

Pulmonary hypertension associated with antiphospholipid antibody: Call for a screening tool?

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Summary

Antiphospholipid (aPL) antibodies are antibodies specific for anionic phospholipids. They are immunoglobulins that attack phospholipids, phospholipid-binding proteins, or phospholipid-protein complexes and are detected in anticardiolipin and lupus anticoagulant assays. aPL antibodies are often associated with antiphospholipid syndrome (APS) which can be idiopathic or from secondary causes such as systemic lupus erythematosus (SLE), infection or drugs. They have also been shown to be associated with Pulmonary Hypertension. We conducted a review of the literature that included all articles on PubMed with keywords 'antiphospholipid antibody' and 'pulmonary hypertension' between January 1980 and July 2017 and identified 217 articles. A total of 47 articles were found to be relevant to the topic and included as references. We ascertained that aPL antibodies have been implicated in the development of both idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue disease (CTD). aPL antibodies were also noted to be associated with left-sided valvular heart disease that can lead to pulmonary venous hypertension (PVH). Patients with antiphospholipid antibody syndrome (Diagnostic criteria includes +aPL antibodies) were noted to have a high risk of developing chronic thromboembolic pulmonary hypertension (CTEPH). A recent study also found a positive association of aPL antibodies with ILD and PH in patients with systemic sclerosis. While association between autoimmune thyroid disease and PH (Group V PH), and autoimmune thyroid disease and aPL antibodies is established, no studies linked these three phenomena together. Thus, aPL antibodies had an association with all WHO groups of Pulmonary hypertension (PH). In this review article, we study the association and discuss the need for screening for PH in patients with positive aPL antibodies.

Keywords: Pulmonary hypertension, antiphospholipid antibodies, antiphospholipid antibody syndrome, chronic thromboembolic pulmonary hypertension, systemic lupus erythematosus

1. Introduction

Antiphospholipid antibodies (aPL) are antibodies specific for anionic phospholipids. They are immunoglobulins that attack phospholipids, phospholipid-binding proteins,

or phospholipid-protein complexes (Figure 1) (1). They are usually detected in anticardiolipin assays. Due to their ability to prolong coagulation tests they are also identified in lupus anticoagulant assays (2). aPL antibodies are usually associated with antiphospholipid syndrome (APS). APS is an autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss associated with persistently detected aPL antibodies on two or more occasions at least 12 weeks apart. It can be idiopathic or from

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secondary causes such as systemic lupus erythematosus (SLE), infection and drugs. The criteria for definite APS classification were first proposed in 1999 and updated in 2005 (Figure 2) (3). APS is usually detected for the first time as a blood clot in an artery or vein, or as recurrent pregnancy loss. Catastrophic antiphospholipid syndrome (CAPS) is a rare, serious, and often fatal type of APS characterized by multi-organ failure in a span of a few days to weeks.

Pulmonary manifestations of APS with positive aPL antibodies include pulmonary embolism and infarction, acute respiratory distress syndrome (ARDS), intra-alveolar bleeding, primary thrombosis of lung vessels,

pulmonary capillaritis or fibrosing alveolitis (4-6). aPL antibodies have also been shown to be associated with pulmonary hypertension (Figure 3). In this article we review the existing literature regarding the association of aPL antibodies with various groups of PH and discuss the possible implications in clinical practice.

2. Methodology

We conducted a review of the literature that included all articles on PubMed with keywords "antiphospholipid antibody" and "pulmonary hypertension" between January 1980 and July 2017. These articles were independently examined by 2 reviewers AA and RP. We largely selected publications from the last 20 years, but did not exclude any older publications that were widely referenced and highly regarded. A total of 217 articles were identified from PubMed for review by this strategy. All pertinent reports were retrieved and the relative reference lists were systematically searched in order to identify any potential additional studies that could be included. For less researched topics, we included case reports for purposes of our review. For topics with available retrospective and prospective studies and metanalysis, we excluded case series and case reports. Thus a total of 47 articles were found to be relevant to the topic with pertinent information and were included as references in this review.

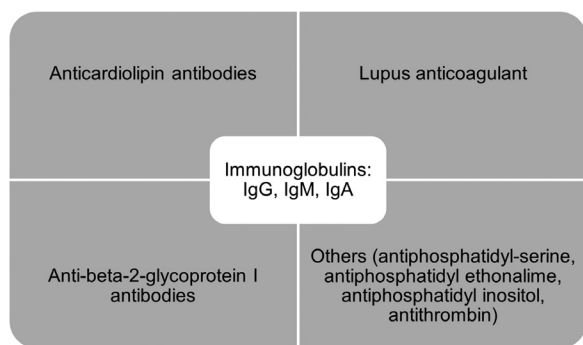


Figure 1. Different types of antiphospholipid antibodies.

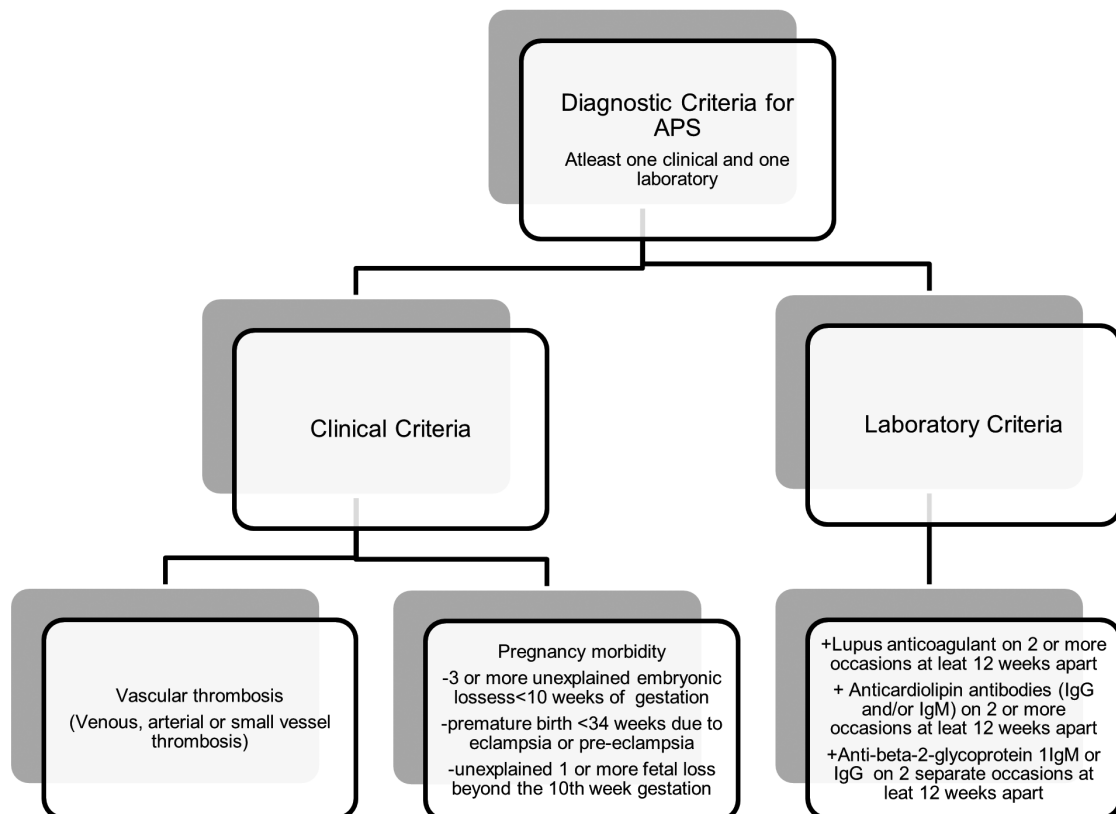


Figure 2. Diagnostic criteria of antiphospholipid syndrome (APS).

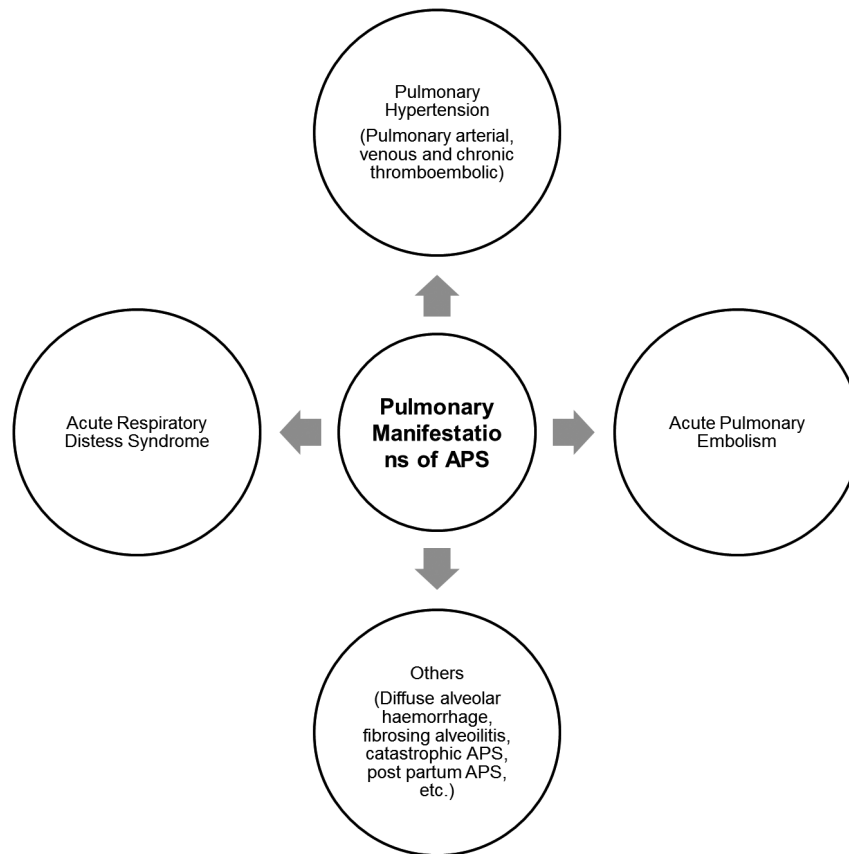


Figure 3. Pulmonary manifestations of antiphospholipid syndrome (APS).

3. aPL antibodies and pulmonary hypertension

Pulmonary hypertension is a chronic and progressive condition defined by a mean pulmonary artery pressure > 25 mm Hg at rest (7,8). The World Health Organization (WHO) currently classifies PH into 5 groups (Table 1) (9). Recent evidence suggests the association of PH with the presence of aPL antibodies (10). Hypotheses regarding the pathophysiology include large vessel and small vessel thrombosis, chronic thromboemboli and associated endothelial remodeling (10). Recent findings of exuberant inflammation and lymphoid neogenesis in remodeled vessels have suggested a role of inflammation in PH, especially pulmonary arterial hypertension (PAH) (11,12). Pioneering work from Soon *et al.* demonstrated significantly increased levels of a broad range of inflammatory cytokines in patients with PAH. It has been well established that aPL antibodies have proinflammatory cellular effects. Thus we hypothesize that pro-inflammatory effects of aPL antibodies may also be contributing to the pathogenesis of PH in such patients.

Asherson *et al.* first reported the association of aPL antibodies with PH in 1985 (13). Karmochkine *et al.* went on to document a high prevalence of aPL antibodies in pre-capillary PH. In this study of 38

patients with PH, 4/9 (44%) patients with primary pulmonary hypertension (PPH) and 7/29 (24%) patients with secondary pulmonary hypertension (SPH) were found to have positive aPL antibodies. Most patients had IgG alone (22/33). Multiple studies since then have studied the association of aPL antibodies with PH. A thorough review of the literature suggested that aPL antibodies are associated with PH across all five WHO groups. aPL antibodies have been noted in patients with WHO Group I PH including idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with connective tissue disorders and rarely PH associated with pulmonary veno-occlusive disease. aPL antibodies can be associated with cardiac valvular disease and thus can lead to pulmonary venous hypertension (WHO Group II PH). These antibodies have also been noted in patients with interstitial lung disease associated with connective tissue disorders like SLE and scleroderma (WHO Group III PH). It is well known that patients with positive aPL antibodies and APS have an increased incidence of recurrent venous thromboembolism leading to CTEPH (Group IV PH). While association between autoimmune thyroid disease and PH (Group V PH), and autoimmune thyroid disease and aPL antibodies, no studies have yet linked these three phenomenon together. Studies with association

Table 1. Classification of pulmonary hypertension based on etiology (9)

Group 1	- Idiopathic - Heritable - Drug induced - Associated with conditions like connective tissue disease, HIV, congenital heart disease, schistosomiasis or chronic hemolytic anemia - Pulmonary veno occlusive disease (PVOD) and pulmonary capillary hemangiomatosis
Group 2	- Left heart diseases - Heart failure (systolic or diastolic) - Valvular heart disease
Group 3	- Underlying lung diseases like chronic obstructive lung disease, interstitial lung disease (ILD) and restrictive lung disease - Induced hypoxia due to sleep disorder, alveolar hypoventilation or chronic exposure to high altitude
Group 4	- Pulmonary hypertension due to chronic thromboembolic events also known as chronic thromboembolic pulmonary hypertension (CTEPH)

of aPL antibodies and various WHO groups of PH are listed in Table 2.

4. Group I PH – pulmonary arterial hypertension

4.1. Idiopathic pulmonary arterial hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is defined as the presence of pulmonary arterial hypertension in the absence of another underlying disease. The presence of aPL antibodies has been reported in patients with IPAH (14). While the causative role of aPL antibodies in these patients is unclear, possible mechanisms include both platelet and endothelin-1 activation. Endothelin-1 (ET-1) is a potent vasoconstrictor and its role in PAH is well established (15). Platelet and endothelin activation can also lead to pulmonary vascular remodeling eventually leading to elevated pulmonary arterial pressures. This hypothesis is supported by the fact that increased levels of circulating ET-1 have been observed in patients with aPL antibodies present (16).

4.2. Pulmonary hypertension associated with connective tissue disease

PH associated with connective tissue disorders (CTD) is classified as Group I PH. aPL antibodies have been identified in patients with CTD's such as SLE and scleroderma. A study compared the presence of aPL antibodies in patients with CTD and found the prevalence of aPL antibodies in SLE patients to be roughly six times more than those with scleroderma (17). Tanaseanu *et al.* studied the prevalence of aPL antibodies and its relationship with PAH in 30 patients with SLE. Presence of aPL antibodies was noted in all patients with SLE and PAH (15/15) as compared to only 5/15 in patients with SLE without PAH. Multiple studies have noted the presence of positive anticardiolipin antibodies (aCL) has a significant association with PAH

and SLE patients (18-21). Similarly Houman *et al.* found out that the frequency of PAH in SLE was higher in patients with antibodies against B2Glycoprotein I (B2GPI) than those without these antibodies (22).

Most patients with aPL antibodies do not have APS, but have symptoms similar to IPAH thereby suggesting a role of aPL antibodies in pulmonary vasculopathy. The role of aPL antibodies in CTD-PAH development is unknown. Zuily *et al.* did a meta-analysis of 31 studies with about 4,480 patients with SLE and showed that people with positive aPL antibodies had a higher prevalence of PH (12.3%) as compared with aPL antibody negative SLE patients (7.3%). The overall OR for PH in aPL-positive versus aPL-negative SLE patients was 2.28 (95% CI, 1.65 to 3.15; $p < 0.0001$).

The treatment of these patients is similar to other patients with pulmonary arterial hypertension with special focus on anticoagulation due to higher risk of VTE in patients with aPL antibodies (1). Current guidelines suggest the use of oral anticoagulants in patients with idiopathic PAH and PH associated with CTD on an individual basis and based upon the presence of thrombophilic predisposition (Grade II b, Level C) (23). The COMPERA study conformed the benefit of anticoagulation in IPAH. The number of SLE or other CTD patients was too small to draw any inferences (24). Thus it is unknown whether anticoagulation is of benefit in aPL antibody positive SLE patients with PH without thrombosis. In thrombotic APS patients with PH, anticoagulation is recommended (25). The presence of PH in SLE patients markedly worsens prognosis (26,27). It is unclear if aPL antibody positivity is a prognostic marker for survival or lung transplantation in these patients (10,27).

Pulmonary veno-occlusive disease (PVOD) is another subset of group I PH that is seen in patients with CTD, HIV infection, bone marrow transplantation, sarcoidosis and pulmonary langerhans cell granulomatosis (28). The authors are aware of only 1 case reporting the possible association of aPL antibodies to PVOD (29).

Table 2. Studies on Association of antiphospholipid antibody with pulmonary hypertension

Author/Year	Type of Study	Number of subjects	Results
Karmochkine <i>et al.</i> (55) 1996	Prospective	<i>n</i> = 38 PH (9PPH+29 SPH) aPL	(11/30) +aPL in pre capillary PAH (4/9) +aPL in PPH (44%) (7/29) +aPL in SPH (24%)
Wolf <i>et al.</i> (45) 2000	Prospective	<i>n</i> = 116: CTEPH <i>n</i> = 83 : PPH	(25/116) CTEPH + APA (8/83) PPH +APA Among 33 CTEPH or PPH patients: (22) + IgG (7) + IgG+IgM (4) + IgM, High titers of antibody 20% in CTEPH & 10% in PPH
Tanaseanu <i>et al.</i> (56) 2007	Prospective	30 SLE (15PH+/15PH-) 30 COPD (15 PH+/15PH-)	Frequency of aPL antibody: SLE: (15/15(100%) in SLE+/PH) & (33% in SLE-/PH) COPD: (8/15(53%) in COPD+/PH) & (13% IN COPD-/PH)
Fois <i>et al.</i> (19) 2010	Retrospective	12 patients: SLE+/PH 9 SLE/+ isolated PH (Group1); 1 SLE/+ PH due to left heart disease(group2); 2 SLE+/PH related to lung disease (group3)	(9/12) SLE+/PH had a + aCL antibody (frequency 75%) 2 SLE+/PH related due to lung disease: +aCL antibody 2/2 in this group
Kamel <i>et al.</i> (57) 2011	Cross-sectional	Total SLE: 74 SLE+/PH: 8	7/8 (88%): SLE with PH/ + (aPL IgG), <i>p</i> = 0.08 Linear regression analysis: + aCL were significantly associated with PAH occurrence in SLE with <i>p</i> value of 0.006
Cefle <i>et al.</i> (18) 2011	Retrospective	10: SLE+/PH 97: SLE-/PH	SLE+/PH: Total 10 2: + aCL IgG 4: + both aCL IgG & + aCL IgM 1: + aCL IgG, + aCL IgM, + LAC 1: + aCL IgM, + LAC aPL positivity: SLE+/PH (80%) vs. SLE-/PH (36%), <i>p</i> < 0.005.
Ware <i>et al.</i> (58) 2015	Cross-sectional, observational	<i>n</i> = 50 SLE 23/50: aPL + 11/23: aPL+/+PH	(11/23) aPL+/+PH (14/23) + aCL (3/23) + LAC (16/23) + Anti-beta-2-glycoprotein I antibodies (11) + 2 or more antibodies (PHT) 11/23 APA+ & 2/27 APA- Moderate to severe PH (7/ 11) APA +
Zuily S <i>et al.</i> (59) 2017	Meta analysis	4,480 SLE	Prevalence of PH: + aPL(12.3%) vs. - aPL (7.3%) The highest risk for PH: +LAC & + IgG aCL Low risk: IgM aCL & anti-β-2-glycoprotein I antibodies

aCL: anticardiolipin antibodies; aPL: antiphospholipid antibodies; COPD: chronic obstructive pulmonary disease; CTEPH: Chronic thromboembolic pulmonary hypertension; LAC: lupus anticoagulant; PAH: pulmonary arterial hypertension; PH: Pulmonary hypertension; PPH: primary pulmonary hypertension; SLE: systemic lupus erythematosus; SPH: secondary pulmonary hypertension.

5. Group 2 PH – Pulmonary venous hypertension associated with heart valve disease

Cardiac valvular disease is the most frequent cardiac manifestation in patients with APS, with a prevalence of 30%. Heart valve lesions (vegetation, thickening and dysfunction) are usually reported in patients with APS with and without SLE, and in those with aPL antibodies alone. Several autoantibodies can directly affect the heart tissue. For example, aPL antibodies can affect the heart by enhancing atherosclerosis, causing thrombosis of coronary arteries or via means of an immune-complexes-mediated reaction. They lead to immune complex formation and deposition which acts

as the initial triggers for valvular endothelial activation. This leads to the thickening of the valves or formation of sterile vegetations on these valves (mainly mitral and aortic) (30). This is known as Libman-Sacks endocarditis *i.e.* verrucous endocarditis of valve leaflets, papillary muscles and the mural endocardium. This endocarditis is present in about 20% to 30% of patients with SLE and about a third of patients with primary APS (31-33). These lead to a significant amount of valvular regurgitation and can lead to left heart failure and associated pulmonary venous hypertension (PVH) (34). The risk of valvular heart disease is highest for patients with lupus anticoagulant and anti-cardiolipin antibodies (IgG) (35).

The presence of aPL antibodies in SLE patients is associated with a threefold greater risk of cardiac valvular disease than those without aPL antibodies, leading to thrombotic manifestations on valves because of hypercoagulability. APS patients undergoing valve-replacement surgery are at high risk of thrombotic and bleeding complications. Thus aPL antibody-related cardiac valvular disease affects APS management.

6. Group 3 PH – Pulmonary hypertension associated with interstitial lung disease

Patients with interstitial lung disease (ILD) present with onset of chronic cough, dyspnea, and decreased exercise tolerance. PH-ILD is secondary to parenchymal and vascular remodeling in the lungs. Its prevalence in ILD is estimated at 30-40% and causes severe exercise limitation and dismal prognosis for ILD patients (36). Mejia M *et al.* (37) in 2017 have found several auto-antibodies associated with ILD. Many studies have shown association of ILD with SLE, but there is a paucity of literature showing a specific relationship of aPL antibodies with PH in this group (38). Similarly the association of other CTD's with ILD is well established (39). As discussed earlier, there is an increased incidence of PH in patients with CTD and the presence of aPL antibodies. Thus by association, it is likely that aPL antibodies are present in patients with both ILD and PH, especially in those with underlying CTD.

Morrisroe *et al.* studied 940 patients with systemic sclerosis and found the presence of aPL antibodies in 226 patients. Elevated titres of both anticardiolipin antibody IgM (OR 2.04, 95% CI: 1.4-3.0, $p < 0.0001$) and IgG (OR 1.84, 95% CI: 1.2-2.8, $p = 0.005$) were associated with an increased likelihood of ILD in these patients. Positive anticardiolipin IgG was also noted to be a marker of co-existent ILD and PH (OR 2.10, 95% CI: 1.1-4.2, $p = 0.036$) (40).

7. Group 4 PH – Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is the form of pulmonary hypertension defined as pre-capillary hypertension with at least one segmental perfusion defect at scintigraphy and typical findings at conventional or computed tomographic pulmonary angiography, after at least 3 months of anticoagulation (41). It occurs usually as a consequence of incomplete resolution of acute pulmonary emboli, progressively organized into fibrotic material obstructing large pulmonary arteries, which leads to elevated pulmonary artery pressures (42). There has been an increased awareness regarding the pathogenesis of CTEPH in the last two decades with several reports of association of aPL antibodies and CTEPH. Colorio *et al.* noted a high proportion of positive aPL antibodies (50%) in 24 patients

with CTEPH (43). In a retrospective study, D'Armini *et al.* detected aPL antibodies in 15% of patients (28/184) who underwent pulmonary endarterectomy for CTEPH (44). Wolf *et al.* studied the presence of thrombotic risk factors in patients with CTEPH and PPH. The study showed 20% positive aPL antibodies in patients with CTEPH and 10% positive aPL antibodies in patients with PPH (45). Similarly Martinuzzo *et al.* found a higher prevalence of aPL antibodies in patients with CTEPH as compared to patients with primary or secondary PH (46).

Patients with positive aPL antibodies especially in APS are prone to venous thrombosis and may have a recurrent pulmonary embolism leading to CTEPH. APS is the most common acquired cause of venous thromboembolism (VTE). The curative treatment for CTEPH is pulmonary thromboendarterectomy (PTE), a surgical procedure in which the blood vessels of the lungs are cleared of clot and scar material. But about 20-40% CTEPH patients are not operable either due to distal and inaccessible nature of the lesions or comorbid conditions, and in up to 35% of patients, the disease persists or reoccurs after PTE (47). Although several vasodilators are in the market for the treatment of PAH, none have been shown to be invariably effective in the treatment of CTEPH. Patients that are ineligible for surgery have been treated with Riociguat, a soluble guanylate cyclase stimulator (48). Lifelong anticoagulation is recommended for all patients with CTEPH in order to prevent recurrent VTE and progressive PH. Vitamin K antagonists (*e. g.* warfarin) are used for anticoagulation. Since the underlying mechanism of aPL antibodies causing CTEPH is immunological, the addition of immunosuppressive agents to the therapeutic regimen may be of benefit. It is therefore important to consider CTEPH in all patients with CTDs and PH as the management of CTEPH is significantly different from other forms of PH.

8. Group 5 PH

8.1. PH and autoimmune thyroid disease

WHO group 5 PH includes patients with thyroid disorders, especially hyperthyroidism. It is unclear whether the association between pulmonary hypertension (PH) and hyperthyroidism is an incidental one or if there is an unexplained pathological mechanism (49). The autoimmune hypothesis can possibly help answer this question. Sugiura *et al.* found a direct linear correlation between pulmonary artery pressure's and thyroid stimulating hormone receptor antibodies (TRAb) ($r = 0.74$, $p < 0.001$) (50). This hypothesis is based upon a possible indirect influence of TRAb in inducing immune-mediated damage of the endothelium that could be able to promote endothelial dysfunction leading to PH. Pagi *et al.* and Marongiu *et al.* noted increased incidence of aPL antibodies in patients with autoimmune thyroid

disease, especially Grave's disease. Nabriski *et al.* similarly demonstrated the prevalence of aPL antibodies is increased in patients with autoimmune thyroid disorders. They suggested that non-specific autoantibody production may accompany the synthesis of tissue-specific immunoglobulin in autoimmune disorders (51,52). Thus while there might be an association between autoimmune thyroid disease, aPL antibodies and PH, this has not yet been studied and requires further research.

8.2. PH and Sarcoidosis

Ina *et al.* studied the correlation between aPL antibodies and sarcoidosis. While no correlation was observed between the occurrence of aPL antibodies and disease activity of sarcoidosis, the presence of aPL antibodies in sarcoidosis was found to be a useful index to judge the prolongation of the disease (53). Recently Pathak *et al.* performed a systematic review to study the association of APS and sarcoidosis and identified 4 cases of sarcoidosis in patients with APS. All patients were noted to have a one of the thrombotic manifestations of APS. None of the studies recorded the incidence of association with PH (54). Thus similar to autoimmune thyroid disease the possible association of PH with sarcoidosis and aPL antibodies needs future studies.

9. Conclusion

The association of aPL antibodies with VTE and PE is well established. Now we know that the effects of aPL antibodies on the pulmonary vasculature extend beyond CTEPH with manifestations that are similar to pulmonary arterial hypertension. There is emerging literature studying the association of aPL antibodies with cardiac valvular disease which can eventually lead to pulmonary venous hypertension. Thus the presence of aPL antibodies will make clinicians think about PH across all WHO groups. Our hypothesis is that aPL antibodies are a harbinger of pulmonary vasculopathy and thus the presence of aPL antibodies can be possibly used as a screening tool for PH patients. Further research is needed to clarify the pathogenesis of aPL antibodies and PH, and to lay guidelines regarding the routine screening of these patients.

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