic sclerosis associated-ILD (SS-ILD) and cryptogenic organizing pneumonia (COP). By use of immunohistochemical staining of lung tissue from patients with IPF, these researchers identified TF antigens in type II pneumocytes lining the alveolar septa, cuboidal epithelial cells covering the fibroblastic foci, squamous metaplastic cells located in honeycomb cysts, and in some alveolar macrophages, whereas fibrin antigen seemed to localize primarily to the type II pneumocytes (and adjacent areas). Interestingly, similar staining patterns were identified in lungs from patients with either SS-ILD or COP. These findings suggest that the extrinsic pathway of the coagulation system is activated in ILD, but this may be a response to generic lung injury, rather than a mechanism specific to IPF. Fujii et al. found that more advanced IPF (defined by a PaO₂ of <55 torr while breathing room air, or a vital capacity of <50 % predicted) was associated with higher levels of TF in the lung, suggesting that activation of the coagulation cascade reflects IPF progression [16].

Evidence of a pro-coagulant state

These findings led to additional studies to determine if activation of the coagulation cascade in IPF was met with a parallel increase in natural anticoagulation activity or if there was an imbalance between the two, resulting in a hypercoagulable state (Fig. 2). Although tissue factor pathway inhibitor (TFPI) levels in lavage fluid are higher for IPF patients than for controls, suggesting greater anticoagulant activity in IPF, results from BAL fluid from IPF patients suggest a persistent pro-coagulant state within IPF lungs [16–18].

Evidence of a relative reduction in fibrinolysis

In addition to evidence of a pro-coagulant state in the IPF lung, the fibrinolysis pathway may be down-regulated (or at least not up-regulated proportionally to the increases in procoagulant activity), resulting in persistent fibrin deposition. Like other investigators, Gunther et al. found increased pro-coagulant activity in BAL fluid from IPF (and from other ILDs, including sarcoidosis and hypersensitivity pneumonitis). However, they went on to reveal that fibrinolysis activity in BAL was the same for ILD patients and for controls, suggesting that the increase in pro-coagulant activity may not be met with a parallel increase in fibrinolysis and may result in a state that favors the persistence of fibrin [17]. Levels of u-PA and PAI-1 were reduced, and levels of α 2-antiplasmin were increased, in those with ILD compared with controls, implicating aberrancies in particular components, rather than the entirety, of the fibrinolysis pathway (Fig. 3). These findings, like the increase in procoagulant activity, do not seem to be specific to IPF, but they may be more pronounced for patients with more severe ILD.

Anticoagulation treatment trials

On the basis of the epidemiological and basic science data, two randomized trials of systemic anticoagulation therapy were conducted on subjects with IPF.

Kubo et al. [19] conducted a study of 56 subjects with IPF who were randomized to receive either oral prednisolone alone (the non-anticoagulation group) or prednisolone and oral warfarin (the anticoagulation group) at a dose to maintain the INR between 2.0 and 3.0. If subjects in the anticoagulation group were hospitalized for any reason during the study, warfarin was withheld and low-molecular weight heparin

(intravenous dalteparin) was given for one to two weeks. The primary outcomes were re-hospitalization and survival.

There was no difference in re-hospitalization between the non-anticoagulation and the anticoagulation groups (67 % versus 57 %, respectively; $p=0.6$), and an acute exacerbation of IPF was the most frequent cause of re-hospitalization for both groups (72 % versus 73 %, respectively). However, the mortality from acute exacerbation was higher for the non-anticoagulation group (71 % versus 18 %; $p=0.008$). These investigators concluded that combined therapy of prednisolone and anticoagulation improved survival compared with prednisolone alone, and suggested that this may be a new strategy for treating IPF patients.

Later, Noth et al. [20••] conducted a National Institutes of Health (NIH)-sponsored trial to determine the effectiveness of anticoagulation against progressive IPF (ACE-IPF trial). This double-blinded, randomized, placebo-controlled trial of warfarin had enrolled 72 patients in the warfarin group and 73 patients in the placebo group when an unscheduled interim analysis was conducted because of excess mortality in the warfarin group. Use of warfarin for progressive IPF was associated with an increase in mortality compared with placebo (adjusted hazard ratio, 4.85; 95 % CI=1.38–16.99). Mortality in the warfarin group ($n=14$) was attributed to either respiratory causes ($n=11$), including IPF progression, respiratory failure, or pneumonia, or to cardiac causes ($n=3$), including myocardial infarction or sudden deaths; it was not attributed to bleeding. The investigators speculated that respiratory deaths may have been the result of undiagnosed alveolar hemorrhage (although INR safety data revealed no values outside the target range), unexpected detrimental effects of inhibiting factors II, VII, IX, and X (the vitamin K-dependent warfarin targets), or loss of the beneficial effects of other vitamin K-dependent proteins on inflammation and remodeling. Contrasting results between this study and the study by Kubo et al. may be attributed to differences in the anticoagulant used. Kubo et al. had subjects switched to heparin during hospitalization; heparin increases ATIII, thus reducing thrombin and factor Xa—factors which have been revealed to signal pro-inflammatory and pro-fibrotic responses [13, 21, 22].

Epidemiological and clinical evidence: the association between IPF and CAD

The association between IPF and CAD has been increasingly recognized. In the study by Hubbard et al. described above, IPF was associated with an increased risk of acute coronary syndrome (OR=1.53; 95 % CI=1.15–2.03) and angina (OR=1.84; 95 % CI=1.48–2.29) before diagnosis, and with acute coronary syndrome after diagnosis (OR=3.14; 95 % CI=2.02–4.87) [5].

Several investigators have examined the risk of CAD for IPF patients at the time of lung transplantation. Kizer et al. [23] conducted a cross-sectional study of 630 patients referred for lung transplantation and found a strong association between fibrotic lung diseases—including IPF—and CAD, after adjusting for multiple coronary risk factors. Compared with patients with other indications for lung transplantation, including chronic obstructive pulmonary disease, patients with lung fibrosis had an increased risk for any form of CAD (OR=2.18; 95 % CI=1.17–4.06) and for multi-vessel CAD (OR=4.16; 95 % CI=1.46–11.9).

Two additional studies confirmed these findings. Izbicki et al. [24] assessed the prevalence of CAD among 49 patients with pulmonary fibrosis and 51 patients with emphysema undergoing pre-transplant angiography. Despite the finding that nearly all patients with emphysema were heavy smokers, compared with 31 % heavy smokers among the subjects with lung fibrosis, CAD—defined by at least 50 % stenosis of a coronary artery—was far more common among patients with pulmonary fibrosis (28.6 % vs. 9.8 % of patients with emphysema, $p=0.019$). Nathan et al. [25•] conducted a similar study to determine the risk of CAD for IPF compared with COPD transplant candidates. Assessing CAD status by means of left cardiac catheterization, these researchers found a higher prevalence of CAD among patients with IPF (65.8 %) than with COPD (46.1 %) ($p<0.028$), and a higher prevalence of unsuspected significant CAD among those with IPF (18 % in IPF vs. 10.9 % in COPD, $p<0.004$). The presence of CAD negatively affected outcome: patients with IPF and CAD had higher mortality than patients with IPF alone.

Mechanism of disease

The reasons for the apparent association between IPF and CAD are unknown. However, several hypotheses have been suggested to explain the association:

- 1) common agents and/or exposures give rise to both disease processes;
- 2) an underlying (genetic) predisposition for inflammation and/or fibrosis results in concurrent conditions; and/or
- 3) elevated levels of pro-fibrotic mediators in the lung micro-environment of IPF lead to accelerated atherosclerosis [23].

The first two hypotheses have been regarded as less probable, given the different prevalence of CAD and IPF (i.e. most patients with CAD do not develop IPF) and the results from histopathological and cytokine profile studies that reveal these two disease processes to be distinct [23, 26, 27].

The third hypothesis is regarded as more probable [23, 25•]. Although IPF is regarded as a “lung limited disease,”

increases in both circulating cytokines (e.g., IL-8) [28] and growth factors (e.g., hepatocyte growth factor) [29] have been observed in the sera of patients with IPF, and some of these factors have also been revealed to be involved in pathogenesis of atherosclerosis [26, 30, 31]. Furthermore, hypoxia, which is often encountered in IPF, seems to result in oxidative stress that accelerates atherosclerosis [25•, 32].

Clinical relevance

We maintain a low threshold for evaluating for the presence of clinically-relevant CAD in our patients with IPF. For IPF patients with increasing dyspnea that cannot be attributed to IPF progression, we readily consider the possibility that ischemic coronary disease is contributing. Given the epidemiological and clinical data above, we maintain a high awareness of the possibility of VTE in all patients with IPF, particularly those with acutely worsening or progressive breathlessness. For IPF patients with an acute exacerbation, we usually rule out PE by use of computed tomographic angiography, in accordance with currently accepted guidelines [33]. When VTE is identified, we treat in accordance with current VTE treatment guidelines [3]. Given the results of the study by Noth et al. [20•], we advise against the use of empirical anticoagulation with warfarin.

Conclusion

IPF is associated with an increased risk of both VTE and CAD; treatable conditions that negatively affect outcomes for these patients. Further investigation of the abnormalities in the coagulation and fibrinolysis pathways, and their function in fibrosis and in the association between IPF and CAD, may ultimately yield novel therapy for this condition which, to date, has no known pharmacological treatment.

Compliance with ethics guidelines

Conflict of interest David B. Sprunger declares that he has no conflict of interest.

Evans R. Fernandez-Perez declares that he has no conflict of interest.

Amy L. Olson declares that she has no conflict of interest.

Jeffrey J. Swigris is a paid consultant for Boehringer Ingelheim, Genentech/Roche, Intermune, and UCB. His institution receives money through a grant from Intermune, and he receives reimbursement for travel/accommodations expenses from Boehringer Ingelheim.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by the authors.

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- Of major importance

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