mal proliferation, and nearly complete luminal obstruction. Macaques infected with recombinant chimeric simian immunodeficiency virus (SIV)/HIV (SHIV) constructs in which one or more SIV gene products are replaced with those from HIV represent a model of HIV immunodeficiency in which components of the human virus may be assessed for their potential contributions to pathologic conditions. We surveyed 24 animals from three different cohorts that were infected with various SIV and SHIV constructs, four of which were an SHIV recombinant virus containing the HIV *nef* gene. We observed examples of arteriopathy including medial hypertrophy, perivascular cuffing by inflammatory cells, thrombosis, and pulmonary vascular lesions with recanalized lumens exclusively in tissues from the SHIV *nef* animals. The characterization of these lesions with endothelial and smooth muscle-specific markers by immunohistochemistry revealed that the endothelial cell core of the lesion often stained intensely for platelet-endothelial cell adhesion molecule-l (CD31) and von Willebrand factor (factor VIII), and the thickened media stained with a muscle-specific actin. We propose that the SHIV *nef*-infected macaque provides a novel primate model to explore the development and natural progression of HIV-related pulmonary hypertension and primary pulmonary hypertension.

Pulmonary Endothelin-1 Clearance in Human Pulmonary Arterial Hypertension*

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(CHEST 2005; 128:622S)

Abbreviations: CTD = connective tissue disease; ET = endothelin; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension

Endothelin (ET)-1, the potent vasoconstrictor and smooth muscle mitogen, is a likely mediator of human pulmonary arterial hypertension (PAH). High plasma levels and intrapulmonary synthesis of ET-1 are found in various types of PAH. ET-1 is normally cleared from the pulmonary circulation via ET-B receptors found on endothelial cells. It is not known how PAH, which reduces the amount of perfused vascular surface area in the lung, affects ET-1 clearance. It is also unknown how the amount of ET-B receptor expression, which may be altered in PAH, affects ET-1 clearance. We used an indicator dilution technique to measure the levels of first-pass pulmonary extract of trace quantities of ^{125}I-ET-1 from circulating blood (mean [± SD] levels, 47 ± 7%). We then calculated the permeability surface product (normal range, 18 to 40 mL/s), an index of the functional vascular surface area that is available for ET-1 extraction. Patients with primary pulmonary hypertension (PPH) [n = 17] and PAH from connective tissue disease (CTD) [n = 12] were studied. For both groups, the mean ET extraction was slightly reduced (PPH patients, 39 ± 16%; CTD patients, 36 ± 16%), while the permeability surface product was reduced for most patients (PPH patients, 18 ± 10%; CTD patients, 19 ± 11%). However, 59% of patients had first-pass pulmonary extract levels within the normal range. Thus, in many patients with PAH, despite the reduced functional vascular surface area available for ET-1 clearance, high circulating ET-1 levels may relate more to excess production than to reduced clearance. The fact that ET-B receptor-mediated clearance is preserved in many patients may be of importance to the relative effectiveness of selective vs nonselective ET antagonists.

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This research was supported by the Canadian Institute of Health Research.

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Clinical Challenges in Pulmonary Hypertension*

Roger S. Mitchell Lecture

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Despite major advances in our understanding of the pathophysiologic processes leading to pulmonary arterial hypertension and recent developments in

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Dr. Provencher was the recipient of a fellowship grant from Université Laval, Québec City, QC, Canada, and has received consulting fees from Actelion. Drs. Jais and Yaici have received no financial support and has not been involved with any organization with financial interest in the subject matter. Dr. Sitbon has received consulting and lecture fees from Actelion and Schering AG, and consulting fees from GlaxoSmithKline. Dr. Humbert has received consulting and lecture fees from Actelion and Schering AG, and consulting fees from Pfizer and Myogen. Dr. Simonneau has received consulting and lecture fees from Actelion and Schering AG, and consulting fees from Pfizer and Myogen.
The Centre des Maladies Vasculaires Pulmonaires has been supported by grants from Université Paris-Sud, Legs Poix, INSERM, and the Association Française contre le Myopathies.

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therapeutic approaches, the long-term prognosis for patients with pulmonary arterial hypertension remains unsatisfactory. Early detection and adequate clinical classification of the disease, better assessment of patients' prognosis, and improved therapeutic strategies are important challenges for clinicians in coming years. ***(CHEST 2005; 128:622S–628S)***

Key words: chronic thromboembolic pulmonary hypertension; combination therapy; early detection; venoocclusive disease; walk test

Abbreviations: NYHA = New York Heart Association; PAH = pulmonary arterial hypertension

The most serious chronic disorder of the pulmonary circulation is certainly pulmonary arterial hypertension (PAH), a syndrome of diverse etiology and pathogenesis characterized by the persistent increase in pulmonary vascular resistance potentially leading to right heart failure and death.[1,2] Recent improvements in our understanding of this syndrome have been quite remarkable, including the identification of a gene responsible for inherited forms of PAH, a better understanding of the pathobiological pathways involved in the development of pulmonary hypertension,[3] and the development of medical therapies targeting these different pathways.[4] However, pulmonary hypertension still challenges physicians with both its diagnosis and treatment.

Diagnostic Challenges

Early Detection of Pulmonary Arterial Hypertension

Early recognition of pulmonary hypertension is a real challenge for clinicians. It is thought that the detection and treatment of the disease in the early, and possibly more reversible, stages of the disease might be associated with improved survival. In idiopathic PAH, the initiation of IV epoprostenol at a less advanced stage of the disease, as assessed by the New York Heart Association (NYHA) functional class III compared to class IV, resulted in improved long-term survival in two large cohorts of idiopathic PAH patients.[2,5] NYHA functional class II patients might also benefit from earlier treatment, although specific randomized trials are needed to test this hypothesis. However, pulmonary hypertension does not become clinically manifest until pulmonary vascular disease is advanced.[1] Therefore, strategies allowing the identification of patients at a presymptomatic or very early symptomatic stage are necessary. Because of the low prevalence of PAH in the general population, systematic screening for the early detection of presymptomatic disease will probably remain restricted to individuals who are at moderate-to-high risk of developing the disease such as first-degree relatives of familial PAH patients, patients with congenital heart disease with systemic-to-pulmonary shunts, and patients with the scleroderma spectrum of disease.[6] Moreover, there is still a significant delay between the first symptom of the disease and the diagnosis. In a recent national registry in France,[7] PAH was diagnosed in 75% of patients who were in NYHA functional class III or IV, which is similar to the data obtained > 15 years ago in the National Institutes of Health registry.[1] A high index of suspicion is mandatory in view of unexplained compatible symptoms, especially for patients with predisposing conditions (*eg*, HIV infection and portal hypertension) and for patients with symptoms that are unexplained by the physiologic impairment caused by the concomitant disease. Consequently, educational programs to sensitize clinicians to the nonspecificity of presenting symptoms are clearly needed.

Echocardiography is a noninvasive method providing an estimate of systolic pulmonary artery pressure in most patients.[6] This feature justifies its application as the most commonly used screening tool for pulmonary hypertension despite the fact that the accuracy of echocardiography for the estimation of systolic pulmonary artery pressure is imperfect.[6] In the very early stage of the disease, it is thought that pulmonary artery pressure may be normal at rest but increases to abnormally high levels during conditions of increased blood flow, such as during exercise.[8] However, the significance of the abnormal elevation of estimated pulmonary artery pressure during exercise is not clear.

Finally, germline mutations for the gene coding for the bone morphogenetic protein receptor II have been identified in approximately 50%, 25%, and 10%, respectively, of patients with familial PAH, sporadic idiopathic PAH, and PAH associated with anorexigen exposure.[9] As these mutations are inherited in an autosomal-dominant manner, family members are at risk of developing the disease. However, because the penetration of these mutations may be as low as 10 to 20%, most individuals with the mutation will remain free of the disease. Moreover, the relatives of patients with familial PAH who do not have an identifiable mutation may be at risk of developing the disease. Therefore, the role of genetic testing in the presymptomatic detection of the disease is currently limited.

Adequate Clinical Classification of Pulmonary Hypertension

Numerous conditions are known to lead to or to be associated with the development of pulmonary hypertension (Table 1). These conditions are classified into four distinct groups based on their similar clinical presentation, pathology, pathophysiology, prognosis, and, most of all, similar therapeutic approach.[10] Some aspects of this classification deserve special consideration.

Recognition of proximal chronic thromboembolic pulmonary hypertension is of major importance. It is the only curable form of precapillary pulmonary hypertension. Therefore, a ventilation/perfusion lung scan is mandatory in all patients with pulmonary hypertension as spiral CT scanning cannot rule out chronic thromboembolic pulmonary hypertension.[11] In patients with abnormal ventilation/perfusion lung scan findings, pulmonary angiography is required for the adequate assessment of patient's operability by thromboendarterectomy for thromboendarterectomy. In future years, MRI and multislice CT scanning