ical emboli. As a result, aged patients with platypnea-orthodeoxia may be subjected to surgery.

In the past 15 years increasingly it has been recognized that (1) dyspnea associated with chronic pulmonary disease may be treated safely with opiates, and (2) that the dangers of addiction with this form of treatment is minimal. To our knowledge, opiates have never been used in the treatment of the platypnea-orthodeoxia syndrome.

Accentuation of hypoxemia with opiates, of course, could be managed with oxygen therapy. From the standpoint of safety, we cite the six patients in the literature whose Pco₂ values were published. Five had hypocapnia (increased alveolar ventilation) and one had a normal Pco₂. In the face of alveolar hyperventilation, opiate therapy should be particularly safe. The failure to use opiates resembles treatment of orthopnea, for which opiate therapy had not been used for many years. Opiates are now, of course, an important part of therapy.

In any case, a careful trial of opiate therapy would seem to be a reasonable approach, especially in older patients with platypnea-orthodeoxia. It is a reasonable guess that for most patients, even if they are candidates for surgical closure of an interatrial communication, opiate therapy would have a more favorable risk-benefit and cost-benefit ratio compared to surgery.

In summary, the apparently rare syndrome of platypnea-orthodeoxia has been reviewed. The historical steps in the description of the syndrome have been outlined, the various causes have been classified, the disordered physiology has been analyzed and used to call attention to a more common (and frequently iatrogenic) disease, diffuse endocardial injury, and the use of opiates to treat the syndrome has been suggested.

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The Antiphospholipid Antibody Syndrome
A Vascular Disease With Pulmonary Manifestations

I t is rare that a new disease with respiratory manifestations arrives on the scene. The antiphospholipid antibody syndrome (APS) is a perplexing new entity that is approximately a decade old. APS is a hypercoagulable state characterized by the presence of autoantibodies to membrane phospholipids. Its major clinical features are vascular occlusion (eg, stroke, myocardial infarction, peripheral gangrene, visceral infarct, deep vein thrombosis), fetal loss, and hematologic abnormalities that mimic vasculitis (eg, thrombocytopenia, Coombs’s positive hemolytic anemia, livedo reticularis). Circulating immunoglobul-
lins, anticardiolipin antibody (aCL), and a lupus anticoagulant (LAC) directed against membrane phospholipids play a central role in the pathogenesis of APS.3,4

APS is of interest to the pulmonologist because of its wide spectrum of respiratory manifestations. In this issue of CHEST (see page 1707) Kerr et al reported an atypical case of APS with ARDS features and no other systemic manifestations. The known manifestations of APS, such as recurrent pulmonary emboli with pulmonary hypertension, pulmonary hemorrhage, pulmonary arterial thrombosis, and ARDS, typically occur in the presence of systemic findings.3,4,5 Another unique presentation is postpartum pulmonary artery thrombosis in association with pleural effusions, infiltrates, spiking fevers, and chest pain.6

APS is categorized as “primary” when it presents as an independent entity, or “secondary” when it appears with an underlying autoimmune disorder. The presentation is similar in both categories, but the distinction is important because of different prognostic and therapeutic concerns. For example, the coagulopathy of APS in association with systemic lupus erythematosus (SLE) is treated with anticoagulants, while inflammatory vasculitis secondary to SLE is treated with immunosuppressive drugs. Approximately 50% of APS cases present as primary disorders; the remainder occur in association with SLE, another connective tissue disorder, or less frequently (<10%), idiopathic thrombocytopenic purpura.7,8 The histopathologic marker of APS is a bland, noninflammatory thromboembolic occlusion of small or large vessels.1,8 The vessels contain subendothelial deposits of material that appear positive with periodic acid-Schiff stain (PAS). Thus, APS is a vascular disease involving the endothelium as a primary target. The precise mechanism of the coagulopathy is not well defined, but does involve a complex interaction between antiphospholipid antibodies, clotting factors, and the vascular endothelium.9,10

The protean manifestations of APS make accurate diagnosis a challenge. The temporal relationship of the thromboembolic events and elevated antibody titers is poorly defined.8,10 Since <10% of thromboembolic events are a result of hypercoagulable states, a high index of suspicion is required to identify cases of APS. In the setting of unexplained arterial or venous thrombosis or fetal loss, a first step is to determine the patient’s aCL and LAC titers. In approximately 60% of APS cases, both titers are elevated. The other cases will have an elevation of only one test. Therefore, testing for both aCL and LAC is important. The IgG isotype most often correlates with that of thrombosis.10 Antibody titers may be elevated persistently, or temporarily in response to infections, malignancy, and other acute conditions. One third of patients with SLE have antiphospholipid antibodies present, but many do not develop APS.1,11 Approximately 2% of the general population have detectable antibodies, while 0.2% have high titers.1,7 Low titers of antiphospholipid antibodies may be present in other autoimmune disorders, infectious diseases (HIV, syphilis, Lyme disease), malignancies, and drug reactions (to phenothiazine, procainamide, hydralazine, phenytoin), but may not be associated with thromboembolic events.1,7

Ideal therapeutic intervention for APS is as elusive as its diagnosis. Untreated thromboembolic events tend to be recurrent; the site of the first event often predicts the site of subsequent events. The median time for recurrence is 12 months.8 There are no prospective randomized trials evaluating management strategies. Two retrospective analyses of 247 patients with APS concluded that high-dose warfarin (international normalized ratio [INR] ≥ 3.0) provided the best protection against recurrent events for patients with a confirmed history of thrombosis.7,8 Anticoagulation with low or intermediate intensity warfarin, or heparin, provides limited protection from recurrence. Prophylactic use of aspirin alone provided no protective benefit. The results of these studies were inconclusive in determining whether concurrent use of aspirin and anticoagulants has any additional beneficial effect. While lifelong anticoagulation therapy carries a risk for bleeding, the consensus is that this risk is less than that of untreated APS.1,7,8 Adverse side effects frequently accompany long-term use of steroids, cytotoxic agents, and plasmapheresis. Therefore, caution is warranted in the use of treatments that have not been evaluated in a prospective clinical trial. It is not clear if patients with elevations of antiphospholipid titers but without clinical manifestations of APS benefit from aspirin or anticoagulant prophylaxis. Anticoagulation during pregnancy poses a special concern related to teratogenic problems with warfarin. Pregnant women with histories of recurrent spontaneous abortion may have better clinical outcomes using aspirin in combination with heparin or corticosteroid prophylaxis.12-14

There is limited information concerning optimal treatment of APS-associated pulmonary manifestations. A steroid-responsive form of ARDS may complicate either primary or secondary APS.3,15 These patients appear to respond rapidly to IV steroids within hours or days.3 The occurrence of ARDS is not surprising, since circulating immunoglobulins directed against membrane phospholipids can produce endothelial damage.3,15 The basis for the response to steroids is unclear, and it runs counter to
current recommendations for treating ARDS. A subset of APS patients with autoimmune capillaritis may benefit from combination treatment with steroids and immunosuppressive agents. Crausman et al\(^6\) obtained rapid suppression of alveolar hemorrhage in several patients using methylprednisolone and cyclophosphamide followed by maintenance therapy.

In summary, APS is a noninflammatory pulmonary vasculopathy, including a chronic recurrent form not associated with an underlying disease. A major goal at this time is to clarify the pathogenesis of this complex disorder. In time, a prospective, randomized trial will guide us to the most effective therapeutic intervention. Do all APS cases represent one disease with a unified pathogenesis, or several related entities? Is this a primary disease of the endothelium, or of the clotting factors? What is the initiating factor for production of the auto-antibodies? These questions present a significant challenge; it remains to be seen what we can do for these patients.

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